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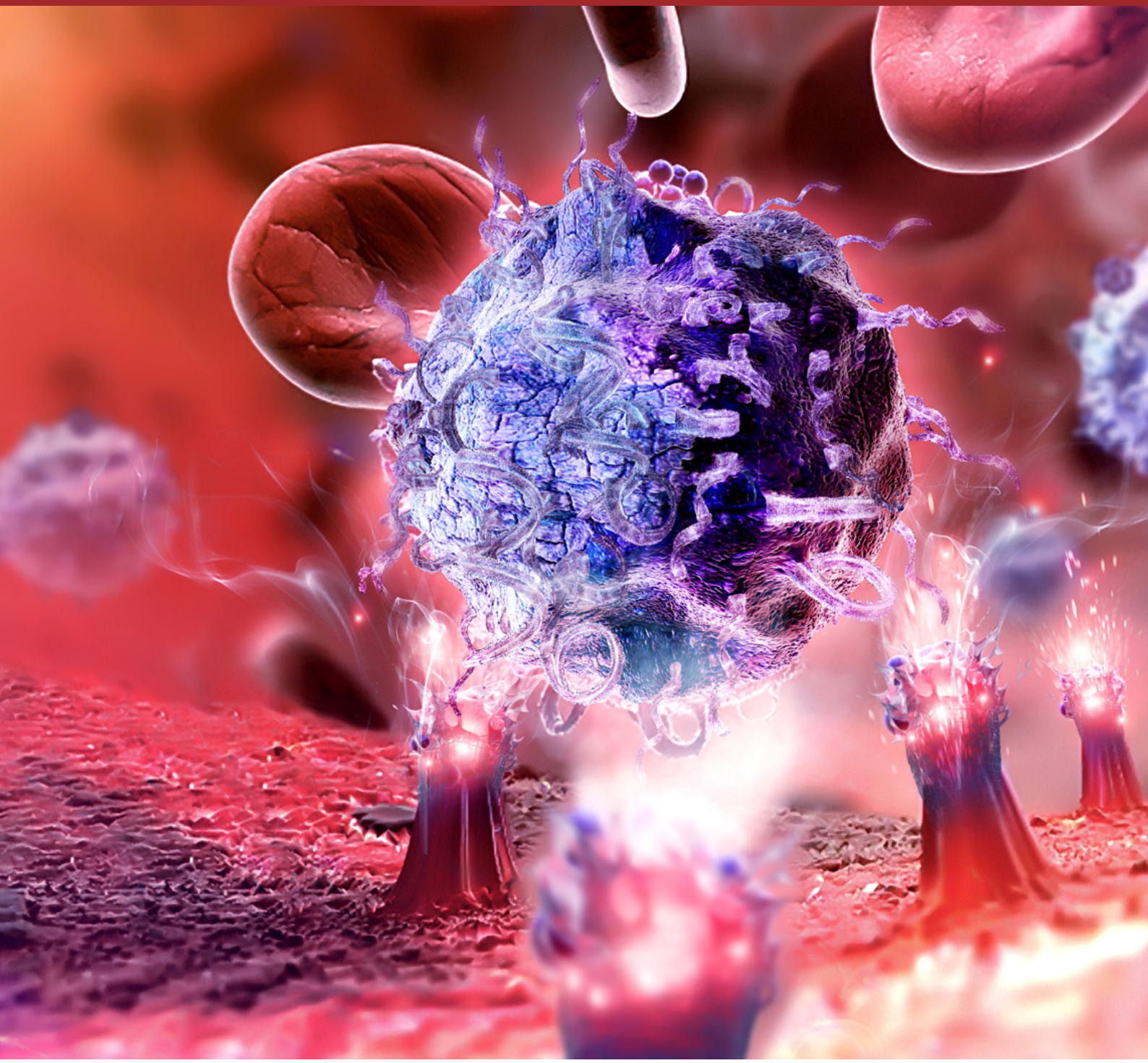

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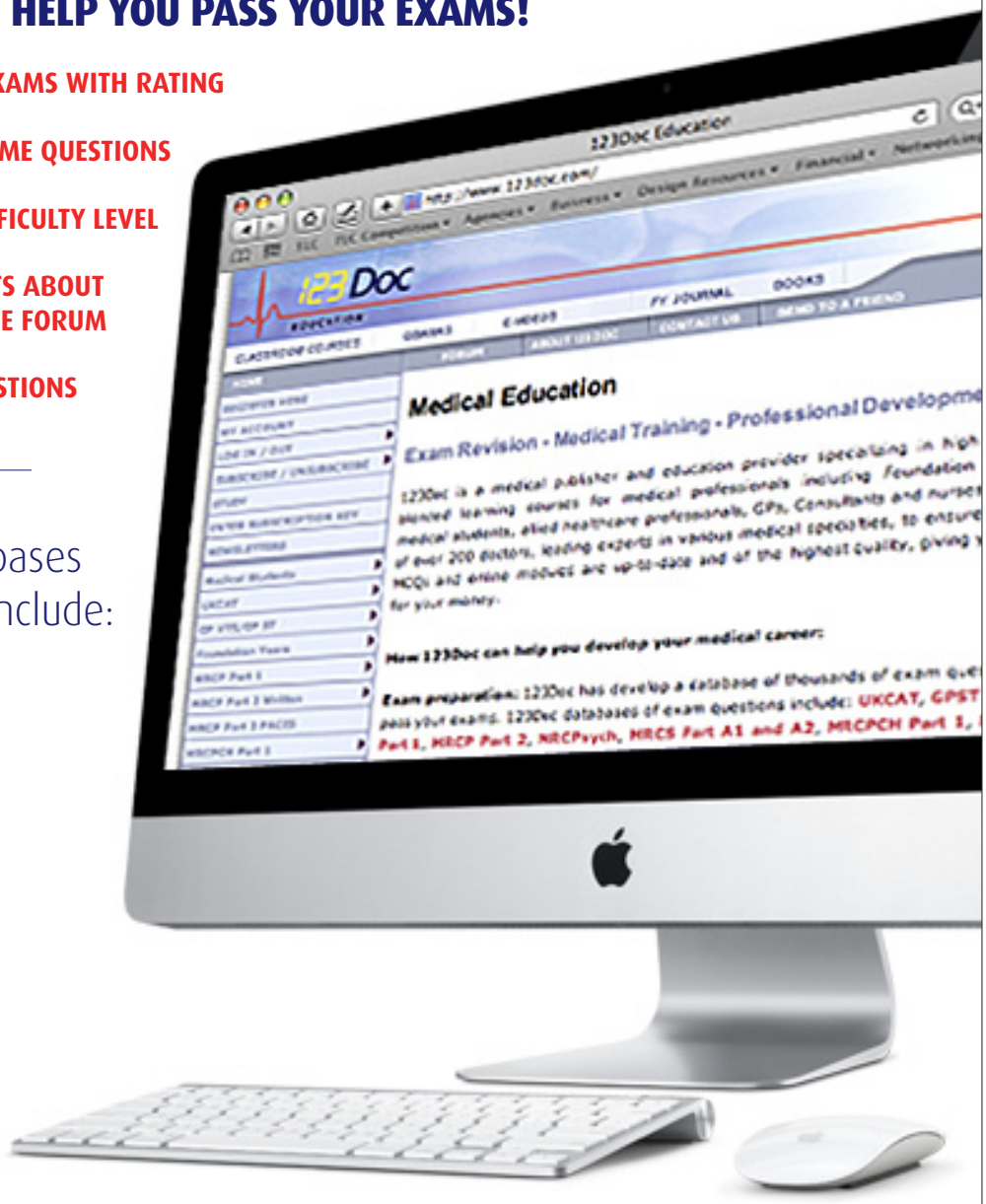

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Volume 11

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TROUBLESOME URTICARIA

E Boules, E Drewe

Abstract

Urticaria and angioedema are common conditions that can present to primary and secondary care. Urticaria is characterised by itchy raised skin lesions resembling nettle rash. Each wheal typically resolves within 24 hours although the course of the condition as a whole can take longer to settle. Urticarial rash can be associated with angioedema which involves swelling of deeper skin and subcutaneous tissue (1).

Angioedema can also affect the eye lids, lips, tongue, gut, upper airway and peripheries. Food allergy can present with urticaria and angioedema but the most common cause is Spontaneous Urticaria (Previously known as Idiopathic Urticaria). Occasionally urticarial rash can be a symptom of an underlying medical disease (2). Angioedema in isolation also requires specific consideration. Taking accurate history will help identify the cause and direct management.

Case History

Presentation to Emergency Department

A 53 year old male attended the emergency department with three days of widespread urticaria. On the morning he attended he had also woken up with swelling of his eyelids and lips which had concerned him and prompted attendance. He had been taking cetirizine 10 mg daily. He was normally well and not on any other medication. He had no family history of urticaria or angioedema. He drank 5 units of alcohol a week and was a non-smoker. He wondered if he was allergic to nuts and dairy food.

On direct questioning he had had no collapse, throat tightness or breathlessness. The case was discussed with the Registrar and as the condition was not progressing and there were no features of anaphylaxis admission was not felt to be required. The patient was discharged on high dose cetirizine, 20mg day increasing to 40 mg daily if needed and referral made to the allergy clinic. The patient was advised to return if he had any features of anaphylaxis.

Allergy clinic review 2 weeks later

Further history was obtained and the patient described he had had intermittent urticaria over the last 3 years but over the last 3 months his symptoms were present on most days. Each patch of urticaria resolved in a few hours without leaving bruising or staining.

He reported that he had had urticaria the day after eating nuts but at other times had eaten nuts without rash. He had tried cutting milk out of the diet but rash had persisted. Symptoms could develop overnight or first thing in the morning before eating. The patient was reassured during the clinical consultation that his condition did not fit with food allergy.

Physical triggers including heat exacerbated his symptoms. He did not however exhibit dermographism (an exaggerated wealing tendancy when the skin is stroked). He was questioned on underlying stresses in his life as stress may be associated with urticaria. Past medical history was reviewed and did not reveal any underlying infectious or inflammatory condition that could be driving his urticaria.

History was suggestive of Chronic Spontaneous Urticaria. Investigations were requested considering possible underlying causes of urticaria and included Full Blood Count, renal and liver function, thyroid function (TSH) and thyroid auto-antibodies (Anti-thyroid peroxidase antibodies). These returned normal. The patient was still having daily urticaria despite 40mg cetirizine and reported severe itching affecting sleep. 10mg Montelukast was added to treatment and he was instructed to fill in Urticaria Activity Scores (UAS7) documenting scores for itching and number of urticarial wheals.

4 weeks later

He was still troubled by daily urticaria and had reduced quality of life. His last UAS7 scores were 38 and 40 out of a maximum of 42. As per NICE guidelines for Chronic Spontaneous Urticaria 4 weekly Omalizumab (anti-IgE monoclonal antibody) subcutaneous injections were initiated. He had good response and scores reduced to 12 after the first injection and 6 after the second.

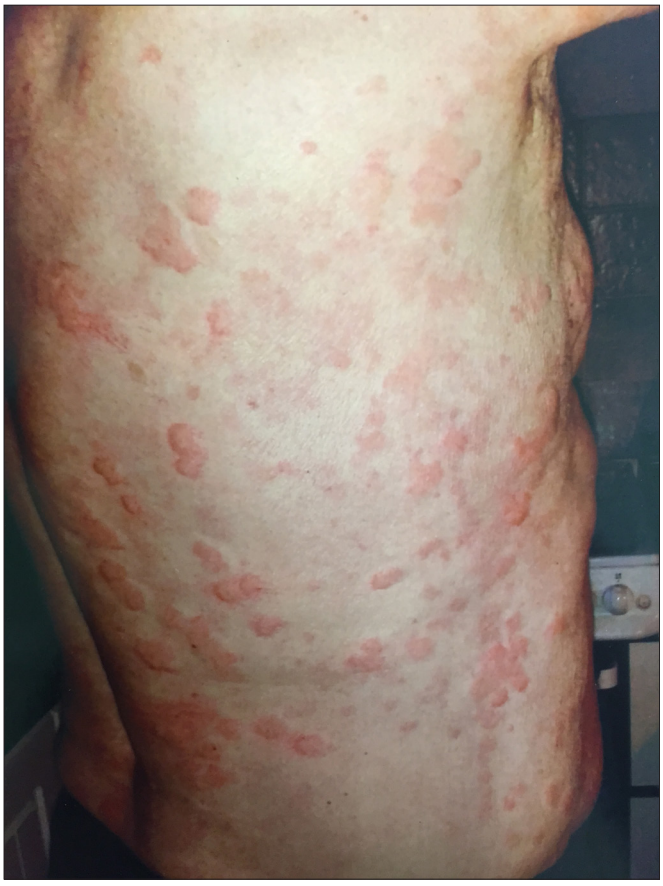

Figure 1: Urticarial rash.

TROUBLESOME URTICARIA

E Boules, E Drewe

Discussion

Urticaria may present to the Emergency Department. Patients and health professionals may think urticaria is due to food allergy and although this is an important differential it is often not the case. Food allergy symptoms tend to occur within an hour of eating the offending food each time the food is eaten. Delayed onset food allergy is however recognised with certain types of food like crustaceans and red meat where onset can be delayed up to 6 hours (3). Symptoms of food allergy usually resolve in 12 hours and do not last several days as in this case. This patient also had angioedema. If angioedema occurs in isolation ACE inhibitors and C1 inhibitor disease / Hereditary angioedema must be considered but in this setting with urticaria these are not implicated.

Urticaria and angioedema can be classified into acute or chronic based on duration of symptoms. Chronic urticaria and angioedema lasts more than 6 weeks and affects 2-3% of the population (4). It can interfere with daily activities and sleep and affects quality of life. Inappropriate activation of mast cells is thought to play an important role in the pathogenesis of this condition. Mast cell degranulation results in the release of inflammatory mediators including histamine and leukotrienes (5).

Chronic Spontaneous Urticaria is the commonest cause of chronic urticaria and unknown stimuli may be involved. In assessment, however, a number of factors require attention. Psychological stress may be contributory and some patients may benefit from psychological therapy in addition to medications. Autoimmune and inducible urticaria eg: due to physical triggers such as heat, exercise and vibration need to be considered.

Chronic infection or inflammation (eg: Helicobacter pylori, sinusitis, dental sepsis and gall bladder inflammation) may be potential drivers of urticaria and should be addressed in history taking. NSAIDS can also be causal. Iron, B12 and folate deficiency may contribute to spontaneous urticaria and levels need to be checked if clinically indicated. A European position paper however recommends only very limited routine diagnostic measures in Chronic Spontaneous Urticaria (6). If individual patches of urticaria last longer than 24-48 hours or leave bruising or staining of the skin urticarial vasculitis should be considered and biopsy may be required (4).

The stepwise management for Chronic Spontaneous Urticaria is illustrated by this case. Initially standard dose anti-histamines are used with second generation antihistamines preferable as less sedative. Anti-histamine doses may be increased to 4x dose if required. If there is still failure of symptom control, a leukotriene receptor antagonist (Montelukast) can be added. UAS7 scores are used to monitor disease activity by scoring level of itching and the number of urticarial patches every day for 7 days.

NICE guideline recommends offering Omalizumab for patients who have a weekly urticarial activity score of 28 or more despite being on maximum dose of antihistamines and leukotriene receptor antagonist (7). 300 mg Omalizumab subcutaneously is given every 4 weeks. Ongoing UAS7 scores are used to assess response to treatment and duration of treatment. This patient had a good response to treatment and improved quality of life, therefore the full course of Omalizumab would be undertaken (6 injections). In line with NICE guidance, treatment would be stopped after the 6th injection, to assess for remission. In practice recurrence of urticaria is common and further treatment with Omalizumab may be necessary (7).

Ciclosporin is also effective in severe unremitting urticaria that has failed to respond to maximum dose of anti-histamines (8). It is as an alternative to Omalizumab but requires careful monitoring for side-effects.

Key points

• Chronic urticaria isn't likely to be due to food allergy.

• Food allergy symptoms tend to occur within an hour of eating the offending food each time the food is eaten.

• The most common cause of chronic urticaria is spontaneous urticaria.

• Psychological stress is an important trigger for chronic spontaneous urticaria.

• A detailed history needs to be taken to identify triggers such as stress, physical factors, infections and medications (NSAIDs).

• Examine the patient to confirm that the rash is an urticarial rash and to exclude dermographism.

• The first line of treatment for chronic urticaria is a second generation antihistamin. The dose can be safely increased to 4 x normal.

• Try and avoid corticosteroids (they cause rebound flare when withdrawn).

• Chlorpheniramine should only be used at night (weak anti-histamine and sedating).

TROUBLESOME URTICARIA

E Boules, E Drewe

Questions: Choose best answer

1. Spontaneous urticaria is characterised by:

a) Rashes that can last for more than 24 hours and are never associated with angioedema

b) Non itchy wheals.

c) Each wheal lasting for less than 24 hours leaving brown staining

d) Being triggered by eating specific types of food

e) Each wheal resolving in 24 hours and may be associated with angioedema

2. With regard to food allergy:

a) Symptoms tend to occur up to 24 hours of eating offending food and resolve in 12 hours

b) Symptoms typically do not happen each time the patient eats the offending food

c) Symptoms tend to occur within 1 hour of eating the offending food. Delayed onset (up to 6 hours) can happen with certain types of food like crustaceans and red meat.

d) Symptoms tend to occur within 1 hour of eating the offending food but can take up to 1 week to resolve

e) This is the commonest cause of urticaria and angioedema in adults

3. With regard to the treatment of Chronic Spontaneous Urticaria:

a) First line of treatment is corticosteroids

b) If patients continue to have symptoms on standard dose of antihistamine, the dose can be increased to up to 4 times the standard dose

c) If patients continue to have symptoms on standard dose of antihistamines, they should be started on Montelukast.

d) According to NICE guideline, if patients fail to respond to maximum dose of antihistamines, the next step is Omalizumab injections.

e) Patients are offered Omalizumab only if their UAS7 scores are 42/week or more.

4. Omalizumab is:

a) First line of treatment for Chronic Spontaneous Urticaria

b) A leukotriene receptor antagonist

c) An anti-IgG monoclonal antibody

d) An anti-Ig E monoclonal antibody

e) An antihistamine

5. Which of the following statements are true:

a) Food allergy is the most common cause of chronic urticaria in adults

b) Chronic Spontaneous Urticaria usually lasts less than 4 weeks

c) Urticarial vasculitis resolves without leaving staining or bruising

d) Inappropriate activation of mast cells is thought to play an important role in the pathogenesis of Chronic Spontaneous Urticaria

e) ACE inhibitors are associated with Chronic Urticaria

Answers

1. Answer e)

Each wheal resolving in 24 hours and may be associated with angioedema. Spontaneous Urticaria is the commonest cause of chronic urticaria in adults. Urticaria is characterised by itchy raised skin lesions resembling nettle rash and can be associated with angioedema. Spontaneous urticaria is not triggered by any specific type of food. It can however be exacerbated by physiological stress, NSAIDs and intercurrent infections. Each wheal tends to last less than 24 hours although the condition as a whole can take longer to settle.

2. Answer c)

Symptoms tend to occur within 1 hour of eating the offending food. Delayed onset (up to 6 hours) can happen with certain types of food like crustaceans and red meat.

Food allergy can present with urticaria and angioedema. It is not however the most common cause. Symptoms tend to appear within 1 hour of eating the offending food and usually resolve in 12 hours. Delayed onset (up to 6 hours) can happen with certain types of food like crustaceans and red meat. Symptoms usually occur each time the patient eats the offending food, with a few exceptions such as when exercise is a co-factor in Wheat-Dependant Exercise Induced Anaphylaxis.

TROUBLESOME URTICARIA

E Boules, E Drewe

3. Answer b)

If patients continue to have symptoms on standard dose of antihistamine, the dose can be increased to up to 4 times the standard dose.

BSACI (British Society of Allergy and Clinical Immunology) guideline has recommended a step wise approach in the management of Spontaneous Urticaria. Initially the standard dose of a second generation anti-histamin is used. This may be increased to 4x dose if required. If there is still failure of symptom control leukotriene receptor antagonist (Montelukast) can be added.

NICE guideline then recommends the use of Omalizumab as an add-on therapy for patients who have a weekly urticarial activity score of 28 (out of 42) or more, despite being on maximum dose of antihistamines and leukotriene receptor antagonist.

4. Answer d)

Anti-Ig E monoclonal antibody. Omalizumab is a monoclonal antibody that binds to immunoglobulin E (IgE). Its exact mechanism of action in Chronic Spontaneous Urticaria is unclear. It is usually well tolerated although not all patients respond. An alternative is ciclosporin although side-effects including hypertension and hirsutism may be encountered.

5. Answer d)

Inappropriate activation of mast cells is thought to play an important role in the pathogenesis of Chronic Spontaneous Urticaria

Urticaria is classified into acute and chronic based on the duration of symptoms. In Chronic urticaria each wheal typically resolves within 24 hours although the course of the condition lasts more than 6 weeks. The most common cause for Chronic urticaria in adults is Spontaneous Urticaria. Other causes include autoimmune urticaria (which may be associated with IgE antibodies to the IgE receptor on mast cells) and inducible urticaria eg: due to physical triggers such as heat, exercise and vibration.

If each wheal lasts more than 24-48 hours or leaves bruising or staining of the skin, then urticarial vasculitis should be considered and skin biopsy may be helpful. Chronic Spontaneous Urticaria can present with associated angioedema. If patients present with angioedema in isolation, however, ACE inhibitors and C1 esterase inhibitor disease (a form of Hereditary Angioedema) must be considered.

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A REVIEW OF THE DIAGNOSIS, MANAGEMENT & IMPACT OF HEPATITIS E

H Abubakar-Waziri, M Roberts, S Assadullah

Abstract

Hepatitis E is one of the most common causes of acute viral hepatitis worldwide. There are an estimated 20 million infections annually, with 60,000 related deaths, highlighting its significant global burden. Since surveillance began in 2003, there has been an increasing trend for reported cases of Hepatitis E in the UK, with studies suggesting its increasing importance in developed countries. This review article aims to provide a brief overview of the epidemiology, diagnosis and management of this common, yet neglected disease.

Case Vignette

A 65 year old man is admitted to hospital with lethargy. He had a history of a JAK-2 positive myeloproliferative disorder. Investigations demonstrate markedly deranged liver function tests with an alanine transaminase of 307 IU/ml, peaking 7 days later at 1460 IU/ml. A careful drug history was undertaken. He was noted to be on hydroxycarbamide but no new medication had been prescribed or illicit drugs consumed. He did not drink alcohol. A standard profile liver screen revealed evidence of past exposure to Hepatitis A (IgG positive), Hepatitis B core antibody negative, Hepatitis C negative, past exposure to Epstein Barr virus (EBNA IgG positive), Cytomegalovirus IgG negative and no evidence of diseases leading to chronic liver disease with normal ferritin, alpha-1-antitrypsin and liver auto-antibody screen.

Further enquiry revealed he had been on a camping trip in the UK 3 weeks earlier. The laboratory protocol for unexplained acute hepatitis was followed with extension to Hepatitis E serology which confirmed a strongly positive IgM with a positive IgG consistent with recent hepatitis E infection. It was purported that he may have acquired this whilst on his camping trip. Public health England had been notified of this and it was concluded likely exposure to water contaminants. Their investigations was not taken any further.

He had quite a protracted acute phase illness but with complete resolution of liver function tests after 3 months. Hepatitis E testing by PCR for RNA was undertaken on stool and blood to ensure that viral clearance had been achieved especially given the underlying immunosuppressive state which is a risk factor for chronic infection.

Introduction

Hepatitis E is a common cause of acute viral hepatitis worldwide. It is caused by the Hepatitis E virus (HEV), an RNA virus and fifth member of the Hepeviridae family. Despite its global distribution, the HEV has a particularly high disease burden in Asia and Africa (1). In these regions, there are an estimated 20 million infections annually (1,2) with nearly 60,000 Hepatitis E related deaths (3). In contrast, Europe, North America and Far East Asia show low endemicity, with sporadic cases of Hepatitis E infection accounting for a minority of cases of acute hepatitis (3).

In the United Kingdom (UK), Hepatitis E is a notifiable disease (4). Since 2003, Public Health England has been running an enhanced programme of surveillance in England and Wales. Recent data suggests an increasing trend for the number of cases reported since 2010 (5), with just over 1200 cases in both 2015 and 2016. This is shown in table 1 (5).

Furthermore, a majority of these cases arise from indigenous strains of the HEV as opposed to being imported by travellers to high risk areas. In 2013, approximately 70% of a total of 691 cases of Hepatitis E reported were shown to derive from indigenous strains of the virus (4). In view of this, Hepatitis E is considered an emerging cause of acute hepatitis in the UK.

Year	Reference laboratory confirmed cases	SGSS reported cases (only reported through SGSS)	Total
2010	276	171 (94)	370
2011	464	270 (86)	550
2012	605	361 (129)	734
2013	731	391 (145)	876
2014	925	598 (184)	1109
2015	959	750 (321)	1280
2016	867	769 (401)	1268

Table 1: This table describes the number of confirmed and reported cases of Hepatitis E by diagnostic laboratories in the UK via the Second Generation Surveillance System (SGSS) since 2010. It demonstrates an increase in the number of cases of non-travel Hepatitis E in England and Wales. Public health England, 2010 (4,5)

Heterogeneity and epidemiological distribution of Hepatitis E

There are 4 sequenced genotypes (G1-G4) of HEV (6,7). HEV G1 and G2 infect humans alone (6) with primary transmission being the faecal-oral route. As a consequence, HEV G1 and G2 are endemic in poorly resourced regions with poor water sanitation (1).

In contrast, HEV G3 and less frequently HEV G4, are both found in humans and animal reservoirs (8). These account for the vast majority of sporadic cases seen in more developed countries (9,10). In these regions, the primary means of transmission is thought to be close contact to infected animals or ingestion of undercooked meat (11). A common reservoir is pigs, with a study conducted in the UK demonstrating 92% of 640 pigs had plasma antibodies against HEV G3 (12) at slaughter. The geographical distribution of the different genotypes is shown in figure 1 (13).

A REVIEW OF THE DIAGNOSIS, MANAGEMENT & IMPACT OF HEPATITIS E

H Abubakar-Waziri, M Roberts, S Assadullah

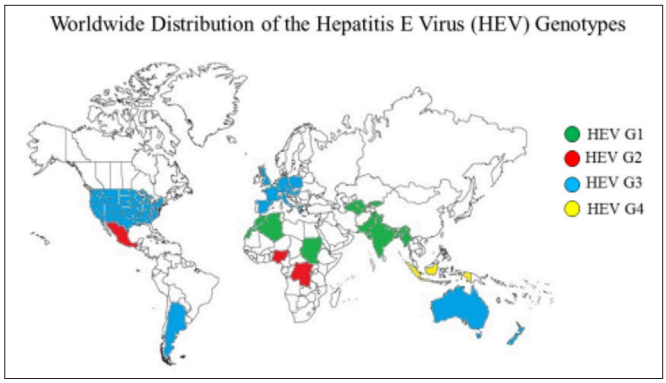

Figure 1: Reproduced from Aggarwal et al. An illustration of the distribution of HEV genotypes in human and animal (mainly swine) reservoir. This figure was based on data from Okamoto, 2007 (33)

Clinical Manifestations of Hepatitis E

HEV most commonly causes an acute, self-limiting hepatitis. Post-exposure, there is an incubation period of 15-60 days (14,15), although only 2-5% of those infected will have significant symptoms (16). Clinical presentation is similar to patients presenting with other causes of acute hepatitis.

Common symptoms include malaise, anorexia, nausea and vomiting, abdominal pain, jaundice and hepatomegaly. Less commonly, patients can present acutely with diarrhoea, pruritus, arthralgia, or even with extra-hepatic manifestations including acute pancreatitis and neurological syndromes including Guillan-Barre (17).

Although Hepatitis E is most commonly self-limiting, in a very small proportion of cases it can lead to acute hepatic failure (13). Clinically, these patients have features of hepatic encephalopathy and impaired synthetic function, leading to deranged clotting tests (13). This is most common in patients whom already have pre-existing liver disease, or in women whom are pregnant (18), with infection in pregnancy found to have high mortality rates, likely secondary to hormonal changes and subsequent immunological changes that alter the immune response to HEV infection (18,19).

Moreover, HEV can also cause chronic infections. This is almost exclusive to the immunosuppressed, particularly in a transplant setting (13,20,21), with HEV G3 most commonly associated (22). Chronic HEV infection is characterised by persistently detectable HEV RNA in serum or stool for at least 3 months, along with persistently raised levels of aminotransferases (23,24). A proportion of those with chronic HEV infection also go on to develop liver cirrhosis (22,24).

In summary, HEV is most commonly a self-limiting illness. However, in selected populations, HEV can lead to fulminant hepatic failure or chronic infections, leading to complications similar to other members of the hepeviridae family, Hepatitis B and C.

Diagnosing Hepatitis E

Hepatitis E should always be considered in patients presenting with features of an acute hepatitis, particularly in those whom have risk factors for HEV infection, including travel to endemic areas or close contact/consumption of high risk animals (mainly pigs) (25,26). We should adopt a low threshold for investigation particularly when dealing with pregnancy, the immunocompromised and patients with underlying liver disease, due to the risk of chronicity and development of fulminant liver failure respectively.

Diagnostic tests for HEV infection include a HEV ribonucleic acid (RNA) assays, performed on serum and stool samples, along with HEV-specific antibody testing. The approach to diagnosing HEV infection is determined by the patient's clinical features and presentation.

In Acute Hepatitis E, acute infection is confirmed on detection of HEV RNA, with or without the detection of HEV specific antibodies. However, HEV only elicits transient viraemia, hence HEV RNA assays may be negative (24,27). Therefore, if tests are negative for HEV RNA, measuring for HEV specific antibodies is essential. Following HEV infection, the initial immune response leads to the production of HEV-specific IgM, which can persist in serum for a number of months (28).

Shortly after initiation of this acute phase, HEV-specific IgG is produced, increasing in titre into the convalescent phase (27). On basis of this pathophysiological process, acute hepatitis E infection is defined as either a positive HEV-RNA, or detection of both HEV-specific IgG and IgM in serum in an acute setting (5). Chronic Hepatitis E on the other hand, is diagnosed on the basis of positive HEV RNA persistent for at least 3 months, with or without the detection of HEV-specific antibodies (5).

Treatment of Acute and Chronic HEV infection

The treatment of Hepatitis E differs in acute and chronic settings and is influenced by the immune-competence of patients.

Acute Hepatitis E is often mild and self-limiting in the immunocompetent. Therefore, treatment is supportive until patients achieve viral clearance spontaneously. In severe cases leading to acute hepatic failure, the mainstay of treatment is liver transplantation. Current data on the role of active antiviral therapy in severe, acute hepatitis is inconclusive (29).

A REVIEW OF THE DIAGNOSIS, MANAGEMENT & IMPACT OF HEPATITIS E

H Abubakar-Waziri, M Roberts, S Assadullah

Chronic Hepatitis E, in contrast, almost exclusively affects the immunocompromised. The main aim of treatment is viral clearance, defined by the absence of HEV RNA 12 weeks after therapy cessation; as measured by serum and/or stool testing for HEV RNA. The initial approach to treatment is influenced by the cause of their immunosuppression.

If the patient is actively being immunosuppressed by therapy, initial treatment involves a reduction in immunosuppressive therapy for up to 12 weeks. This has been shown to result in viral clearance in up to 30% of patients (30). If this fails to clear the virus, or the patient is not actively being immunosuppressed, antiviral therapy should be considered.

Ribavirin monotherapy is recommended for 12 weeks (31), with evidence suggesting this can achieve HEV clearance in a significant proportion of patient with chronic HEV infection (32). The subsequent management of these patients is guided by the response to treatment. Specialist advice should be sought in these cases.

Monitoring of basic laboratory tests (full blood count, urea, creatinine, electrolytes, liver enzymes and bilirubin levels) is recommended at four weeks, with closer monitoring of abnormal results or trends. A common adverse effect of ribavirin is anaemia due to haemolysis which is a dose dependant side effect for which close monitoring of the full blood count is recommended (31).

Prevention

Focus should be placed on transmission prevention with regards to clean drinking water, good sanitation and personal hygiene. Travellers to endemic areas are advised to avoid street food vendors and consuming raw seafood, pork products and raw vegetables.

Recombinant vaccines have proved effective in preventing genotype 1 and genotype 4 infections and are licenced in China (16). This vaccine demonstrated showed 96% and 87% efficacies after 1 year and 4.5 year periods respectively (16). However, the efficacy against genotype 3 is unknown and more evaluation is needed to assess their efficacy in high-risk groups such as the immunocompromised.

Summary

In conclusion, this review article highlights the worldwide importance of Hepatitis E. Data collected since surveillance was introduced in 2003 has since identified an increasing recorded presence of HEV in the UK. Therefore, although much is known about HEV, further research is essential to highlight the optimum treatment for HEV infection in high risk patients and to help identify means of reducing its burden, both in the UK and globally.

MCQs

1. In which region is hepatitis E most Endemic?

a) North America

b) South America

c) Far East Asia and Europe

d) Africa and South Asia

2. What is Public Health England's criteria for confirming a diagnosis of Hepatitis E infection?

a) a positive HEV-DNA, or detection of both HEV-specific IgG and IgM in serum in an acute setting

b) a positive HEV-RNA, or detection of both HEV-specific IgG and IgM in serum in an acute setting

c) a positive HEV-DNA and detection of both HEV-specific IgG and IgM in serum in an acute setting

d) a positive HEV-RNA and detection of both HEV-specific IgG and IgM in serum in an acute setting

3. Which group of patient are most likely to experience severe HEV infection?

a) The elderly and very young

b) Pregnant women and pre-existing liver disease

c) Diabetics

d) HIV infection

Answer

1. Answer: D – Africa and South Asia

Explanation - HEV has a particularly high disease burden in Asia and Africa (1). In these regions, there are an estimated 20 million infections annually (1,2) with nearly 60,000 Hepatitis E related deaths.

2. Answer: B - a positive HEV-RNA, or detection of both HEV-specific IgG and IgM in serum in an acute setting

Explanation - HEV is an RNA virus, discounting answers C and A. Furthermore, a positive HEV RNA confirms HEV infection and does not require the presence of IgG or IgM specific o HEVinfection, the initial immune response leads to the production of HEV-specific IgM, which can remain detectable for up to 2 weeks.

A REVIEW OF THE DIAGNOSIS, MANAGEMENT & IMPACT OF HEPATITIS E

H Abubakar-Waziri, M Roberts, S Assadullah

3. Answer – B – Pregnant women and pre-existing liver disease

Patients whom already have pre-existing liver disease already have a degree of hepatic damage, hence a lower threshold for developing fulminant failure. Infection in pregnancy found to have high mortality rates, likely secondary to hormonal changes and subsequent immunological changes that alter the immune response to HEV infection

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AN INTESTINAL INFLAMMATORY MASS IN A RETURNING TRAVELLER; EXPLORING THE DIFFERENTIAL DIAGNOSIS

V Newman, M Brown

Abstract

Background

This case describes a gentleman who returned from Brazil complaining of fatigue, fevers, night sweats and abdominal pain. Investigations indicated an inflammatory mass in the right iliac fossa secondary to a localised bowel perforation.

Discussion

There are multiple causes of intestinal inflammatory masses in the returning traveller including tropical and non-tropical diagnoses. Specific exposures and targeted investigations can help confirm the diagnosis.

Conclusion

A travel history is important in identifying and excluding rare infectious causes of inflammatory lesions of the intestine, however, the final diagnosis may not relate to the travel history and common conditions should also be considered.

Clinical Case

An 84 year old Caucasian man presented to the Hospital for Tropical Diseases walk-in clinic feeling unwell after returning from a holiday in Brazil.

In May he spent two weeks in Brazil visiting both cities and rural areas. He had occasional insect bites; there was no history of fresh water swimming or trekking. He had been careful about drinking bottled water but ate salads and other local food. In the second week of the holiday he began to feel unwell with flu-like symptoms, extreme fatigue and high fevers of 39°C.

However, he presented to our clinic four months after his return with on-going fatigue, night sweats and weight loss of one stone. There was also a history of occasional right sided abdominal pain. He was a former farmer and had minimal co-morbidities with only ischaemic heart disease, hypertension and diverticular disease to note and no previous foreign travel or exposure to TB. On examination he was pale and had mild non-tender hepatomegaly but otherwise no other abnormalities.

He was admitted for further investigations including bloods which showed raised inflammatory markers with a CRP of 130, white cells of 12 and mildly deranged liver function tests. Three sets of blood cultures failed to grow any organisms. Stool culture and PCR for *Entamoeba histolytica,* amoebic serology and malaria films were all negative. An HIV test was declined, however the patient was low risk.

A CT of the chest, abdomen and pelvis with contrast (figures 1,2) showed an inflammatory mass between the posterior aspect of the caecum and the anterior ileopsoas, which was thought to be secondary to diverticular disease. There was no evidence of pneumoperitoneum. Differentials at this point included appendicitis and a perforated caecal cancer which was thought to be less likely given the lack of solid components. He was discharged with a course of tinidazole and co-amoxiclav with follow-up and repeat CT in four weeks.

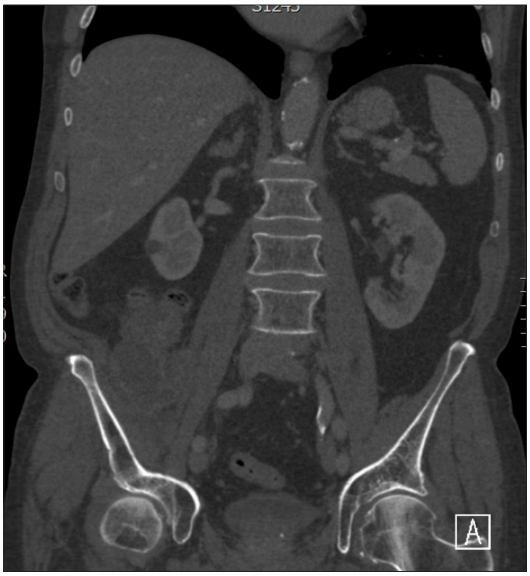

Figure 1: CT abdomen-pelvis in axial view showing the inflammatory mass between the posterior aspect of the caecum and the anterior ileopsoas.

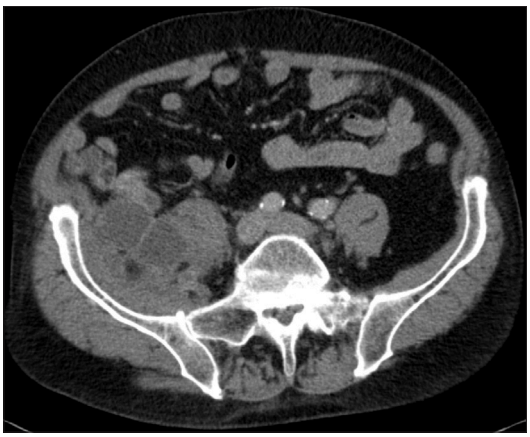

Figure 2: The same CT abdomen-pelvis image in the coronal view.

At the initial four week follow-up the patient was clinically well and a CT scan showed no change in size of the mass. He was reviewed a month later and unfortunately his extreme fatigue and mild lower abdominal pain returned and markers of inflammation persisted; examination revealed an evolving tender right iliac fossa mass. He was readmitted from clinic and underwent a colonoscopy which showed diverticular disease concentrated on the right side, no caecal tumour and a slightly dusky appearance of the appendiceal orifice. Biopsies were taken which showed no malignant changes.

AN INTESTINAL INFLAMMATORY MASS IN A RETURNING TRAVELLER; EXPLORING THE DIFFERENTIAL DIAGNOSIS

V Newman, M Brown

Repeat CT scan showed an apparent retrocaecal appendix lying within the collection compatible with an appendiceal perforation as a cause of the inflammatory caecal mass. The patient was reviewed by the general surgical team on the ward and discussed in the benign luminal multidisciplinary team meeting. The surgeons recommended a conservative approach with prolonged antibiotics in the first instance given the unequivocal colonoscopy results and initial response to co-amoxiclav with follow-up in six weeks.

A further CT scan two months later, following a course of antibiotics showed the collection had now liquefied and coalesced and the pericaecal collection was drained under radiological guidance. 100mls of gelatinous blood tinged pus was drained which grew multiple enteric organisms. Cytological analysis revealed large amounts of proteinaceous material containing numerous macrophages and occasional cohesive groups of mucin secreting epithelial cells with atypical nuclear features.

The appearances were in keeping with mucinous neoplasm likely arising from the appendix. This patient has been referred to the national centre for *Pseudomyxoma peritonei* at Basingstoke Hospital for consideration of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy.

Discussion

In cases of the returning traveller it is important to consider both the tropical and non-infectious causes of the patient's presentation. This patient had returned from South America and therefore infectious causes of intestinal inflammation were considered.

Enteric fever is a major cause of bowel perforation in endemic settings. There is a small but significant risk of contracting typhoid in South America but the area with the highest endemicity is the Indian subcontinent and Pakistan (2). The hallmark of enteric fever is a high fever which presents within three weeks of return from the tropics (1). In this case the patient had hepatomegaly and a transaminitis which can be associated with typhoid infection (1), however typhoid was ruled out early when blood and stool cultures failed to grow Salmonella typhi or S. paratyphi. Serious complications including intestinal perforation can occur in 10-15% of patients but is rarely seen in travellers who return to the UK as there are fewer delays in treatment (2). Perforation associated with typhoid is gradually declining worldwide (3) but when it does occur solitary caecal lesions are the most common type (4).

Amoebiasis is endemic in low income countries such as South America. (5) It is a lethal infection which can invade the intestinal wall causing a severe colitic illness (6), therefore patients present more unwell than this gentleman, often with dysentery. Necrotising colitis is a severe complication that occurs in 0.5% of individuals and can result in bowel perforation (7). Diagnosis is made by identifying amoebic trophozoites in a 'hot' stool sample, by PAS staining of endoscopic biopsies at sites of ulceration or by PCR of stool for *Entaemoeba histolytica* (7). In this case the patient received empirical tinidazole given the significant possibility of amoebiasis, pending the result of the stool PCR.

Yersiniosis caused by Y. enterocolitica and Y. pseudotuberculosis should also be considered in patients with ileocaecal inflammatory lesions. Diagnosis is by faecal culture, but specific media are required and the laboratory must be informed if this is to be specifically sought (8).

Acute Schistosoma mansoni can cause diarrhoea and intestinal bleeding but this is rarely prolonged and does not cause perforation or abscess formation. Most cases are from sub-Saharan Africa and diagnosis is made on microscopy by finding ova in the stool (9). Intestinal hookworm and stronglyoidiasis can also cause localised inflammation and anaemia, however in most cases travellers are minimally symptomatic. Bowel perforation due to strongyloides hyperinfection only occurs, and very rarely, in patients with severe underlying immunosuppression.

Intestinal tuberculosis can present with caecal inflammatory mass but usually in the context of significant terminal ileal disease, in patients with indolent presentation and epidemiological risk factors.

	Laboratory tests	Imaging	Invasive tests
Tropical			
Typhoid	LFTs (transaminitis), 3 blood cultures Stool cultures	Inflammation at Peyer's patches in small intestine	n/a
Amoebic colitis	"Hot stool' for trophozoites, PCR of stool for E. histolytica DNA	Generalised colitis on CT +/- concurrent liver abscess	Ulceration seen on endoscopy
Yersinia	Stool culture, blood culture	n/a	n/a
Helminths	Absolute eosinophilia on FBC. Stool microscopy Schistosoma & strongyloides serology	Minimal changes seen	Adult helminths seen in small bowel. Intestinal polyps may be seen in S. Mansoni infection
Non-tropical			
Diverticulitis	FBC (leucocytosis), gram negative organisms +/- anaerobes on blood cultures	CT abdo-pelvis	Colonoscopy +/- biopsies
Appendicitis	FBC (leucocytosis), CRP	CT abdo-pelvis	Diagnostic laparotomy
Crohn's Disease	FBC (leucocytosis), CRP Stool; faecal calprotectin	CT abdo-pelvis Small bowel MRI	Colonoscopy +/- biopsies
Colorectal Cancer	FBC (anaemia), CEA Stool; faecal occult blood	CT abdo-pelvis CT pneumocolon	Colonoscopy +/- biopsies

Table 1: Targeted investigations to rule out causes of an intestinal inflammatory mass in the returning traveller.

Appendicitis is commonest amongst adolescents and young adults with elderly patients forming 5-10% of cases, however, patients over the age of 60 are four times more likely to perforate (10). Often the elderly patients do not present with the classic triad of right iliac fossa pain, fever and leucocytosis which results in delays in diagnosis and may explain the increased risk of perforation (10). CT abdomen-pelvis scans can help diagnose appendicitis but often invasive diagnostic laparotomy is required to rule this out.

AN INTESTINAL INFLAMMATORY MASS IN A RETURNING TRAVELLER; EXPLORING THE DIFFERENTIAL DIAGNOSIS

V Newman, M Brown

Inflammatory bowel disease is unlikely given the patient's age but it should be considered as a differential diagnosis of an inflammatory intestinal mass in young adults and adolescents. Paracolic abscess formation is more common in Crohn's disease than colitis, however, bowel perforation can occur in both (11).

This patient was known to have diverticular disease concentrated on the right side and therefore his symptoms could have been caused by microperforation of an inflamed diverticulum. In Western societies disease is predominantly left sided but ascending colonic involvement is well described especially in younger people and Afro-Caribbean patients (12). Patients present with fever, abdominal pain and mild leucocytosis and therefore a perforated caecal diverticulum is clinically indistinguishable from acute appendicitis (12).

Concerns about colon cancer are raised in elderly patients who present with anaemia, change in bowel habit and weight loss. Diagnosis is made from a combination of bed side tests including faecal occult blood in the stool and anaemia followed by a CT scan and colonoscopy with biopsies. Colonic cancers are most commonly adenocarcinomas whereas mucinous neoplasms of the appendix are very rare making up less than 0.5% of gastrointestinal cancers (13). The diagnosis was difficult in this gentleman as his CT scan did not show obvious colonic wall thickening and biopsies did not show any malignant changes.

Conclusion

Mucinous neoplasms of the appendix are rare and difficult to diagnose. They are often mistaken for appendicitis or perforated diverticulum because they present with right iliac fossa pain and lack the red flag symptoms of conventional colorectal cancers. In this case the patient presented with infectious symptoms, epidemiological risk factors and initial investigations which leaned towards an infectious cause.

However the patient's age, duration and nature of symptoms were suspicious of malignancy and unfortunately this was the final diagnosis. This case exemplifies that history taking, physical examination and exploring differential diagnoses are essential skills developed in foundation years which can help with complicated cases such as this one.

Test yourself

1) What is the typical incubation period for S. typhi infection?

a) 48 hours

b) 1-7 days

c) 7-21 days

d) More than 21 days

2) What is the first line treatment for symptomatic Amoebiasis?

a) Fluroquinolones

b) Cephalosporins

c) Nitroimidazoles (metronidazole or tinidazole)

d) Co-amoxiclav

3) Which species is not predominantly associated with intestinal granulomas and faecal egg excretion?

a) S haematobium

b) S mansoni

c) S japonicum

d) S mekongi

4) What is the most common change in FBC associated with strongyloides infection?

a) Leucocytosis

b) Eosinophilia

c) Neutrophilia

d) Anaemia

5) Which area is responsible for >95% of schistosomiasis cases returning to the UK?

a) South-East Asia

b) South America

c) North Africa

d) Sub-Saharan Africa

AN INTESTINAL INFLAMMATORY MASS IN A RETURNING TRAVELLER; EXPLORING THE DIFFERENTIAL DIAGNOSIS

V Newman, M Brown

Answers

1) 7-21 days.

The hallmark of typhoid infection is a fever which develops within the first three weeks of returning from the tropics (1). Literature reports the typical incubation period as 2-3 weeks although the range is between 3 and 60 days (1). They may also present with a dull frontal headache and anorexia.

2) Metronidazole.

First line treatment of amoebiasis is with nitroimidazoles including metronidazole or tinidazole which is usually recommended for all patients with amoebiasis. Patients will usually be given a 10 day course of diloxanide or paromomycin to prevent relapse (14).

3) S haematobium.

Once matured, schistosomes settle in the venous system. S mansoni most commonly resides in the vasculature near the colon, S japonicum and S mekongi near the small intestine. S haematobium resides in the vesical veins draining the bladder, generating bladder inflammation with associated haematuria and fibrosis.

4) Eosinophilia.

Strongyloides is a helminth infection, and so commonly associated with a high absolute eosinophil count of more than 400 cell/uL (15). Other helminths also cause eosinophilia, and a travel history (even a distant one) should be sought in all patients with a raised absolute eosinophil count. Differential diagnosis of eosinophilia includes medications, atopic disease, vasculitis, sarcoidosis and various myeloproliferative neoplasms.

5) Sub-Saharan Africa.

Almost all cases (>95%) of schistosomiasis in the UK are imported by returning travellers from sub-Saharan Africa (9). The responsible schistosoma species depends on geographic distribution of the snail host.

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BRUCELLOSIS PRESENTING WITH SUSPECTED IGA NEPHROPATHY

L Liu, W Han, G Sandhu

Abstract

A 43 year old Somali man had recently returned to the UK and presented with malaise, fever, brown urine and vomiting. Urine dip showed blood and protein, and blood tests showed deranged renal function and raised IgA, with suspected IgA nephropathy. After four days, blood cultures were positive for Brucella melintensis and this was confirmed by positive brucella serology.

He was treated with doxycycline and rifampicin and his inflammatory markers and renal function improved, suggestive of IgA nephropathy secondary to brucellosis. The is a rare presentation of brucellosis, and this case highlights that brucellosis can present in many ways and is an important differential in travelers with pyrexia of unknown origin.

Case History

A 43 year old Somali man had recently returned to the UK, having been in Somalia for the past five months. In the last two months of his trip, he started reporting malaise and fever. He was initially diagnosed in Mogadishu (capital of Somalia) with Dengue, but sought further opinion in Nairobi when he started to feel more unwell with headaches and the sensation of feeling cold all the time. In Nairobi, he was treated with a three day course of unknown antibiotics for a urinary tract infection. This caused mild improvement, but a few days later he noticed that he started to pass "light coffee" coloured urine and developed vomiting and diarrhea.

It is at this stage that he decided to fly back to England and he was seen at a London Hospital in November 2016. On examination, he was febrile at 39°C, tachycardic (heart rate 100bpm) and mildly hypertensive (BP 130/64). Malarial blood films were negative. Chest X-ray was clear and cardiac echocardiogram showed no vegetations. Urine dip was positive for protein and blood. Laboratory results showed a urinary RBC of 4219 cmm.

Blood tests showed acute kidney injury with creatinine at 181 umol/L, raised inflammatory markers with C-reactive protein at 35.4 mg/L and a raised Immunoglobulin A level of 15.23 g/L. His ALT was mildly raised at 79 IU/L.

Ultrasound abdomen showed grade 2 bilateral renal parenchymal changes, and anti-ASO titre was negative. Urine albumin to creatinine ratio was later found to be raised at 102.3 mg/mmol. A CT abdomen and pelvis was performed which did not identify any abnormalities.

He was initially started on IV co-amoxiclav and IV fluids but was still febrile despite this.

Blood culture taken came back with the growth of a gram positive rod in aerobic bottle after four days incubation. This was later confirmed to be Brucella melitensis. This is further confirmed by positive brucella serology (table 1). We then revisited the patient's history and he told us that he had been regularly drinking camel's milk in Somalia.

Brucellacapt (Total IgG/IgM)	10240
Brucella ELISA IgG	>2560
Brucella ELISA IgM	>2560
Brucella C.F.T	>256
Brucella microagglutination	>2560

Table 1: Brucella serology.

Although there has been some evidence that the combination of doxycycline-streptomycin may be significantly superior to doxycycline-rifampicin, mainly with regards to relapse (1), there have also been reports that the doxycycline-rifampicin combination is more preferred by patients and doctors for its convenience (2).

Our patient was eventually started on a combination of doxycycline and rifampicin. He was followed up in ambulatory care and further laboratory test showed marked improvement in both the inflammatory markers and kidney function (figure 1,2). Of note, his ALT markers also decreased from 79 IU/L to 26 IU/L within 1 week of the correct treatment.

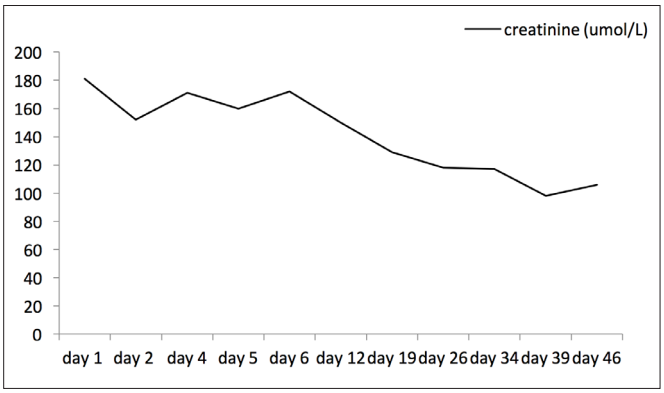

Figure 1: Trend of creatinine level throughout admission and follow up.

BRUCELLOSIS PRESENTING WITH SUSPECTED IGA NEPHROPATHY

L Liu, W Han, G Sandhu

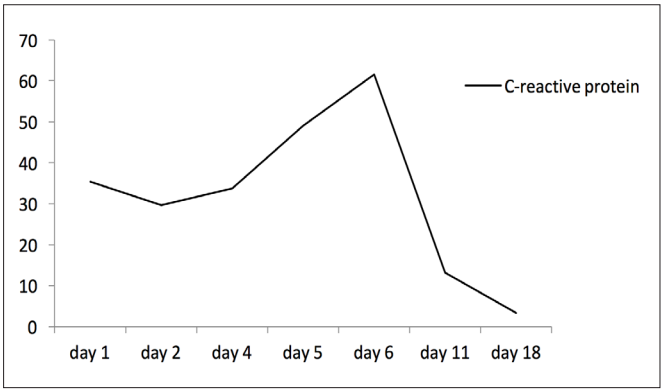

Figure 2: Trend of CRP level throughout admission and follow up.

Discussion

Brucellosis is a rare zoonotic disease in the UK, with an average of ten cases reported per year in England and Wales, the majority of cases having a history of recent travel abroad (3). The systemic disease usually has an incubation period of one to four weeks, and often presents with a febrile illness, night sweats (with a peculiar odour), arthralgia, anorexia and myalgia.

Many complications have been described, with osteoarticular, pulmonary, gastrointestinal and haematological involvement being most common. However, there has only been two documented cases of brucellosis presenting with IgA nephropathy, the last case report being in 1992 (4,5).

IgA nephropathy is a common cause of glomerulonephritis worldwide and half of all cases presents with visible haematuria. Less than 10% of cases present with nephrotic syndrome or rapidly progressive glomerulonephritis. IgA nephropathy has been associated with diseases such as coeliac disease, liver cirrhosis and HIV. It is thought that the development of IgA nephropathy secondary to infection may be due to an aberrant IgA immune response rather than the infectious antigen itself (6).

The definitive investigation is a renal biopsy, but this is usually only performed when there are signs of more severe disease such as hypertension, raised creatinine or persistent proteinuria. In our case, the high IgA level and deranged renal function in the blood tests was suggestive of IgA nephropathy and the renal registrar felt a biopsy would be unnecessary as it would be unlikely to change management. IgA nephropathy is usually treated in two ways.

The first approach would be to slow the rate of renal disease progression with general medications that are not specific to IgA nephropathy, such as antihypertensives. The second approach is controversial and involves the use of systemic steroids, but this is often only used in severe progressive disease.

In our case, treatment with antibiotics was accompanied by an improvement in renal function and inflammatory markers over several weeks, and suggests that brucellosis was a reversible cause for suspected IgA nephropathy. In Nunan's case, they describe a similar improvement in renal function and an improvement in serum IgA concentration after treatment. However, it is interesting to note that in that particular case, there was persistent mesangial deposition despite treatment.

We feel the findings of this case report are important, as they have been rarely reported in the past and suggests a causal relationship between brucellosis and IgA nephropathy. As brucellosis is rare disease in the UK and often presents with a variety of vague symptoms, it may be difficult to diagnose.

As we had not suspected the diagnosis until the blood cultures had come back positive, there was a delay is initiating the correct antibiotics in this case. It would have been helpful to ask about risk factors such as drinking unpasteruised milk, and this may be an important question to ask in future of travellers with pyrexia of unknown origin. Had we suspected brucellosis earlier, we could have also notified the laboratory so that they could use the correct culture techniques to reduce the risk of transmission to lab workers.

The findings also suggest that the IgA nephropathy is potentially reversible with treatment of brucellosis, and this may be an important differential before starting systemic glucocorticoid therapy.

BRUCELLOSIS PRESENTING WITH SUSPECTED IGA NEPHROPATHY

L Liu, W Han, G Sandhu

Best of Five MCQ

Q1. Brucellosis is often contracted by

1. Drinking unpasteurised milk

2. Blood transfusions and organ transplants

3. Insect vector

4. Vertical transmission

5. Contact with contaminated freshwater

2. One recognised way to treat uncomplicated brucellosis is:

1. IV Co-amoxiclav

2. Tetracyclines + Streptomycin

3. Macrolides

4. No antibiotics as it is self-limiting

5. Quinolones

Answers

1. Drinking unpasteurised milk

Brucellosis is a zoonotic infection transmitted by contact with fluids from infected animals such as cows, goats, pigs; or unpasteurised milk and cheese. Human to human transmission is unusual, although there have been rare cases of transmission through blood transfusions and organ transplants. Schistosomiasis is transmitted by swimming in contaminated freshwater.

2. There are two recognised regimens for the treatment of brucellosis.

The first is a combination of oral doxycycline and intramuscular streptomycin. The second combination is oral doxycycline and rifampicin. The doxycycline-streptomycin combination has been found in some studies as having a lower rate of relapse than than doxycycline and rifampicin, although this is arguably more inconvenient for the patient as they would need to have regular intramuscular injections.

Although there are trials looking at using quinolones, they are currently not recommended in combination therapy as they have been found to be less effective than the current regimens. For the treatment of children and pregnant women, specialist advice should be sought as tetracyclines should be avoided.

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MENINGITIS IN AN IMMUNOCOMPROMISED PATIENT

R Ganatra, P Gothard

Abstract

Meningitis in immunocompromised patients carries a significant morbidity and mortality. Here we present a case of meningitis caused by Cryptococcus neoformans in a patient who was on multiple immunosuppressive agents for cardiac and pulmonary sarcoidosis. He responded well to induction therapy but had a temporary deterioration after his immunosuppressive therapy was reduced. We explore the common differential diagnoses and recommendations for diagnostic tests in this setting.

History & Examination

A 35-year-old man presented to University College Hospital in London with an episode of urinary incontinence and a 10-day history of headaches. Collateral history was obtained from the patient's aunt who reported that the headaches were incapacitating and worse in the mornings. His Glasgow Coma Scale score was 9. There was no photophobia, fever or neck stiffness and no localising neurological signs. Fundoscopy revealed bilateral papilloedema. Examination was otherwise normal.

The patient was admitted to hospital and commenced on ceftriaxone, amoxicillin and aciclovir for probable meningo-encephalitis.

Background

This presentation was on a background of persistently active sarcoidosis with cardiac infiltration, diagnosed three years earlier as part of investigations for syncope due to ventricular tachycardia. He was initially treated with high dose prednisolone and showed significant improvement. Unfortunately, weaning the prednisolone resulted in relapse of symptomatic ventricular tachycardia and he was subsequently treated with methotrexate followed by mycophenolate mofetil. Most recently he received two cycles of infliximab.

Investigations

Initial blood analysis was unremarkable, apart from a mildly elevated white cell count of 12.33 x 10^9/L and CRP of 32. A contrast-enhanced computed tomography (CT) head scan showed no evidence of intracranial pathology. MRI was contraindicated as the patient had an implantable cardioverter-defribillator. Lumbar puncture revealed a high opening pressure of 30cmH_2O, a white cell count of 4 x 10^6/L, protein of 0.47g/L and glucose of 4.3mmol/L (blood glucose 7.5mmol/L). India Ink staining of CSF was positive, as was CSF Cryptococcal antigen (CRAG) at a titre of 1:1000. Blood and CSF cultures came back positive for Cryptococcus neoformans var neoformans the following day.

Diagnosis

The patient was diagnosed with cryptococcal meningitis secondary to immunosuppressive treatment for sarcoidosis.

Treatment

Empirical antibiotics were ceased and he was commenced on intravenous AmBisome (liposomal formulation of amphotericin B) and 5-flucytosine. He showed rapid improvement with almost complete resolution of his headache. The lumbar puncture was repeated six days in to treatment and the opening pressure had fallen to 18cmH_2O. He was HIV negative but his CD4 count was only 50 cells/mm^3 (normal range 600 to 1200 cells/mm^3).

He was therefore given co-trimoxazole for primary prophylaxis against other opportunistic infections. Mycophenolate mofetil was stopped and prednisolone slowly reduced. After 14 days the Ambisome was replaced with high dose oral fluconazole (800mg daily).

Unfortunately, two months following discharge the patient's headache returned. Repeat lumbar puncture was performed to exclude a possible recurrence of cryptococcal meningitis. CSF analysis revealed an opening pressure of 14 cmH_2O, 18 mononuclear cells, a protein of 0.44g/L, a CRAG of 1:16 and positive India ink stain. However CSF culture was negative.

The patient's CD4 count had risen by over 600% to 320 cells/mm^3 and a diagnosis of immune reconstitution inflammatory syndrome (IRIS) was made based on the increased CSF inflammation without evidence of microbiological failure. The catalyst for this was the rapid withdrawal of immunosuppressive treatment. Prednisolone was increased to 30mg daily and his symptoms resolved confirming the diagnosis of cryptococcal IRIS. 18-months later the patient remains well on a maintenance dose of fluconazole 200mg plus azathioprine, hydroxychloroquine and low-dose prednisolone. His sarcoidosis is stable.

Discussion

Defective cell-mediated immunity, whether due to HIV or immunosuppressive therapy, increases a patient's susceptibility to a range of opportunistic infections. Recognition is often challenging as patients may present with atypical signs due to an inadequate immune response to infection. For example in this case the patient was afebrile and CSF analysis on admission showed a normal white cell count, protein and CSF/serum glucose ratio. India Ink staining and CRAG testing are not routinely performed on CSF samples: the clinician needs to be aware of the potential diagnosis and request these tests.

The spectrum of CNS infections is broader in an immunocompromised host. Table 1 summarises the principal pathogens to consider in this setting.

Bacteria	Virus	Fungi	Parasite
Streptococcus pneumoniae	Herpes simplex virus (HSV) 1&2	Cryptococcus neoformans (Cryptococcus gatti less commonly)	Toxoplasma gondii
Listeria monocytogenes	Varicella zoster virus (VZV)	Histoplasma capsulatum Coccidiodes immitis (travel to the Americas)	
Mycobacterium tuberculosis	Cytomegalovirus (CMV)		
Nocardia asteroides	LCMV, HHV6		

In an immunocompetent patient neuroimaging should not delay lumbar puncture unless there is clinical evidence of raised intracranial pressure or lateralising neurology (2). However in immunocompromised patients alternative diagnoses such as space-occupying lesions are more common, therefore imaging prior to lumbar puncture is warranted. Our patient had papilloedema and a lumbar puncture was therefore contraindicated until imaging had excluded a space-occupying lesion.

MENINGITIS IN AN IMMUNOCOMPROMISED PATIENT

R Ganatra, P Gothard

If CNS infection is suspected prompt lumbar puncture is essential, as results will guide management and reduce exposure to potentially toxic therapy. The opening pressure should be recorded. An elevated opening pressure, typically defined as greater than 20cmH_20, occurs in many patients with bacterial and cryptococcal meningitis. CSF samples should be sent for cell count and differential, protein, glucose (with a paired serum glucose), Gram's stain, bacterial and fungal culture, viral PCR, Indian ink staining for cryptococcus, Cryptococcal antigen and cytology. Some of these investigations are not routinely done and need to be requested by the clinician. If in doubt its worth phoning the microbiology lab to discuss the case.

The initial management of an immunocompromised patient with meningitis is largely similar to that of an immunocompentent individual. Empirical treatment for bacterial meningitis should be commenced with 2g ceftriaxone 12-hourly. As Listeria meningitis is more common these patients should also receive 2g amoxicillin 4-hourly (2).

In patients with cell-mediated immunodeficiency where no definitive diagnosis has been reached empirical treatment for tuberculous meningitis should be considered. In this case CSF samples of greater volume should be sent, as detection of acid-fast bacilli is directly dependent on the volume of CSF (5).

Cryptococcal meningitis

The management of cryptococcal meningitis combines treatment with established antifungal regimes along with a reduction in the underlying immunosuppressive therapy or initiation of antiretroviral therapy (ART) in HIV positive patients. Pharmacological management typically consists of three stages; induction, consolidation, and maintenance therapy. Induction therapy is usually two-weeks of amphotericin B plus 5-flucytosine.

This is consolidated by 400-800mg of fluconazole for a minimum of 8 weeks, which can then be reduced to 200mg as part of maintenance regime. In HIV-infected patients fluconazole maintenance therapy should be continued until the CD4 count is above 100 and the viral load is undetectable. Organ-transplant patients and those on immunosuppressive agents should remain on a maintenance dose of fluconazole for 6-12 months (3).

There is a difficult balance between too much and too little immunosuppression particularly in the complexity of treatment response. Cryptococcal IRIS is a well-described phenomenon in HIV patients who start ART within the first month. Patients initially improve with antifungal treatment but then clinically deteriorate as a result the restoration of immune function due to ART (1). This also applies to other patient groups with defective cell-mediated immunity. The graph below shows how an improvement in the CD4 count coincided with a recurrence of our patient's symptoms.

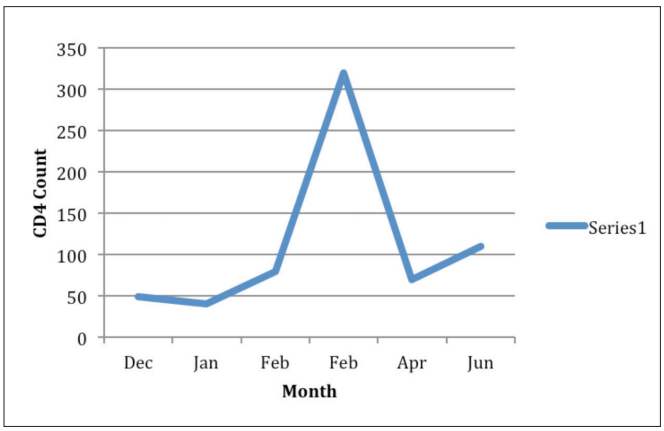

Figure 1: CD4 count against month. Peak in CD4 count coincides with the patient's recurrence of symptoms and readmission to hospital.

Conclusion

In summary meningitis in immunocompromised patients may present atypically. Clinicians should have a low threshold for performing a lumbar puncture; this would need to be preceded by a CT head scan, as space-occupying lesions are more common in this group of patients.

CSF culture is the gold standard for diagnosing cryptococcal meningitis (4); however a raised opening pressure and a benign CSF are useful clues and indications for requesting a CSF CRAG and India Ink stain. Reducing immunosuppressive therapy is an important aspect of management but if this is done too quickly the patient risks developing an immune reconstitution inflammatory syndrome.

MCQs

1) Which of the following is the correct induction therapy for cryptococcal meningitis?

a) Amphotericin B and fluconazole
b) Ketoconazole and fluconazole
c) Caspofungin alone
d) Amphotericin B and 5-flucytosine
e) Fluconazole alone

2) What is the gold standard test for the diagnosis of cryptococcal meningitis?

a) Blood culture
b) CSF India ink
c) CSF culture
d) CSF CRAG
e) Serum CRAG

MENINGITIS IN AN IMMUNOCOMPROMISED PATIENT

R Ganatra, P Gothard

3) In an immunosuppressed patient, what antibiotic should be added to ceftriaxone if bacterial meningitis is suspected?

a) Amoxicillin
b) Vancomycin
c) Ceftazidime
d) Ciprofloxacin
e) Gentamicin

4) Which one of the following is not an indication for CT head prior to lumbar puncture?

a) Papilloedema on fundoscopy
b) Focal neurological signs
c) Continuous or uncontrolled seizures
d) Inability to adequately view the fundus
e) GCS < 12

5) Which one of these pathogens is a Gram's positive coccobacillus that causes meningitis especially in the immunocompromised?

a) Cryptococcus neoformans
b) Streptococcus pneumoniae
c) Neisseria meningitidis
d) Haemophilus influenzae
e) Listeria monocytogenes

Answers

1. D: *As per the 2010 Guidelines for Management of Cryptococcosis, Amphotericin B plus 5-flucytosine are the recommended first-line agents for induction therapy. Ketoconazole does not cross the blood-brain barrier and is therefore inappropriate in the treatment of cryptococcal meningitis. Cryptococcus neoformans is resistant both in vitro and in vivo to caspofungin and other echinocandins.*

2. C: *CSF culture is the gold standard test for diagnosing Cryptococcal meningitis. Antigen detection tests are used for early detection of cryptococcal infection. They have a sensitivity of over >90% and provide a rapid result. India ink staining is usually performed on the CSF to diagnose cryptococcal meningitis quickly. However, it has a low sensitivity (high rate of false negatives). It can also remain positive even after successful treatment.*

3. A: *Listeria meningitis is more common in the elderly and in patients who are immunocompromised including pregnant mothers. Listeria monocytogenes responds poorly to cephalosporins therefore amoxicillin should be added. The age at which amoxicillin should be added is unclear. Evidence suggests that Listeria meningitis is rare in immunocompetent adults under the age of 60.*

4. D: *Guidelines strongly advise that neuroimaging should not delay lumbar puncture unless there are features of raised intracranial pressure. Focal neurological signs, uncontrolled seizures, papilloedema and low GCS are all indications for CT imaging head prior to lumbar puncture. Guidelines specifically state that an inability to view the fundus is not a contraindication to lumbar puncture, especially if the presentation is of acute onset.*

5. E: *Listeria monocytogenes is a Gram's positive coccobacillus that causes meningitis in the immunocompromised. Streptococcus pneumoniae is a Gram's positive diplococcus and the most common cause of meningitis in immunocompetent adults. Neisseria meningitidis is a Gram's negative diplococcus. Haemophilus influenzae is a Gram's negative coccobacillus that typically causes meningitis in young children. Cryptococcus neoformans is an encapsulated yeast that causes meningitis in immunocompromised patients.*

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CASE REPORT OF A MULTI-DRUG RESISTANT INFECTED AORTIC GRAFT

K Townsend, R Allen, W Lynn

Abstract

Antibiotic-resistant organisms were first identified 70 years ago. (1) Increasing use of antibiotics over the past seven decades has led to the emergence of a multitude of multi-drug resistant organisms, which can leave very few treatment options for severely unwell patients. (2)(3)

This case illustrates the impact of antibiotic resistance in a patient host to several extremely-drug resistant organisms, establishing a platform for discussion on how this public health threat can be combatted.

Case History

Mr H was a sixty-six year old gentleman with a complex past medical history, including aortic stenosis, ischaemic heart disease with a previous myocardial infarct, type two diabetes and a high BMI. His notable clinical narrative begins in December 2013, when he underwent endovascular aneurysm replacement (EVAR) for an abdominal aortic aneurysm.

His post-operative recovery was complicated by a deep wound infection of coliforms, and he was treated with intravenous piperacillin/tazobactam and gentamicin. However, in the ensuing weeks he developed a left psoas collection which cultured Proteus species, and Proteus mirabilis bacteraemia. Imaging revealed proximity between the collection and the aneurysmal sac with convincing evidence of a connection, and he was deemed to have an infected retroperitoneal haematoma with infected graft.

His reduced mobility, catheterisation, HDU stays and immunocompromise rendered him vulnerable to nosocomial infection, and he continued to receive prolonged courses of broad-spectrum antibiotics for hospital acquired pneumonia and suspected catheter-related urinary tract infections. In April, after several months in hospital, methicillin-resistant Staphylococcus aureus (MRSA) was cultured from a throat swab on routine screening. He underwent MRSA decolonisation and by the end of April, he was able to be discharged for rehabilitation with prophylactic doxycycline and ciprofloxacin.

He was readmitted less than six months later in September 2014 with general malaise after a fall, and was found to be heavily recolonised with MRSA in association with raised inflammatory markers. His aortogram demonstrated locules of gas surrounding the EVAR graft wall, in keeping with infection. He was treated with intravenous antibiotics but continued to experience infectious complications. He had a total of six prolonged hospital admissions at two hospital secondary to infections with MRSA, Escherichia coli, Proteus species and Klebsiella species.

A CT PET scan (Figure 1) confirmed infection throughout the graft. The possibility of graft removal for source control was considered. However, on review by vascular surgeons, the operation was deemed too high risk. Instead, he was prescribed long-term suppressive antimicrobial therapy with progressively more broad-spectrum antibiotics, from ciprofloxacin, to doxycycline plus cefixime, to co-trimoxazole plus cefixime.

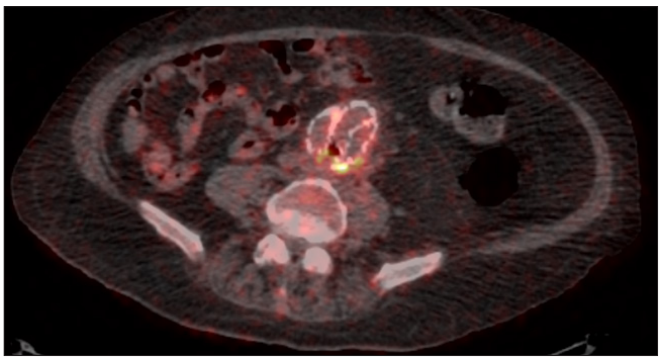

Figure 1: Positron-emission Tomography CT (CT-PET) showing an infected collection at the level of the bifurcation of the aorto-biliac graft. The graft is indicated by arrow A. There is a collection of gas posterior to the graft (arrow B) suggesting abscess formation with intense activity due to uptake of labelled fluorodeoxyglucose (FDG) seen on the edge of the abscess (arrow C).

Although MRSA remained suppressed, cultures showed increasingly resistant gram-negative bacteria, with limited viable options for therapeutic antibiotics (Figure 2).

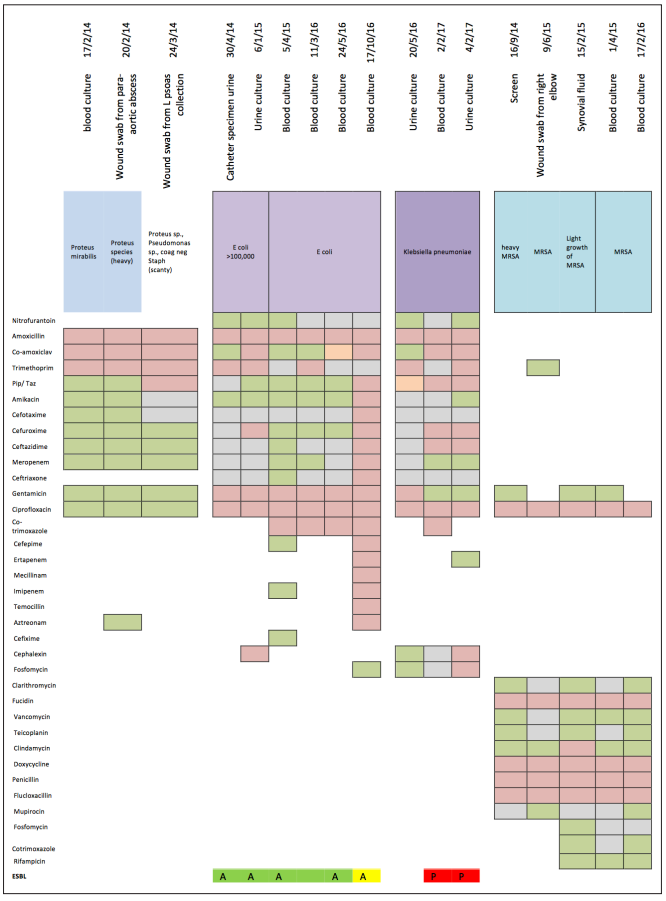

Figure 2: This schematic shows the progression of antimicrobial resistance.

Green: fully sensitive **Grey: not tested** **Red: fully resistant**

CASE REPORT OF A MULTI-DRUG RESISTANT INFECTED AORTIC GRAFT

K Townsend, R Allen, W Lynn

His quality of life was extremely limited due to recurrent infection and he was dependent on full nursing home care. Towards the end of 2016, blood cultures grew a carbapenem-resistant Escherichia coli with MIC showing resistance to all antibiotics except colistin and fosfomycin.

His final admission was in January 2017 with severe sepsis and multi-organ failure. In accordance with his wishes he was managed palliatively and died within 48 hours.

Discussion

Healthcare professionals and the public are becoming increasingly aware of the potential for a 'post-antibiotic' era, in which common bacteria are resistant to most or all treatment options available. Chief medical officer Dame Sally Davies described the situation as "apocalyptic." Approaches to antibiotic stewardship for preventing this are manifold, including restriction, education, and modifying infrastructure, and can be considered on both an individual and systems level. (4)(5)(6)

The indications for antibiotic use were based on cultures and sensitivity data reviewed regularly by the Infectious Diseases team, microbiologists and the Trust antimicrobial pharmacist. Culture and sensitivity reports specified the need for discussion with a microbiologist in cases where clinical relevance was uncertain. He was managed in strict isolation to minimise risk of transmission to other patients. Surgical intervention was reviewed and considered frequently. However, options for source control were limited.

Once Mr H had developed deep seated infection his clinical trajectory was very difficult to alter. (7) In this setting antibiotics may be used to induce a clinical remission and this was achieved on several occasions. Nevertheless, prolonged antibiotics also led to more resistance, clinical relapse and eventually his death. Unfortunately, the combination of comorbidities, difficult source control, and extended hospital stays increasing susceptibility to nosocomial microbes, meant multi-drug resistant organisms were difficult to eliminate.

This case clearly demonstrates the sequence of events once multiple-resistant bacteria cause deep seated infection in a patient where source eradication is not possible. One could posit that given this lack of source eradication, there may have been an argument for implementing a palliative approach earlier in his management. In these challenging cases, use of an independent clinical review panel to facilitate discussions about the efficacy of ongoing active treatment may be beneficial. However, ideally, preventing patients like Mr H from acquiring drug resistant bacteria should be a priority. Effective preventative strategies require a concerted multidisciplinary effort at every level of healthcare, including National and International interventions.

Local strategies include

1. Antibiotic ward rounds and multi-disciplinary meetings involving Infectious Diseases, Microbiology and a designated Trust antimicrobial pharmacist. This should facilitate regular review of clinical indication for antibiotic, duration of treatment and opportunity for use of a narrow-spectrum agent. (5)(6)

2. Restriction of sensitivities made available to clinicians by Microbiologists: local laboratories may choose to release only sensitivities for those antimicrobials deemed appropriate in a specific clinical scenario.

3. Adaptation of local guidelines for local resistance patterns and burden of disease.

4. Regular education for all clinicians on infection control, resistance and appropriate antibiotic prescribing.

Nationally, infrastructure and guidance for the above approaches are available, (8)(9) but not coordinated or implemented consistently. (2) Indeed a third of antimicrobial prescriptions used today are deemed inappropriate. (10)(11) Delay in diagnosis further increases the likelihood of inappropriate prescriptions or broad-spectrum therapy and physicians yield to perceived pressure from patients wanting a definitive treatment for their symptoms. (11)

In order to combat 'the greatest health crisis of our time,' (12) we need infrastructure for consistent national surveillance, continued education for healthcare professionals, patients and the public, and drive for innovation in the field. Fortunately, we are making progress.

The FDA has approved six new antimicrobial therapies since 2014. (13) Techniques for more rapid detection of bacterial versus viral infections can help reduce unwarranted prescriptions or favour choice of a narrow-spectrum agent. Other innovations in the field include alternatives to antibiotics such as vaccination, or enteric therapies in gastro-intestinal disease such as Clostridium difficile.

Nevertheless, if we continue to use antibiotics inappropriately or in excess at the present-day magnitude, we will run out of options before new solutions are available. In the fabled words of Alexander Fleming, "There is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant." (14) Reducing ignorance and improving stewardship of current antibiotics is essential to allow their continued application for this generation.

CASE REPORT OF A MULTI-DRUG RESISTANT INFECTED AORTIC GRAFT

K Townsend, R Allen, W Lynn

Test Yourself- Multiple Choice Questions

1: A 22 year old female history student presents to the emergency department with a 3 day history of dysuria and a 1 day history of fever and right flank pain. She has had no previous urinary infections, no significant PMH, is sexually active with one partner and has no allergies. Her temperature is 39.2, HR 110 and BP 110/70. On examination she has mild right flank tenderness. Her WCC is 14.5 and CRP 42. Her renal function is normal. The most appropriate choice of first line antibiotics are:

a) Oral Co-Amoxiclav
b) Oral Trimethoprim
c) IV Co-Amoxiclav
d) IV Ceftriaxone
e) IV Co-Amoxiclav plus Gentamycin

2: Which antibiotic is least likely to increase the risk of Clostridium difficile infection?

a) Cefotaxime
b) Moxifloxacin
c) Tetracycline
d) Trimethoprim
e) Clindamycin

3: A 73 year old man, recently discharged from another hospital following a 3 week admission for an E.coli bacteraemia secondary to catheter associated urosepsis and complicated by a hospital acquired pneumonia, presents generally unwell with decreased responsiveness, fever and hypotension. He has a background of IHD, T2DM, mild cognitive impairment and a long term catheter for prostatic symptoms.

He has previously grown E. Coli and mixed coliforms and has received several courses of oral antibiotics for suspected UTI in the last 12 months. He has no allergies. His temperature is 34.7, his RR is 34, SpO_2 94% on 35% FiO_2, HR 128 (irregular) and BP 95/45. On examination he is unwell, peripherally cool and responsive only to pain. His chest has widespread crackles and he has minimal residual urine in his catheter bag. The most appropriate choice of first line antibiotics are:

a) IV Piperacillin-Tazobactam
b) IV Co-Amoxiclav
c) IV Piperacillin-Tazobactam and Gentamycin
d) IV Meropenam
e) IV Ceftriaxone

4: Define Minimum Inhibitory Concentration. How is it calculated?

5: Which of the following is not a typical mechanism of resistance in Enterobacteriae?

a. Enzymatic inactivation of antibiotic - production of beta lactamases
b. Expression of membrane efflux pumps
c. Altering of peptidoglycan wall resulting in a reduced affinity for the antibiotic
d. Alteration of DNA gyrase/topoisomerase
e. Alteration of outer membrane permeability

Answers

1. A: IV Co-Amoxiclav

a) Might be appropriate, but given fever, tachycardia and flank pain IV antibiotics should be first line
b) Not appropriate for upper urinary tract symptoms
c) Best answer; good gram negative cover, IV preferred route in first 24 hours for this patient
d) May be appropriate if plan was for daily antibiotics via, for example, an ambulatory care service, but for inpatient management it is very broad spectrum and more likely to promote multi-drug resistant organisms. If there was concern for pelvic / sexually transmitted infection then this may be an appropriate choice.
e) Given she is a young, healthy woman with no previous history of UTI, she is unlikely to have developed a resistant organism. Therefore, addition of an aminoglycoside is unlikely to be of benefit.

2. A: Tetracycline.

NICE guidance published in March 2015 ('Clostridium difficile infection: risk with broad-spectrum antibiotics') specified the following antibiotics as associated with an increased risk of C difficile infection: cephalosporins (8 studies; OR 1.97, class includes cefotaxime); quinolones (10 studies; OR 1.66, class includes moxifloxacin); trimethoprim and sulfonamides (5 studies; OR 1.78); clindamycin (6 studies; Odds Ratio (OR) 2.86); carbapenems (6 studies; OR 1.84, 95%).

3. A: IV Meropenam

a) Likely to have been treated with this for HAP in his recent admission. In addition, would not cover for ESBL, which may be present given multiple catheter associated UTIs.
b) Not broad spectrum enough to cover for HAP or for possible resistant organisms.
c) May be appropriate as would cover for HAP and for most resistant ESBL organisms, although some resistance is developing.
d) Most appropriate answer with good gram negative, gram positive and anaerobic cover. Also likely to treat ESBL producing gram negative bacteria.
e) ESBL producing gram negative bacteria are resistant to cephalosporins and it is not the best choice for HAP.

CASE REPORT OF A MULTI-DRUG RESISTANT INFECTED AORTIC GRAFT

K Townsend, R Allen, W Lynn

4. A: The lowest concentration of an antibiotic that will inhibit growth of a micro-organism after incubation overnight. This may be contrasted with Minimum Bacteriocidal concentration, the concentration causing microbe death. It is an in vitro quantification of resistance.

In a Tube Dilution Assay, the percent concentration of an antibiotic is serially increased in a set of tubes containing a micro-organism rich broth. The greater the turbidity of the tube, the higher the microbial growth. A low minimum inhibitory concentration indicates the antibiotic will function at a low dosage.

5. A: Altering of peptidoglycan wall resulting in a reduced affinity for the antibiotic:

a) Enzymatic inactivation of antibiotic - e.g. extended spectrum beta-lactamases; cephalosporinases; carbapenemases conferring resistance to beta-lactam classes.
b) Expression of membrane efflux pumps e.g. ertapenem-resistant Klebsiella pneumoniae upregulate acrB efflux pump gene.
c) Altering of peptidoglycan wall resulting in a reduced affinity for the antibiotic: this is more typically a gram positive bacterial mechanism of resistance.
d) Alteration of DNA gyrase/topoisomerase: modification of amino acid sequences in these enzymes confers resistance to flouroquinolones.
e) Alteration of outer membrane permeability: The outer membrane (OM) of gram-negative bacteria acts as a selective barrier for entry. Antibiotics enter via either porins (smaller hydrophilic drugs, e.g. Ð-lactams) or diffusion across lipid bilayer (hydrophobic drugs e.g. macrolides). Gram negative bacteria can modify the lipid or protein composition to reduce antibiotic sensitivity.

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STAPHYLOCOCCUS AUREUS BACTERAEMIA - A CASE STUDY

J Smyth

Abstract

Staphylococcus aureus is a common pathogen responsible for severe infection and mortality across the world. From the production of toxins to the development of antimicrobial resistant strains, *S. aureus* has many attributes that make it a pathogen physicians cannot afford to ignore. Utilising the case of a patient treated for *S. aureus* meningitis, this article will explore the core principles involved in diagnosing and treating *S. aureus* bacteraemia (SAB). Overall, diagnosis of a SAB should prompt swift investigation and treatment, along with input from the local microbiology and infectious disease specialists.

Introduction

S. aureus is a common cause of bacteraemia, morbidity, and mortality within the UK and across the globe (1, 2). As commensals, they dwell most commonly within the anterior nares and are consider to be part of the normal human flora, however they are just as able to colonise other mucosal areas until they create an entry point into the systemic circulation (3).

S. aureus owes its impressive virulence to several factors, such as toxin production, surface proteins and enzyme production (4). These attributes all contribute to the fact that *S. aureus* can cause a wide variety of clinical diseases, such as cellulitis, infective endocarditis, osteomyelitis and in the case patient's situation, meningitis.

Adding to the problems caused by SAB is the rising incidence of methicillin-resistant *S. aureus* infection requiring alternative antibiotics. These often require further monitoring and can cause additional organ damage, without offering the same effectiveness as traditional B-lactams (5).

This case review will aim to provide the key information required by a junior doctor to plan a diagnostic workup to isolate the source of a S. aureus bacteraemia and then manage it appropriately.

Abbreviations

Acronym	Meaning
SAB	Staphylococcus aureus bacteraemia
CSF	Cerebrospinal fluid
MRI	Magnetic resonance imaging
SSTI	Skin and Soft Tissue Infection
MSSA	Methicillin-sensitive *S. aureus*
MRSA	Methicillin-resistant *S. aureus*
PVC	Peripheral venous catheter
PVL	Panton-Valentine leukocidin
TTE	Trans-thoracic echocardiogram
TOE	Trans-oesophageal echocardiogram
MDR	Multi-drug resistant
CIED	Cardiovascular implantable electronic device

Case Study

A 59-year-old, otherwise healthy gentleman presented to hospital with confusion and reduced consciousness, requiring intubation and admission to intensive care. A lumbar puncture was performed, and analysis of the CSF revealed protein of 24563 mg/L, glucose 0.6 mg/L and scanty growth of *Staphylococcus aureus,* consistent with a diagnosis of bacterial meningitis. MRI scanning of the spine on admission revealed a collection within the right erector spinae muscle extending from S2- L2 (Figure 1), and an anterior subdural empyema of the spinal cord and brain stem (Figure 2). Repeat scanning three weeks later showed florid subarachnoid enhancement, generalised deterioration of cord appearances and an anterior epidural collection at L1-L2 (Figure 3), along with new vertebral enhancement in L3-L5 (Figure 4).

The patient was commenced on high dose flucloxacillin as per sensitivities from CSF and blood cultures. Daptomycin was later added due to ongoing bacteraemia. After recovering enough to maintain his own airway, the patient was extubated and fitted with a tracheostomy. It was also noted that with the extensive spinal pathology, the patient was now paraplegic from T4 downwards. He then spent the next month in intensive care, before being stepped down to a high dependency unit, and eventually to the Infectious Diseases ward to complete his antimicrobial treatment. Following completion of his therapy and clinical stabilisation, the patient was transferred to a neurological rehabilitation unit.

Unfortunately, the patient represented one week later with pyrexia and sepsis secondary to an infected sacral ulcer. During this readmission, it was noted that the patient's blood film contained myeloblasts, supporting a new diagnosis of acute myeloid leukaemia. Haematological review deemed that in view of the patient's recent medical history and current physical state, palliation was the only amenable option. As of the time of writing, the patient is currently receiving supportive and symptomatic management in a secondary care setting.

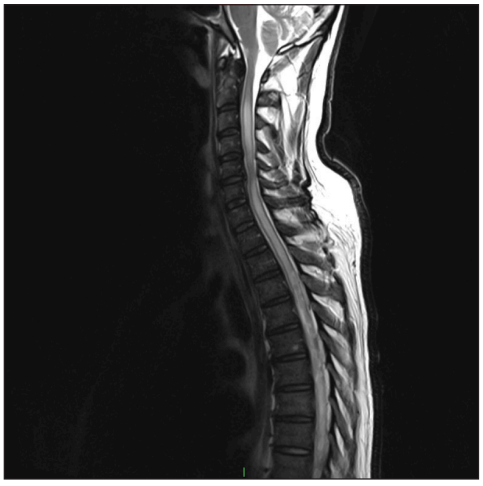
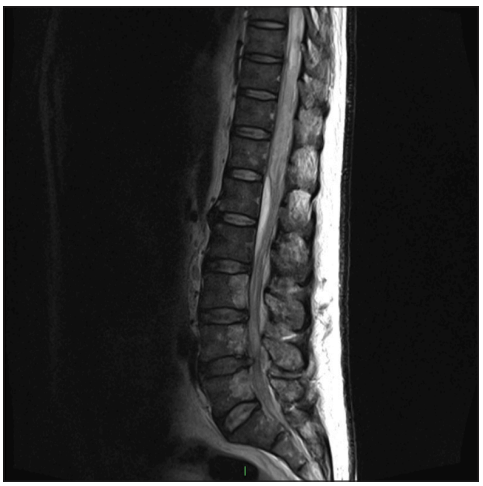


Figure 1

STAPHYLOCOCCUS AUREUS BACTERAEMIA - A CASE STUDY

J Smyth



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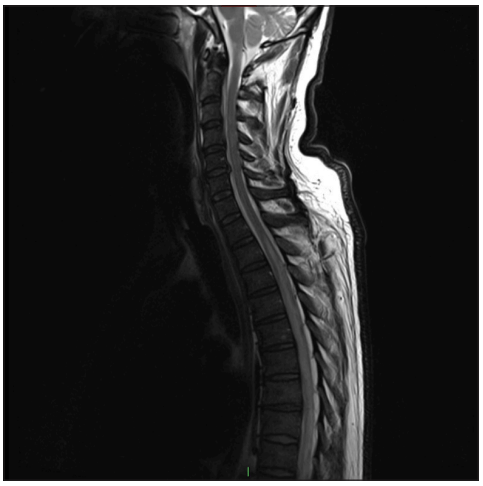

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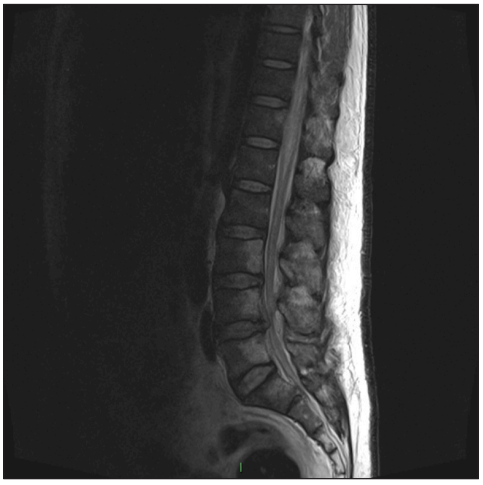

Figure 4

The Spectrum

S. aureus bacteraemia can arise from and subsequently lead to a variety of clinical conditions. As such, the search for a source becomes as important as the aggressive use of antimicrobial therapy with which it is treated.

The prevalence of each source varies with geography and demographics, however overall the most commonly found sources are as follows (6), in order of most to least common;

1) Line-related infections
2) Skin and Soft Tissue Infections (SSTI's)
3) Pleuropulmonary infections
4) Osteoarticular Infections
5) Infective Endocarditis
6) Other (device-related infections and other less common sites)

As such, the clinical workup for patients whose blood cultures return positive results for *Staphylococcus aureus* should aim to rule out infection in these six areas.

Diagnostics

Definitively diagnosing *S. aureus* infection requires isolation of the microbe through culture and microscopy. Depending on the infectious foci available, the samples provided and the methods used to obtain them will vary.

In detecting bacteraemia, blood cultures remain the most effective method of diagnosis. However, the test is not without its limitations, largely due to the possibility of false positive results from skin contaminants. Rates vary from centre to centre, however research from Ninewells Hospital, Dundee reported a contamination rate of 4.74% from cultures taken in their emergency department from early 2013 until late 2014 (7).

In these situations, appropriate management is delayed due to inaccurate culture results, whereby other organisms are targeted. In these situations, coagulase - negative Staphylococcal pathogens such as *S. epidermidis* are the most common contaminants, but can also be linked to true infection in patients with implanted medical devices or lines (8).

As such, care should be taken in interpreting blood culture results, especially where the organism cultured doesn't correlate with the patient's clinical syndrome. Emphasis is placed on obtaining these specimens prior to the commencement of antimicrobial therapy, as research indicates that pre-treatment cultures are more likely to be positive, thus aiding in prompt diagnosis and appropriate management (9).

Other culture specimens can include sputum samples in the context of pneumonia, bone clippings when osteomyelitis is suspected and blood cultures are negative, and wound swabs from ulcers and abscesses.

Depending on the presentation of disease, radiological investigations may also be useful. They will be discussed within the sections addressing the clinical manifestations that warrant their use.

STAPHYLOCOCCUS AUREUS BACTERAEMIA - A CASE STUDY

J Smyth

Management

When it comes to clinically treating a proven SAB, there are two principles:

1) Achieving source control
2) Appropriate antimicrobial therapy

Source Control

The methods by which this can be achieved vary depending on the site of infection. Frequently, there will not be a removable source of bacteraemia, thus requiring emphasis on the second principle. However, in many other cases there will be a surgical option for treatment by which the locus can be drained, excised or debrided. The minimum recommended duration of treatment for bacteraemia is 14 days, with IV therapy.

Antimicrobial Therapy

For Staphylococcal infections B-lactams remain the antibiotic class of choice, most often in the form of Flucloxacillin. Recommended duration however, will vary depending on the infected site and the presence of bacteraemia. These antibiotics will of course have very little effect on infections caused by MRSA. In these situations, alternatives such as vancomycin, teicoplanin, daptomycin or linezolid should be utilised, dependent on the source of infection (5).

In cases of bacteraemia and deep-seated infections such as osteomyelitis or endocarditis, therapy should be continued for a minimum of 14 days using IV administrations.

Key Management Principles

Line Related Infections

History taking and clinical examination skills should be utilised to check if patients have any current indwelling lines or have had any removed in the recent past. These include peripheral venous catheters, peripherally inserted venous catheters, central venous catheters, or any other form of vascular access. To prevent these infections, aseptic non-touch technique should be used in the insertion of PVC's, and complete sterility used in the insertion of other lines.

Once inserted, the lines should be reviewed daily to ensure that there are no signs of local inflammation/infection around the site. There is no clinical evidence to suggest that routine replacement of peripheral lines prevents infection any more than replacing them when clinically indicated (10). In cases of suspected infection of lines capable of allowing blood draw (e.g. CVC/PICCs etc.), paired cultures should be taken from peripheral sites in addition to that line. This enables a comparison between microbes found secondary to bacteraemia from other sources and those found colonising the line in question.

Achieving source control in these infections should be done by prompt removal of any inserted lines (11). Antimicrobial therapy should be provided for two weeks if bacteraemia is confirmed and no other deep source identified.

Strain	Treatment	Duration
MSSA	Flucloxacillin	14 days (if no deep source identified)
MRSA	Vancomycin (Teicoplanin/Daptomycin could be considered)	14 days (if no deep source identified)

Skin & Soft Tissue Infections

Across the world, *S. aureus* is the most commonly implicated pathogen in skin and soft tissue infections (12). As such, any assessment of the patient with positive blood cultures should involve a full top-to-toe examination of the skin looking for any signs of cellulitis, follicular infections, or hidradenitis. Seemingly minor skin infections can occasionally lead to metastatic infection such as infective endocarditis and osteomyelitis through haematogenous spread.

In the absence of SAB, superficial abscesses can be incised and drained without the need for further antibiotics. However, in situations of systemic illness such as bacteraemia, antibiotic therapy is recommended (13). Duration of antibiotics is variable, depending on the patient's response to treatment. As above, if blood cultures isolate *S. aureus* and bacteraemia is confirmed, treatment should be continued for a minimum of 14 days.

Strain	Treatment	Duration
MSSA	Oral / IV Flucloxacillin (depending on severity)	5-10 days (depending on response duration may have to be extended)
MRSA	IV Vancomycin (Teicoplanin/Daptomycin could be considered)	5-10 days (depending on response duration may have to be extended)
MSSA Bacteraemia	IV Flucloxacillin	14 days (depending on response duration may have to be extended)
MRSA Bacteraemia	IV Vancomycin (Teicoplanin/Daptomycin could be considered)	14 days (depending on response duration may have to be extended)

Pleuropulmonary Infections

Secondary to its ability to produce a variety of potent toxins, *S. aureus* can cause a severe necrotizing pneumonia. The toxin most commonly implicated in this presentation is known as Panton-Valentine leukocidin (PVL). *S. aureus* pneumonia commonly occurs following an episode of viral "flu-like" illness and requires particularly aggressive therapy considering the high rates of complications and mortality (14, 15). Unfortunately, diagnosing a *S. aureus* pneumonia isn't straightforward (16) and most common modalities have their weaknesses. As such, a strong-clinical suspicion is essential.

Dependent on the presence of empyema, chest drains can be used to help in attaining source control (16). Considering the high mortality rate caused by Staphylococcal pneumonia, prompt and appropriate anti-microbial therapy is vital. Treatment of MRSA with vancomycin in the clinical setting of pneumonia is unfortunately associated with a particularly high failure rate (16, 17) due to vancomycin's poor penetration of alveolar lining fluid.

STAPHYLOCOCCUS AUREUS BACTERAEMIA - A CASE STUDY

J Smyth

Furthermore, at sub-inhibitory levels vancomycin has no effect on the concentration of PVL produced by the bacteria, whilst sub-inhibitory levels of B-lactams increase production of the toxin (18). As such, treatment with Linezolid is preferable. If PVL S. aureus pneumonia is suspected a combination of linezolid and clindamycin with or without rifampicin should be considered. This is based on an observed in-vitro synergy and ability of linezolid and clindamycin to switch off toxin production.

Strain	Treatment	Duration
MSSA (Non-PVL)	Flucloxacillin	10-14 days (depending on response duration may have to be extended)
MRSA (Non-PVL)	Vancomycin/Linezolid	10-14 days (depending on response duration may have to be extended)
PVL-producing SA	Linzeolid + Clindamycin +/- Rifampicin	14 days

Osteoarticular Infections

In cases of osteomyelitis and septic arthritis, *Staphylococcus aureus* remains the most common causative organism (19, 20). As in other presentations, clinical skills remain important in guiding diagnosis, in these cases specifically looking for hot, swollen joints, back pain, decreased range of movement in the affected limb etc.

For osteomyelitis and spondylodiscitis, prompt MRI imaging remains the gold standard of diagnostic imaging due to its ability to differentiate between surrounding soft tissue infections and bony destruction. In septic arthritis, fluid aspirate microscopy and culture is vital to isolate causative pathogens and rule out any potential crystal arthropathies.

In acute haematogenous osteomyelitis, surgical debridement is rarely necessary and instead can be managed with antimicrobial therapy (20, 21). Septic arthritis secondary to infection with S. aureus will often require drainage or debridement with additional antibiotics (21).

Strain	Treatment	Duration
MSSA	Flucloxacillin	Osteomyelitis – 6-12 weeks Septic Arthritis – 4-6 weeks
MRSA	Vancomycin / Daptomycin	Osteomyelitis – 6-12 weeks Septic Arthritis – 4-6 weeks

Infective Endocarditis

S. aureus is commonly associated with Infective Endocarditis, especially in the presence of damaged or prosthetic heart valves. For this reason, even in the absence of clinical signs and symptoms of endocarditis, all patients should have a trans-thoracic echocardiogram (TTE) (22). In negative studies, high risk patients should then have a trans-oesophageal echocardiogram (TOE) owing to the evidence that TTE's aren't as sensitive and consequently do not detect all cases of endocarditis (23).

A surgical opinion should be sought for every patient with endocarditis and in whom the following factors are present (23):

1) Heart Failure (Aortic/Mitral endocarditis with...

a. Severe acute aortic regurgitation or valve obstruction causing pulmonary oedema/shock

b. Fistula into a cardiac chamber/pericardium causing pulmonary oedema/shock

c. Severe acute aortic regurgitation or valve obstruction and persisting heart failure

d. Severe regurgitation and no heart failure

2) Uncontrolled Infection

a. Locally uncontrolled infection including abscesses, pseudoaneurysms or enlarging vegetations

b. Persisting fevers and positive blood cultures > 10 days after commencing appropriate medical therapy

c. Infection caused by MDR organisms

3) Prevention of embolism

a. Large aortic/mitral vegetations (>10mm) resulting in one or more embolic events

b. Large aortic/mitral vegetations (>10mm) and other predictors of complicated course (heart failure, persisting infection or abscess)

c. Isolated very large vegetations (>15mm)

Antibiotic choice not only depends on whether the isolated S. aureus is methicillin-sensitive, but also on whether the infected valves are native or prosthetic.

In prosthetic valvular infection, MSSA isolates should prompt six weeks of rifampicin, high-dose flucloxacillin, and twice daily gentamicin. MRSA isolates however should be treated with rifampicin, vancomycin, and gentamicin for six weeks (23).

It is worth noting that in patients with a history of intravenous drug abuse, infection with S. aureus is particularly common. This risk factor increases the probability of developing bacteraemia through direct inoculation and the subsequent dissemination of infection to distant sites. In this demographic, the right side of the heart is more commonly affected.

STAPHYLOCOCCUS AUREUS BACTERAEMIA - A CASE STUDY

J Smyth

Strain / Valve type	Treatment	Duration
Native valve MSSA	Flucloxacillin	4 weeks
Native valve MRSA	Vancomycin + Rifampicin	4 weeks
Native valve MRSA, Vancomycin resistant, Daptomycin sensitive	Daptomycin + Gentamicin or Rifampicin	4 weeks
Prosthetic valve MSSA	Flucloxacillin + Gentamicin + Rifampicin	6 weeks (2 weeks of gentamicin)
Prosthetic valve MRSA	Vancomycin + Gentamicin + Rifampicin	6 weeks (2 weeks of gentamicin)
Prosthetic valve MRSA, Vancomycin resistant, Daptomycin sensitive	Daptomycin + Gentamicin + Rifampicin	6 weeks (2 weeks of gentamicin)

Implanted Medical Devices

S. aureus can create a biofilm on prosthetic devices such as joint replacements and cardiac devices, making source control difficult to achieve without removal of the infected prosthesis. A high index of suspicion should be involved when infection arises shortly after implantation of a medical device, however delayed presentations are possible.

Currently, there are no routinely recommended investigations available for the detection of bacterial biofilms. However, the American Heart Association suggests the use of transoesophageal echocardiography in the detection of cardiovascular implantable electronic device (CIED) infection related endocarditis (24). Positron emission tomography has also shown some promise in the diagnosis of these infections, however there are no formal guidelines supporting their use (25).

In early onset infections, removal of the implanted device can be avoided through the prompt use of appropriate antimicrobial therapy.

In cases of prosthetic joints, infections that manifest less than two months after surgery can be treated with similar antimicrobial therapy to osteoarticular infections plus rifampicin. In cases of haematogenous spread, antimicrobial therapy, and debridement (with retention of the device) is often sufficient (21). Prompt removal of the device is indicated in situations of late-onset, prolonged illness, and unstable prostheses.

For CIED's, superficial or incisional pocket infections can be treated with retention of the device provided the device itself is not involved. In these cases, seven-ten days of therapy with flucloxacillin or vancomycin is appropriate. Complete removal of the device and all wiring is indicated in established CIED infection (26) and in all circumstances where patients undergo surgical management of infective endocarditis. In these situations, adjunctive antimicrobial therapy should be provided, with a following ten-fourteen days of therapy following removal of the device.

Strain	Treatment	Duration
Prosthetic Joint MSSA	Flucloxacillin + Rifampicin	Variable, 2 -6weeks IV flucloxacillin, followed by oral regime
Prosthetic Joint MRSA	Vancomycin/Daptomycin + Rifampicin	Variable,6 weeks IV followed by oral regime if able
CIED Pocket MSSA	Flucloxacillin	7-10 days
CIED Pocket MRSA	Vancomycin	7-10 days
CIED MSSA	Flucloxacillin	Until removal of device then 10-14 days after
CIED MRSA	Vancomycin	Until removal of device then 10-14 days after

The Case Patient

As with the case study in this review, on occasion *S. aureus* bacteraemia presents with metastatic infection of other sites within the body. In the above patient, infection likely spread from the collection in the paraspinal muscles to involve the vertebral, before entering the spinal cord by translocation. This resulted in a presentation of bacterial meningitis. In this situation, lumbar puncture and MRI imaging were essential in reaching a diagnosis and assessing the degree of spread through the CNS, spine and surrounding soft tissues. He was treated with parenteral flucloxacillin and due to persisting bacteraemia, daptomycin was added.

There are no formalised guidelines for the management of *S. aureus* meningitis, however due to the patient's presence on an Infectious Diseases ward, specialists were on hand to manage the unusual presentation. In cases such as these, where guidelines are unavailable or presenting syndromes are not commonly seen, advice should always be sought from the local microbiology and infectious diseases teams (27).

From the little literature that exists surrounding the topic, it is suggested that Linezolid could also be useful in the treatment of meningitis and other brain infections, both secondary to surgery and haematogenous spread (28). However, in this case the patient's meningitis appeared to arise secondary to infection in the vertebral bodies and paraspinal muscles. As such, empirical treatment with Flucloxacillin and Daptomycin as per the guidelines was appropriate.

Conclusion

Staphylococcus aureus can present in several ways given its ability to create metastatic infection. The clinician responsible for patients in whom *S. aureus* bacteraemia is a suspected or proven diagnosis must be thorough in their examination and diagnostic work-up until all other sources can be excluded. Once a source is identified, it must be treated appropriately with the necessary surgical measures if appropriate, and aggressive antimicrobial therapy. Liaison with specialists in infectious diseases and microbiology is important at an early step to guide investigations and antimicrobial choice.

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STAPHYLOCOCCUS AUREUS BACTERAEMIA - A CASE STUDY

J Smyth

Questions

1) In SAB arising from vascular line insertion, how long should antimicrobial cover be provided for, assuming no other focus of infection can be found?

a. One week
b. Two weeks
c. Four weeks
d. Ten days
e. Five days

2) A patient with prosthetic heart valves is found to have infective endocarditis. Bloods cultures have grown MRSA. Which antibiotics should be given as treatment?

a. Flucloxacillin + Rifampicin
b. Flucloxacillin + Rifampicin + Gentamicin
c. Daptomycin + Vancomycin
d. Vancomycin + Rifampicin + Gentamicin
e. Vancomycin + Rifampicin

3) Why is vancomycin a poor choice in treating MRSA pneumonia?

a. Poor S. aureus cover
b. Low bioavailability
c. Poor penetration of alveolar lining fluid
d. Increased production of PVL
e. Need for regular blood level monitoring

4) In which situations caused by infection, should a CIED be removed?

a. Never
b. Pocket infection
c. Any infections caused by S. aureus
d. Device infection
e. Erythema around insertion site

5) In which of the following circumstances should a surgical opinion be sought for a patient with infective endocarditis?

a. Persisting fever and positive blood cultures 7 days after commencing appropriate therapy
b. Vegetation sized >10mm on ultrasound, in a previously fit patient whose blood cultures are now clear
c. Moderate valve obstruction with a degree of pre-existing heart failure
d. Severe aortic regurgitation with no signs of heart failure
e. MRSA on blood cultures, resistant only to Ð-lactams

Answers

1) Answer: B

In all cases of line-related SAB, patients should have all lines removed and receive 2 weeks of antimicrobial therapy in the absence of a deeper focus i.e. endocarditis or osteomyelitis.

If another source is found, then treatment should be adjusted accordingly to match the guidelines above.

2) Answer: D

Since cultures have grown MRSA, using flucloxacillin is ill-advised. Vancomycin is required to treat the resistant organism. Furthermore, gentamicin is added due to synergistic action between the two, wherein gentamicin enhances the bactericidal activity of vancomycin. Rifampicin is also effective against biofilms, making in useful in the treatment of infected implanted medical devices.

3) Answer: C

Vancomycin is a large molecule, and as such has difficulty in penetrating the alveolar lining fluids of the lungs. Vancomycin is routinely used for its ability to treat MRSA infections, although not quite as effective as Ð-lactams. It has no overall effect on the concentration or production of PVL, unlike linezolid or flucloxacillin. Orally, vancomycin has a very poor bioavailability but parenteral administration avoids this. Although it requires routine monitoring to achieve therapeutic range, this is not a valid cause for dismissal.

4) Answer: D

Superficial erythema or pocket infections can be treated with antibiotics, provided the infection is contained. If the infection spreads to the device or the wiring, then it must be removed due to the difficulty in clearing bacterial biofilms. Although infection with S. aureus can make device involvement more likely, it does not always necessitate removal.

5) Answer: D

Severe valvular regurgitation is an indication for surgical input regardless of whether or not cardiac failure is present. Blood cultures must be positive for more than 10 days following the commencement of therapy for surgical input to be considered, and although MRSA is a resistant organism, this strain is not multi-drug resistant. For vegetations >10mm, there must be a history of embolic events or complicating factors such as heart failure or abscesses to warrant surgery. To act on size alone, a single vegetation must be larger than 15mm.

STAPHYLOCOCCUS AUREUS BACTERAEMIA - A CASE STUDY

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A DIFFICULT CASE OF METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS CATHETER-RELATED BLOOD STREAM INFECTION WITH EXTENSIVE METASTATIC INFECTIONS IN A HAEMODIALYSIS PATIENT

ARK Tng, JTW Ong, KG Lee, S Baikunje

Abstract

Catheter-related blood stream infections are a recognized complication of haemodialysis catheters. Common organisms involved include Staphylococcus aureus, which has a risk of metastatic seeding to multiple body sites. Herein, we describe a case of an end-stage renal disease patient who developed Methicillin-Resistant Staphylococcus aureus bacteraemia from his haemodialysis tunnelled vascular catheter, discuss its subsequent complications, as well as discuss the current concepts in its management.

Case History

A 62 year-old man was referred by his dialysis centre to the emergency department for a blocked tunnelled vascular catheter. He had end- stage renal disease (ESRD) secondary to diabetic kidney disease, for which he was undergoing regular haemodialysis via a right internal jugular tunnelled vascular catheter. His past medical history included peripheral vascular disease with previous right lower limb angioplasty, ischemic heart disease with cardiomyopathy and a left ventricular ejection fraction of 25%, with previous ventricular fibrillatory collapse. He had an automated implantable cardioverter-defibrillator (AICD).

On arrival at the emergency department, the patient was noted to be febrile and hypotensive. He was also noted to be confused intermittently. Other physical findings included evidence of fluid overload in the form of an elevated jugular venous pressure, reduced air entry bibasally on chest auscultation and bilateral pedal oedema. His inflammatory markers were elevated. There was no alternative source of sepsis clinically. Blood cultures were taken both peripherally and from the tunnelled dialysis vascular catheter, and the patient was started empirically on intravenous (IV) Piperacillin/Tazobactam and Vancomycin as per institution protocol.

Both sets of blood cultures subsequently returned positive for methicillin-resistant Staphylococcus aureus (MRSA). The catheter was removed and the tip was sent for culture which grew the same organism. He was dialysed with a temporary catheter.

Despite removal of the infected catheter, appropriate antibiotics and therapeutic trough levels, the patient remained persistently bacteraemic with MRSA in subsequent blood cultures. Antibiotics were escalated to IV Daptomycin, and further investigations were arranged to look for metastatic infections. A transthoracic echocardiogram done on admission did not show any intracardiac thrombus. A transesophageal echocardiogram subsequently showed a 1.2 x 0.5cm thrombus attached to the right atrial portion of the AICD lead, as well as a thrombus partially filling the superior vena cava.

A computed tomographic (CT) scan of the thorax, abdomen and pelvis subsequently showed multiple areas of seeding which include a non-occlusive thrombus in the distal segment of the right internal jugular vein extending through the right brachiocephalic vein into the superior vena cava (Fig.1); several ill-defined nodules in both lungs with some cavitation suggestive of septic embolic (Fig.2); hypodense area of lower left psoas muscle suspicious for developing abscess (Fig.3); and endplate irregularities with disc space narrowing at L4-5 level suggestive of infective spondylitis (Fig.4).

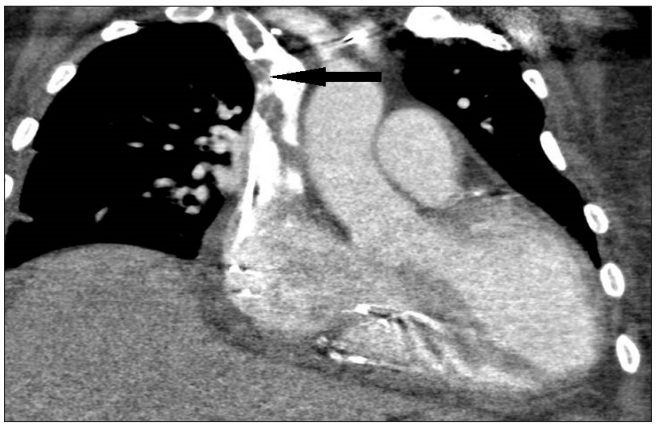

Figure 1: CT scan of the thorax shows thrombus extending from right internal jugular vein to the brachiocephalic vein and the superior vena cava at the cavoatrial junction (arrow).

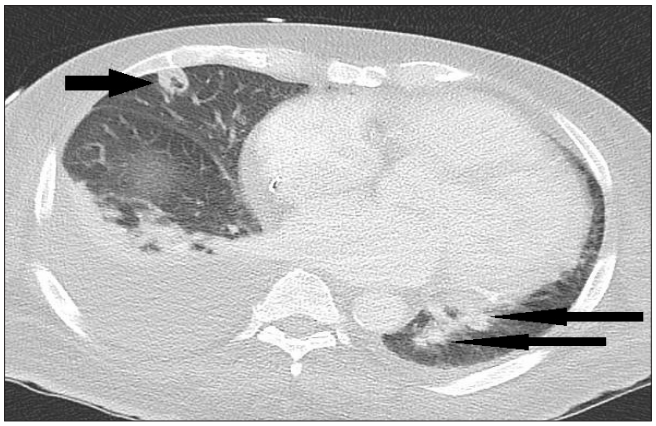

Figure 2: CT scan of the thorax shows ill-defined nodules (long arrows) in both lungs, with cavitation in right middle lobe nodule (short arrow).

A DIFFICULT CASE OF METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS CATHETER-RELATED BLOOD STREAM INFECTION WITH EXTENSIVE METASTATIC INFECTIONS IN A HAEMODIALYSIS PATIENT

ARK Tng, JTW Ong, KG Lee, S Baikunje

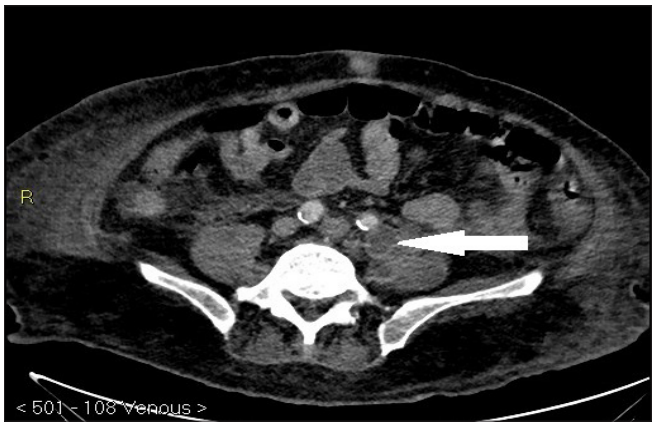

Figure 3: CT scan of the abdomen shows area of hypodensity along medial aspect of left psoas muscle (adjacent to L5 vertebrae) suspicious for early abscess formation (arrow).

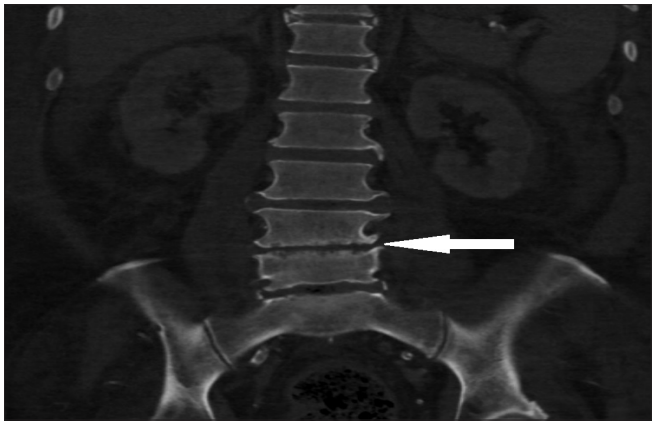

Figure 4: CT scan of the abdomen shows endplate irregularity and disc space narrowing of L4/5 suspicious of spondylitis (arrow).

The patient was managed by a multidisciplinary team involving a nephrologist, cardiologist and an infectious disease specialist. The infected AICD lead was removed and he was treated with a combination of IV Ceftaroline and oral Rifampicin for a total of 6 weeks. A repeat transthoracic echocardiogram showed no clots in the atrium; while a repeat CT scan of the thorax 4 weeks later showed improvement in size of the thrombus in the superior vena cava. The patient remained well, and a new AICD was eventually re-implanted for the patient.

Discussion

Evaluation Of Staphylococcus Aureus Crbsi

It is important to have a low threshold of suspicion for an occult site infection in patients with Staphylococcus aureus bacteraemia who develop symptoms such as back or joint pain, symptoms of persistent fever, or persistent bacteraemia which fail to clear despite appropriate antibiotics (Table 1).

Possible Metastatic Sites of Infection	Symptoms	Signs	Investigations to Consider
Cardiovascular • Infective endocarditis	• Chest pain • Breathlessness	• Cardiac murmur	• Transthoracic echocardiogram • Transesophageal echocardiogram
Respiratory • Septic emboli • Lung abscess • Empyema	• Chest pain • Cough	• Crepitations • Dullness on percussion	• Chest X-ray • CT thorax
Central Nervous System • Brain abscess • Meninges	• Headache • Vomitting	• Altered mentation • Neck stiffness • Cranial nerve signs	• CT brain (contrast) • MRI brain • Lumbar puncture
Central Nervous System – Spinal Cord	• Weakness or sensory symptoms in limbs • Back ache	• Long tract signs in upper limbs and /or lower limbs	• MRI spine • (Thoraco/lumbo/sacral)
Abdominal • Liver abscess • Splenic abscess	• Abdominal pain • Nausea, vomitting	• Abdominal tenderness • Enlarged spleen, liver	• Liver panel • Ultrasound abdomen • CT abdomen
Musculoskeletal - , • Discitis • Abscess in muscle groups • Osteomyelitis of affected bones • Joints	• Back ache • Bone pain • Joint swelling and pain	• Neurological signs corresponding to appropriate sensory level • Joint effusion, redness, tenderness, limited range of motion	• X-ray of affected bone / joints • CT spine / MRI of affected region • Joint aspiration
No obvious seeding site, yet persistently febrile and positive blood cultures		• Persistent fever with no obvious other localizing symptoms	• Nuclear scan (positron emission tomography, PET)

Table 1: Possible metastatic site of Staphylococcus aureus infections, clinical features and the specific investigations.

Best of 5 MCQs

Question 1: What is the commonest pathogen encountered in haemodialysis catheter- related blood stream infection (CRBSI)?

A. Staphylococcus aureus

B. Coagulase- negative staphylococci

C. Escherichia coli

D. Pseudomonas species

E. Klebsiella species

A DIFFICULT CASE OF METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS CATHETER-RELATED BLOOD STREAM INFECTION WITH EXTENSIVE METASTATIC INFECTIONS IN A HAEMODIALYSIS PATIENT

ARK Tng, JTW Ong, KG Lee, S Baikunje

Question 2: Which of the following modes of dialysis access is associated with greatest risk of bacteraemia?

A. AVF

B. AVG

C. Cuffed dialysis catheters

D. Uncuffed dialysis catheters

E. None of the above

Question 3: The following are true about blood cultures in the setting of suspected CRBSI in a haemodialysis patient except:

A. Paired blood cultures drawn from the catheter and a peripheral vein should be obtained before antibiotics initiation.

B. When a peripheral blood sample cannot be obtained, samples may be obtained during dialysis from blood lines connected to the dialysis catheter.

C. When cultures from a catheter grow coagulase- negative staphylococci, systemic antibiotics and antibiotics lock therapy should be initiated regardless of peripheral blood culture being positive.

D. In CRBSI, when a dialysis catheter is removed, a long term catheter can be placed once blood cultures yield negative growth.

E. For CRBSI patients for whom catheter salvage is attempted, persistently positive cultures after 72 hours after antibiotic therapy initiation is an indication for catheter removal.

Question 4: What is the most appropriate treatment of staphylococcus aureus CRBSI?

A. Catheter guidewire exchange + systemic antibiotics

B. Systemic antibiotics only

C. Antibiotic lock + systemic antibiotics

D. Catheter removal + systemic antibiotics

E. None of the above

Question 5: Which of the following regarding MRSA is false?

A. Methicillin resistance is caused by mecA gene.

B. Methicillin resistance genetic exchange/ transmission is horizontal.

C. MRSA incidence is related to immunosuppression.

D. Daptomycin should be used in MRSA with minimum inhibitory concentration (MIC) > 2.

E. There is no difference in mortality between MRSA and MSSA CRBSI.

Answers

1. The answer is A.

A majority of CRBSI is caused by staphylococci, as proven by a study [1] that implicates staphylococci in 49.3% of CRBSI. Of this, staphylococcus aureus represents 25.9%, and coagulase- negative staphylococci 23.4%. 22.0% are caused by gram- negative bacteria (Escherichia coli, Pseudomonas species, Klebsiella species).

MRSA bacteraemia was 100 times more common in dialysis patients than the general population, and this was compounded by 8- 10 times in patients dialyzing via a catheter versus an AVF [2].

2. The answer is D.

Haemodialysis is well known to be associated with bacteraemic mortality. 7.6 bacteraemic episodes per 100 patient years have been reported in a study [3], of which 48% are associated with access related infections.

The greatest predictors of infective mortality in dialysis accesses are listed in ascending order: AVFs, arteriovenous grafts (AVGs), cuffed dialysis catheters followed by uncuffed catheters. In relation to AVFs, AVGs bear a risk ratio (RR) of 1.47 for bacteraemia; cuffed catheters 8.49, and finally uncuffed catheters 9.87 [4].

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3. The answer is C.

Bacterial biofilm that form inside the catheters are niduses for CRBSI [5]. Intravenous antibiotics are ineffective in eradicating the bacteria embedded in established biofilm. Routine cultures in asymptomatic patients are not recommended. In the event that cultures from a dialysis catheter return positive without evidence of systemic sepsis, it is quite likely that the organism grown is a colonizer but it is important to do peripheral blood cultures before deciding on treatment.

In the event that cultures from the dialysis catheter grow coagulase- negative staphylococci or gram- negative bacilli (except Pseudomonas species) in an asymptomatic individual with negative peripheral cultures, antibiotic lock therapy can be given for 10- 14 days without systemic antibiotic therapy [6]. However, if catheter cultures grow Staphylococcus aureus and peripheral cultures are negative, the patient should receive a 5-7 day course of antibiotics and close monitoring for sepsis. Repeat blood cultures may be indicated.

4. The answer is D.

Infectious Diseases Society of America (IDSA) guidelines [6] indicate the need for blood cultures, empirical antibiotics and antibiotic lock once CRBSI is suspected.

Bacterial blood culture positivity can be categorized into 3: coagulase-negative staphylococcus, gram- negative bacilli, and staphylococcus aureus. Positivity for any of the first two (other than Pseudomonas species) warrant antibiotics for 14 days. Catheter salvage may be possible.

Dialysis access was implicated in majority of cases of Staphylococcus Aureus CRBSI, with a higher incidence associated with dialysis catheters versus AVFs or AVGs. This necessitates prompt removal of the catheter, and a non-tunnelled catheter be re- sited. The same goes for Pseudomonas species bacteraemia.

Antibiotics should continue for 4- 6 weeks post- removal after negative blood cultures. Some exceptions (uncomplicated cases, immunocompetent hosts) may be considered for a shorter duration of antibiotics but the minimum duration is 2 weeks). Also, a trans-oesophageal echocardiogram should be done to assess for cardiac valvular vegetations.

If future alternative vascular access options are limited, guidewire exchange can be considered. Guidewire exchange (with systemic antibiotics) in MRSA CRBSI had a 67% cure proportion as opposed to using systemic antibiotics alone (45%) or with antibiotic lock together with systemic antibiotics (57%) [1].

Antibiotic lock therapy with systemic antibiotics is a treatment option for gram-negative CRBSI and Staphylococcus Epidermidis CRBSI; but it has a poor track record against Staphylococcus aureus CRRSI with only a 40% success rate [7].

5. The answer is E.

MRSA bears a significantly greater risk of bacteraemic mortality as compared to MSSA, with a risk ratio of up to 2.12 [8]. MRSA is also more prevalent in patients with comorbidities or immunosuppression such as cancers or haemodialysis.

In addition, some MRSA strains exhibit an increased MIC for vancomycin, and these impart higher mortality risks as initial presumptive therapy would be that of vancomycin as opposed to daptomycin[9].

Methicillin resistance is encoded by the mecA gene, located in the staphylococcal cassette chromosome mec (SCCmec) element chain. This is a dynamic gene which enables horizontal exchange of genomic data between different Staphylococcal species to confer penicillin resistance [10].

To summarise, MRSA CRBSI can have devastating morbidity and sometimes mortality associated with it. Metastatic infections can occur in various different sites and sometimes in multiple sites as in the above patient. AVF should always be the preferred access option in long term haemodialysis patients.

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ATYPICAL HAEMOLYTIC URAEMIC SYNDROME - PRESENTATION, MANAGEMENT & TREATMENT

DV Milford, R M O'Sullivan

Abstract

A 5 year old boy presented to his local hospital with vomiting, jaundice and abdominal pain. We will discuss the key elements of the history, examination and initial investigations that will lead you to the diagnosis. Next we will cover further investigations to uncover the cause of the illness and discuss the most appropriate management.

Introduction

A 5 year old boy presented to his local hospital with vomiting, jaundice and abdominal pain. On examination he was noted to be pale and jaundiced with obvious petechiae but nothing else significant to note on systems examination. Routine investigations showed anaemia (Hb 66 g/L), thrombocytopenia (platelets 20 x10^9/L) and acute kidney injury (creatinine 262µmol/L); urine dip testing showed proteinuria (4+) and haematuria (1+). The differential diagnoses included disseminated intravascular coagulation secondary to sepsis, haemolytic uraemic syndrome and haemolytic anaemia (eg secondary to mycoplasma infection).

What other information or investigations would be useful in reaching a diagnosis?

The triad of thrombocytopenia, acute kidney injury and (a microangiopathic haemolytic) anaemia should make you think of the possibility of Haemolytic Uraemic Syndrome (HUS). First line investigations to determine if the anaemia is due to haemolysis include a blood film for fragmented red cells, lactate dehydrogenase (LDH), haptoglobins and unconjugated bilirubin (1). In this case the patient's LDH was raised at 6714 IU/L and there were fragmented cells seen on the blood film, both of which supported ongoing haemolysis.

Once you are considering HUS it is important to identify the cause. In the paediatric population about 90% of cases of HUS are associated with a prodrome of diarrhoea, often bloody and most often caused by Shiga toxin producing strains of Escherichia-Coli (STEC) (2).

This is commonly referred to as 'D+HUS' or typical HUS. Another infectious cause of HUS is Streptococcus Pneumonia, with signs of HUS manifesting with a lower respiratory tract infection (2). The remaining cases are mostly non-infectious in nature and caused by inherited or acquired dysregulation of the complement system (2) (figure 1).

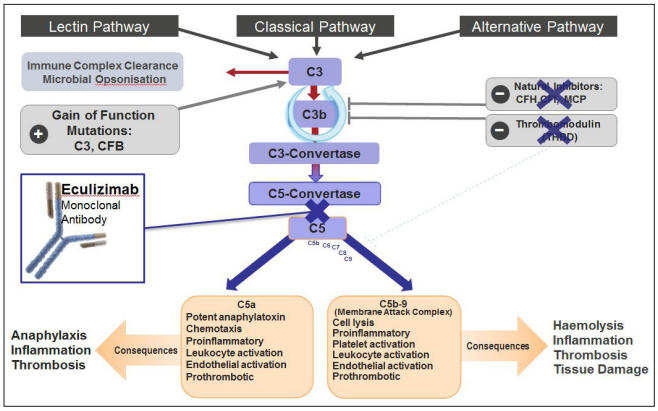

Figure 1: Diagram showing the three pathways of complement activation.

Loss of function mutations prevent the complement pathway inhibitors Complement Factor H (CFH), Complement Factor I (CFI), Membrane Co-Factor Protein (MCP, also known as CD46) and Thrombomodulin (THBD) from preventing uncontrolled C3b generation with consequent activation of the terminal pathway.

Gain of function mutations in C3 and Complement Factor B (CFB) increase C3b generation with consequent activation of the terminal pathway. Eculizumab (trade name Soliris) binds to C5 preventing the action of C5 convertase preventing the generation of C5a and C5b-9, so stopping the activation of the terminal pathway.

These are classed as 'D-HUS' or atypical Haemolytic Uraemic Syndrome (aHUS). In this case there was no diarrhoea and no recent or inter-current respiratory illness. Of note is that in up to 5% of cases of STEC associated HUS there is no diarrhoeal prodrome (5). Conversely, 30% of aHUS cases can present with diarrhoea, as there is often an infective trigger to the initiation of the disease process (5).

The local hospital team suspected HUS and liaised with their paediatric nephrology department for the patient's care to be transferred. Once there he was noted to have a brother who had a mild episode of HUS five years previously; a diagnosis of familial aHUS was made, highlighting the importance of taking a thorough family history. As he was oliguric he was placed on a fluid restriction and his fluid balance was carefully monitored. He was noted to be hypertensive so was commenced on amlodipine. A series of investigations, both serum and stool, were sent off and daily plasma exchange was commenced.

What further investigations can help differentiate between HUS and aHUS?

A number of investigations are required prior to starting any therapies in patients with suspected aHUS.

It is important to rule out infectious causes of HUS, therefore stool samples should be sent for E-coli O157 and serum +/- urine sent for Streptococcus pneumonia (7). A key investigation is determining 'ADAMTS-13' activity (7). Deficiency of this enzyme prevents breakdown of Von Willebrand factor antigen resulting in intravascular clotting and is associated with Thrombotic Thrombocytopenic Purpura (TTP) (3). TTP is a condition which can have a similar presentation to HUS but requires different management (5).

Baseline investigations into the complement system are also required, with C3, C4, Factor H and Factor I levels recommended alongside serum for complement genetics (3).

There is a checklist of investigations available for clinicians on the 'RareRenal.org' website **(http://rarerenal.org/clinician-information/atypical-haemolytic-uraemic-syndrome-ahus-clinician-information/).**

ATYPICAL HAEMOLYTIC URAEMIC SYNDROME - PRESENTATION, MANAGEMENT & TREATMENT

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What are the treatment options in aHUS?

The complement system is part of the immune system and is triggered via a classical, alternative or lectin pathway (figure 1); dysregulation of the alternative pathway is associated with aHUS (3). This pathway can be directly activated by invading micro-organisms, triggering a cascade resulting in the formation of a 'membrane attack complex' composed of complement factors C5b-C9 (3, 4).

The membrane attack complex favours microthrombosis, initiates inflammation and causes local cell damage, especially to endothelial cells (3,4). Regulatory proteins, including Factor H, Factor I and CD46 control the complement cascade and the formation of the membrane attack complex (3,4). 50-80% of patients with aHUS have an underlying complement abnormality which may be inherited and/or acquired (5). This results in dysregulation of the cascade (2).

Plasma exchange used to be the treatment of choice (4). The patient's plasma is exchanged for pooled plasma thus allowing complement regulatory proteins to be replaced, inducing remission by achieving sufficient levels of regulatory proteins to restore control of the complement cascade (4). This treatment could initially be effective but many patients developed long-term sequalae of aHUS including hypertension and end stage renal disease (5).

Eculizimab, a recombinant, humanised monocloncal antibody against C5a is now the treatment of choice in aHUS patients (3) but requires application to a national aHUS service for funding approval. By targeting C5a it blocks the formation of the membrane attack complex (2). The dosing of Eculizimab and the schedule of infusions depends upon weight and details are available on the RareRenal.org website.

Other complement inhibitors have been discovered but are in the early stages of clinical trials and offer potential therapies for the future (3).

Other considerations when prescribing Eculizimab

By blocking the formation of the complement membrane attack complex entirely, Eculizimab also renders patients at increased risk of infection, especially from encapsulated bacteria (3). Consequently all patients should be vaccinated against Meningitis B, ACW and Y (3). As it is not known if vaccination alone is sufficient protection in the face of on-going complement blockade penicillin prophylaxis is recommended throughout the duration of treatment and for three months after its discontinuation (5).

This patient was initially commenced on daily plasma exchanges until approval for Eculizimab funding was obtained. He responded well to daily plasma exchange and these were then reduced to thrice weekly as his blood parameters improved and he went into remission. Eculizimab was approved so plasma exchanges were stopped and infusions commenced. Remission was maintained with normal renal function on an infusion every three weeks (figures 2A, B and C).

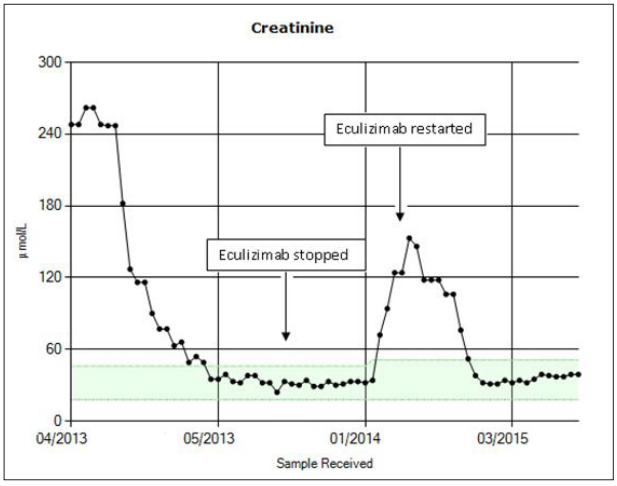
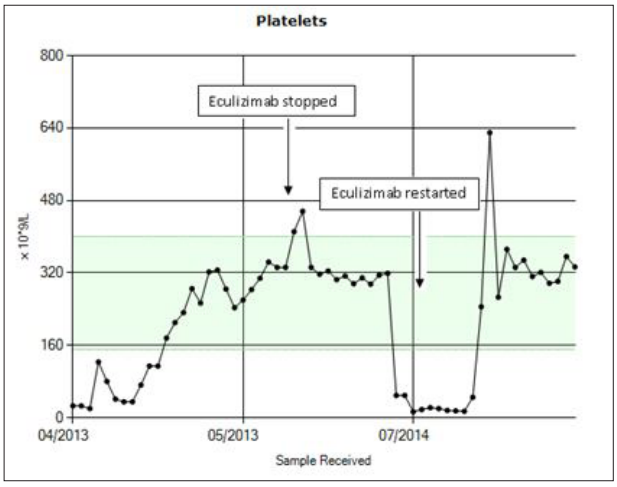
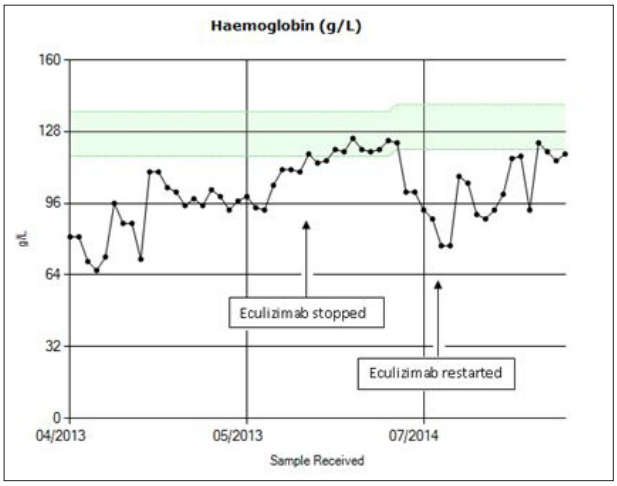


Figure 2A: Change in plasma creatinine showing relapse of aHUS with rise in creatinine after discontinuation of eculizumab.





Figures 2B and 2C showing normalisation of platelets and haemoglobin after presentation and subsequent fall with relapse and recovery after treatment with Eculizumab.

ATYPICAL HAEMOLYTIC URAEMIC SYNDROME - PRESENTATION, MANAGEMENT & TREATMENT

DV Milford, R M O'Sullivan

What is the recommended duration of treatment with Eculizimab?

Treatment with Eculizimab is expensive and currently there are no guidelines for how long maintenance infusions should continue (3). There is no consensus for withdrawal but also no evidence for lifelong treatment (6). As such the current recommendation in decision making is on an individual patient basis with discussion with the patient and care-giver (6). If the decision is made to withdraw the infusions the patient needs to be closely monitored as it is not yet possible to predict which patients can safely have Eculizimab withdrawn without relapsing (3).

This patient had Eculizimab discontinued after 4 months but was closely monitored. Nine months later, during an inter-current viral upper respiratory tract infection, the patient developed proteinuria and haematuria on home urine dip testing. Investigations showed he had relapsed with recurrence of anaemia (Hb 77 g/L), thrombocytopenia (platelets 15 $x10^9$/L) and acute kidney injury (creatinine 150µmol/L).

He received a blood and platelet transfusion and Eculizimab was re-started the same day (figure 2A,B and C). He went back into remission without requiring plasma exchange or renal replacement therapy. Since then he has been maintained on Eculizimab infusions every three weeks with penicillin prophylaxis against meningococcal infection.

Was a cause identified for his aHUS?

The patient was identified as having a heterozygous mutation in CD46 which is a regulatory component of the complement system. It has cofactor activity with Factor I for inhibiting complement factor C3b/C4b therefore preventing the terminal cascade formation of the membrane attack complex (9).

The underlying genetic variant is thought to influence disease progression and response to treatment (5). There is incomplete disease penetrance amongst carriers of complement regulatory gene mutations so relatives of affected individuals may carry the mutation but appear unaffected (3). Consequently first degree relatives of patients with a known complement abnormality should be screened (3). In this case the patient's older brother was found to have the same CD46 mutation.

Summary

Haemolytic uraemic syndrome is uncommon and aHUS has an incidence of 1.5-1.8 per million inhabitants in Europe (3). It is an uncommon cause of acute kidney injury in paediatric patients and can lead to chronic kidney disease; making the diagnosis quickly is important because effective treatment is available.

Eculizimab is a relatively new treatment for aHUS that has changed the approach to managing this condition. In the first year 43 patients were commenced on Eculizimab infusions, of which 23 patients (9 paediatric) were new diagnoses of aHUS (6). Of note is that 8 patients who required dialysis prior to Eculizimab subsequently recovered their renal function, however, 7 patients did not (6). Of the 43 patients who started Eculizimab, 31 remained on infusions at the end of year one. Further research is required to determine optimum treatment duration and to investigate the variability in patient response to treatment.

Multiple choice questions

1. What triad composes haemolytic uraemic syndrome?

a. Acute kidney injury, thrombocytosis, haemolytic anaemia
b. Acute kidney injury, thrombocytopenia, haemolytic anaemia
c. Chronic kidney disease, thrombocytopenia, haemolytic anaemia
d. Chronic kidney disease, thrombocytosis, haemolytic anaemia
e. Acute kidney injury, thrombocytopenia, macrocytic anaemia

2. Which of these is not an investigation into whether anaemia is caused by haemolysis?

a. Lactate dehydrogenase
b. Creatinine
c. Blood film
d. Haptoglobins
e. Unconjugated bilirubin

3. Atypical Haemolytic Uraemic Syndrome is commonly caused by?

a. Dysregulation of the complement cascade
b. Streptococcus Pneumonia
c. ADAMTS-13 deficiency
d. Shiga-toxin producing Escherichia-Coli
e. Acute kidney injury

4. Which of these is a regulatory protein in the complement system?

a. ADAMST-13
b. Membrane attack complex
c. C9
d. Factor H
e. C5

5. Eculizimab is a recombinant, humanised monoclonal antibody targeting?

a. C3b
b. C4b
c. C5
d. The membrane attack complex
e. ADAMST-13

ATYPICAL HAEMOLYTIC URAEMIC SYNDROME - PRESENTATION, MANAGEMENT & TREATMENT

DV Milford, R M O'Sullivan

Answers

1b

Haemolytic uraemic syndrome is a triad of acute kidney injury, thrombocytopenia and a microangiopathic haemolytic anaemia

2b

Creatinine is not an investigation that will identify if anaemia is due to haemolysis or not.

3a

Atypical haemolytic uraemic syndrome is commonly caused by dysregulation of the complement cascade. Up to 80% of patients will have an inherited and/or acquired abnormality in their complement system.

4d

Factor H is a regulatory protein in the complement system. C5, C9 and the membrane attack complex are part of the complement cascade. ADAMST-13 is an enzyme responsible for breaking down von Willebrand factor.

5c

Eculizimab targets C5 and prevents the downstream formation of the membrane attack complex by preventing the generation of C5a an C5b-9

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CARING FOR THE DIALYSIS PATIENT IN HOSPITAL: WHAT EVERY JUNIOR DOCTOR NEEDS TO KNOW

S.S.N Chan, J Baharani

Abstract

At present, there are increasing numbers of patients on renal replacement therapy (RRT). In UK, there are approximately 55,000 adults receiving haemodialysis (HD), peritoneal dialysis (PD) or have a functioning kidney transplant (1). For many junior doctors, the inpatient care of dialysis patients can be daunting. This brief review aims to provide both clinical and practical information for caring of such patients.

Background

Mr P is a 60 year old man who presents to the Acute Medical Unit (AMU) with a three day history of shortness of breath. He has a past medical history of gastro-oesophageal reflux disease, type 2 diabetes mellitus- diet controlled and end stage renal failure. He started haemodialysis recently due to chronic nephropathy. Regular medications include Darbepoetin alfa 100micrograms s/c injection every 7 days and Lansoprazole 20mg once daily. The AMU consultant asks you to review the patient.

Basics of RRT

The intricate details of RRT are beyond the scope of this article.

Broadly speaking, there are three different types of RRT: Haemodialysis, Peritoneal dialysis and kidney transplantation.

In dialysis, there is diffusion of products between the patient's blood and an artificial solution (dialysate) across a semi-permeable membrane. In renal failure, there are increasing levels of toxic waste substances e.g. urea , as well as abnormal electrolytes levels (e.g. hyperkalaemia). Patients can be fluid overloaded and also in a state of metabolic acidosis. Dialysis aims to correct these abnormalities (2).

Haemodialysis

In HD, dialysis is achieved with the use of a man-made semi-permeable membrane. Blood is transferred from the body to the dialyser machine, before returning to the body. Blood flows in the opposite direction to the dialysate solution ('counter current' flow method). Patients require regular sessions ; normally a three times a week regime (Monday/Wednesday/Friday or Tuesday/Thursday/Saturday). Each session lasts around 3-4 hours in duration (3).

Different vascular access methods are used. These include:

Permanent

Arteriovenous fistula (AVF): *surgically crafted anastomosis between adjacent artery and vein, often in the upper limb e.g. radio-cephalic, radio-basilic and brachio-cephalic. High pressure arterial blood flow over months leads to dilatation and thickening of the venous wall, thus creating a platform for repeated dialysis needle insertion.*

AVF can become infected, stenosed or clotted.

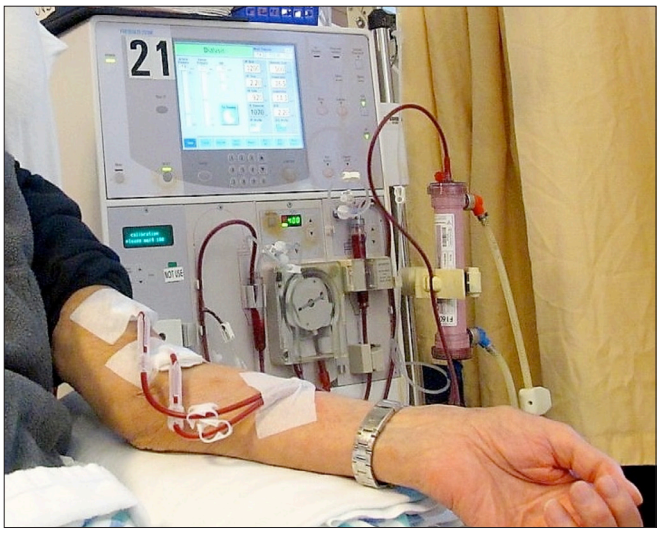


Image of Arteriovenous Fistula in use

Bridging graft

Bridging graft: Synthetic graft made of Polytetrafluoroethylene (PTFE) connects artery and vein. Examples include forearm loop between the brachial artery and cephalic vein.

Temporary

Tunnelled cuffed catheter: *These catheters are inserted in a large central vein (often the right internal jugular vein). As the catheter's insertion site is separate to the exit site (catheter passes under skin), there is decreased risk of infection compared to non-tunnelled catheters. These can be used for long term vascular access.*

Non-tunnelled cuffed catheter: *Ultrasound guided insertion into the right internal jugular vein ('neck line') or femoral vein ('femoral line').*

A common complication is infection. Thus it is vital to know duration of catheter insertion and whether removal/replacement is needed (2,3).

CARING FOR THE DIALYSIS PATIENT IN HOSPITAL: WHAT EVERY JUNIOR DOCTOR NEEDS TO KNOW

S.S.N Chan, J Baharani

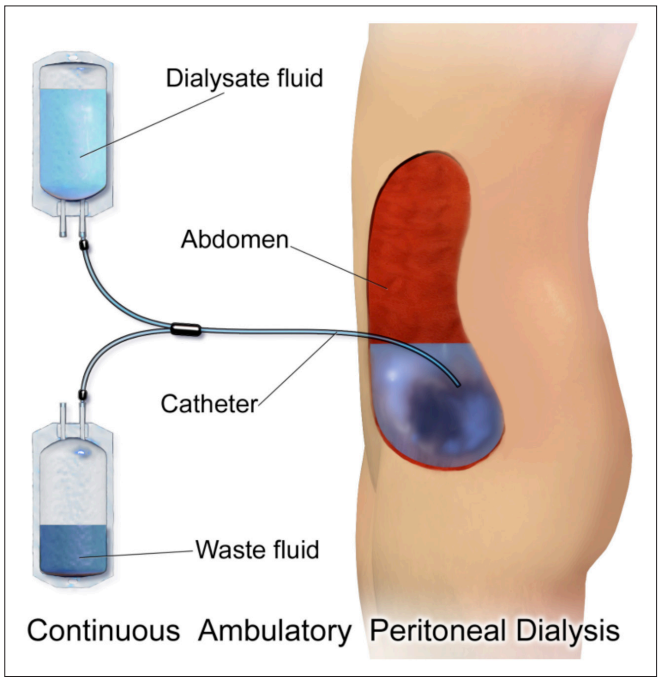
Peritoneal Dialysis

In PD, the peritoneum is used as a semi permeable membrane. Dialysate solution is pumped into the peritoneal cavity via a permanent tunnelled catheter. Diffusion of products occurs and the dialysate solution is drained out (4).

Two main methods are known:

- Continuous Ambulatory Peritoneal Dialysis (CAPD): *Manual exchanges of several bags of dialysate fluid over a 24 hour period.*

- Automated Peritoneal Dialysis: *Quick exchanges of dialysate fluid bags overnight.*



A common complication of PD is catheter exit site infection. This can be seen as erythema, tenderness around the exit site. PD peritonitis can occur. Rare complications e.g. Encapsulating Peritoneal Sclerosis have also been reported (2,3,4).

Role of Ultrafiltration

To remove excess fluid from a dialysis patient effectively, ultrafiltration can be used in adjunct to their normal dialysis regime. In HD patients, negative pressure exerted on the dialysate fluid leads to a hydrostatic pressure gradient, thus osmosis occurs. Similarly in PD, an osmotic gradient can be created with the use of hypertonic solution e.g. higher concentration of glucose (2).

Assessment of the dialysis patient

In this section, we will discuss factors to consider when assessing the dialysis patient.

Fluids status assessment

Fluid balance input and output is vital information to elicit. The usual recommended daily fluid allowance for dialysis patients is around 500-1000ml per day.

Urine output can vary between patients. For the majority of long term HD (and sometimes PD) patients, the extent of deterioration in glomerular filtration rate means they are oliguric/anuric. However for those patients who have PD or have recently started HD, they preserve some residual renal function, thus are able to pass good volume of urine. Given time, their renal function deteriorates and they will become anuric. One should bear this in mind, when considering if such patient needs urinary catheterisation for 'low urine output'.

On examination, fluid overload status may be indicated by:

- General appearance: *Normal skin turgor, hydrated mucous membranes, normal capillary refill time, pitting pedal oedema.*

- Cardiovascular system: *Raised Jugular Venous Pressure (JVP), presence of chest bi-basal crepitations on auscultation.*

- Observations: *Hypertension (can be related to positional stance), tachycardia, increased dry weight */weight from previous dialysis session (5)*

*Dry weight: *target weight at which patient's has normal fluid balance i.e. no signs of fluid overload, no pitting oedema, normal JVP but hydrated sufficiently as well. This weight should ideally be the lowest possible the patient can tolerate. Regular weight review is needed.*

Chest X ray is useful in highlighting pulmonary oedema.

Ultimately, management of fluid overload involves fluid removal*. Methods used were discussed earlier. In those patients who have adequate urine output, diuretics can be used.

**It is important to review blood pressure status prior to haemodialysis session. HD +/- ultrafiltration leads to fluid body volume changes and thus decreases blood pressure. If any concerns, always involve the renal dialysis team (3,5).*

CARING FOR THE DIALYSIS PATIENT IN HOSPITAL: WHAT EVERY JUNIOR DOCTOR NEEDS TO KNOW

S.S.N Chan, J Baharani

Assessment of vascular/dialysis access

As discussed earlier, there are many modalities of vascular/dialysis access. A quick review of the patient's access should be done.

For AV fistula, ensure that the patient has a red wristband on the fistulated arm. Tight clothing and accessories e.g. wrist watches should not be on the ipslateral fistula side. Similarly, do not place blood pressure cuff or insert any needles for cannulation/venepuncture. Palpate fistula for thrill and auscultate for bruit. Slow flow may suggest stenosis.

Review surrounding area for infection (erythema, tenderness). Swelling around the fistula site may suggest aneursymal formation and require urgent vascular surgeon review. Lastly, always inspect the distal aspects to the fistula. Reduced circulation to the peripheral area can lead to distal ischaemia. Palpate the distal pulses and look out for skin discolouration. Again, seek vascular opinion if required (6).

For any iatrogenic vascular access catheter, review for signs of infection and vessel clotting (highlighted by inability to get good dialysis flow).

With PD catheter, exit site infection must be considered if tenderness, erythema, purulent discharge is present. Cloudy peritoneal fluid with associated abdominal tenderness may suggest PD peritonitis (3,6).

Other important assessments

Indeed, given the systemic effects of renal failure, dialysis patients are at increased risk of various complications. These complications are discussed later in this review.

Diet

Patient with renal failure have specific dietary needs as the kidney have an important role in protein and electrolyte control. Renal dietician input is important (7).

For those with chronic kidney disease, but not on dialysis ('pre-dialysis'), a low protein diet is encouraged to slow down renal impairment. In contrast, for HD and PD patient, a high protein diet is required. Foods include meat, fish, egg and poultry products. Other drug supplementation may be required (8).

Potassium levels may accumulate in renal failure and although potassium levels can be corrected during haemodialysis, it is important to limit oral potassium intake. Fruit/fruit juice, nuts, milk, salt substitutes, crisps, coffee have high potassium content.

Oral sodium intake required monitoring, as sodium play a vital role in achieving adequate fluid balance status. 'Processed/ready-made' meals, crisps and smoked food intake should be limited.

Phosphate levels can rise with end stage renal failure and unlike potassium, there is often inadequate body clearance when using dialysis alone. Phosphate binder medications are often taken in adjunct. Sources of high phosphate content include dairy products, nuts, dried beans and peas (2, 4, 7).

Prescribing

For patient on dialysis, prescribing of medications must be done with caution. This is especially for renal excreted medications. If in doubt, consult the British National Formulary (9) or Renal Drug Handbook (10).

Analgesia

Simple analgesia like paracetamol is often a good choice for dialysis patients.

Non-Steroidal Anti-Inflammatory (NSAID) medications should be avoided. They have an adverse effect on glomerular filtration rate and will further compromise those with residual renal function.

Selected opioids should be used with caution. Codeine and morphine are mainly renal excreted thus levels can accumulate quickly. Other opioids like tramadol can be used at lower dose. For chronic pain, fentanyl transdermal skin patches are ideal, given it is predominantly metabolised by the liver (10, 11).

Phosphate binders

As discussed before, hyperphosphatemia is seen in renal failure patients. Phosphate binder medications are taken at each meal and essentially 'bind' to phosphate, preventing their intestinal absorption. Examples include calcium carbonate, calcium acetate, aluminium hydroxide, sevelamer hydrochloride/carbonate and lanthanum carbonate.

Sevelamer hydrochloride /carbonate do not contain calcium, whereas calcium containing binder can lead to hypercalcaemia. Common side effects for both include gastrointestinal upsets (3, 10).

CARING FOR THE DIALYSIS PATIENT IN HOSPITAL: WHAT EVERY JUNIOR DOCTOR NEEDS TO KNOW

S.S.N Chan, J Baharani

Erythropoietic stimulating agents

Referring back to our case scenario, Mr P has Darbepoetin alfa 100micrograms injection subcutaneously every 7 days. Erythropoietic stimulating agents (ESA) play a key role in managing symptomatic anaemia in renal failure patients. Erythropoietin (EPO) hormone produced by the kidney is vital in the production of red blood cells. Levels are reduced due to decreased kidney function.

Symptomatic pre-dialysis and dialysis patients may benefit from recombinant forms of erythropoietin. One should consider ESA who display signs/ symptoms of anaemia or have haemoglobin level <10g/dL. Other correctable causes like iron deficiency should be sought prior to initiation of ESA (4).

Side effects include hypertension, which occurs in up to 50% of patients (10).

Common complications seen in the dialysis patient

We have previously discussed fluid overload status in the dialysis patient. We will outline other common complications.

Cardiovascular disease

Pre-dialysis and end stage renal failure patients on dialysis are at higher risk of cardiovascular morbidity and mortality compared to the general population. It is the most common cause of death in dialysis patients, accounting for 50-60% of cases. Others non-cardiac factors like anaemia, hyperparathyroidism, hyperphosphatemia and uraemia; all contribute to adverse cardiac events.

When assessing a dialysis patient, it is vital to remember that they may present with atypical signs and symptoms of ischaemic cardiovascular disease.

Infection

Infection is common in dialysis patients and is the second most common cause of mortality (up to 30% of end stage renal failure deaths).

As dialysis patient are in an immunosuppressed status, they are prone to more severe infection- both related to vascular access and non-vascular access (respiratory, urinary etc) (3,4).

Others

Other complications include uraemia, hyperkalaemia and metabolic acidosis. Emergency treatment of the underlying cause +/- urgent haemodialysis session is imperative (2).

Summary and Questions

Mr P presented with shortness of breath. He has a significant background history of chronic nephropathy with regular haemodialysis three times a week via his AVF.

On further questioning, he has shortness of breath at rest for the past few days since he missed his last regular dialysis session. He highlights bilateral non tender swelling in his legs. No chest pain noted. No other symptoms elicited. Otherwise he feels well in himself. He normally passes minimal volume of urine.

1) What would the most likely provisional diagnosis?

a) Acute Myocardial infarction

b) Pulmonary Embolism

c) Pulmonary Oedema

d) Lymphoedema

e) Bilateral Cellulitis

His observations: *Heart rate of 100 beats per minute, Respiratory rate of 20 breaths per minute, Oxygen saturations of 97% on air, Blood pressure 160/100mmHg, Temperature of 36.7 degrees Celsius.*

On examination, he has increased respiratory effort, presence of chest bi-basal crepitations on auscultation, JVP is raised at 5cm above the sternal angle and bilateral pitting oedema above the knees.

2) What initial imaging modality would be useful in your assessment?

a) Transthoracic Echocardiogram

b) Chest X ray

c) Ultrasound leg doppler

d) CT abdomen

e) Ventilation Perfusion scan

CARING FOR THE DIALYSIS PATIENT IN HOSPITAL: WHAT EVERY JUNIOR DOCTOR NEEDS TO KNOW

S.S.N Chan, J Baharani

3) What would be a suitable management plan for this patient?

a) Sitting upright position, bloods tests, Glyceryl Trinitrate infusion, Diamorphine infusion and Intravenous furosemide 80mg infusion

b) Sitting upright, high flow oxygen, bloods tests and call the renal registrar for urgent haemodialysis and ultrafiltration

c) Sitting upright position, Glyceryl Trinitrate infusion, High flow Oxygen, Diamorphine infusion, Intravenous Furosemide 80mg infusion, bloods tests, urgent haemodialysis

d) Call the Renal Registrar for Continuous positive airway pressure and urgent haemodialysis

e) Bloods tests, Diamorphine infusion and await for routine haemodialysis

Miss B is a lady who has recently begun peritoneal dialysis. She notices frank pus discharging from the abdominal site of the PD catheter with associated erythema.

4) What organism is most commonly associated with this complication?

a) Clostridium difficile

b) Streptococcus pneumoniae

c) Methicillin-resistant Staphylococcus aureus

d) Staphylococcus epidermidis

e) Staphylococcus aureus

The same patient later complains of abdominal pain and fever. PD fluid was cloudy on drainage.

5) What would be a definite management plan?

a) Send blood cultures and treat with broad spectrum intravenous antibiotics, tailoring antibiotics to sensitivities later

b) Send blood cultures and treat with intravenous antibiotics

c) Sent blood cultures and await blood cultures sensitivities, then treat

d) Send peritoneal fluid cultures, await peritoneal fluid cultures sensitivities, then treat with intraperitoneal antibiotics

e) Send peritoneal fluid culture and start intraperitoneal antibiotics

Answer

1) C – Fluid overload would be the most likely diagnosis.

2) B – Findings are consistent with fluid overload.

The first initial imaging investigation should be a chest x ray to rule the most likely pulmonary oedema. (a) would be ideal choice in the outpatient setting if we suspect new diagnosis heart failure, unlikely given this patient's medical history.

3) B - The key point to this question is that the patient has minimal urine output.

In 'standard heart failure patients' with pulmonary oedema, the standard regime would include loop diuretics. In oligoanuric HD patients, such use would be futile. In a patient who is critically unwell with severe respiratory distress, continuous positive airway pressure may be helpful as a short term symptomatic reliever. Ultimately given this patient has known vascular access, he should have urgent haemodialysis with ultrafiltration to remove excess fluid.

4) E - This patient has likely exit site infection of the PD catheter.

Most commonly this is due to Staphlococcus aureus and Pseudomonas spp.

5) E - The patient most likely has PD peritonitis.

There should be no delay in starting antibiotics. Most hospitals treat with intraperitoneal antibiotics because no intravenous access is required and better peritoneum absorption occurs.

CARING FOR THE DIALYSIS PATIENT IN HOSPITAL: WHAT EVERY JUNIOR DOCTOR NEEDS TO KNOW

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PREVENTION & MANAGEMENT OF ACUTE KIDNEY INJURY (AKI)

C Nolan, C Brown, M Harty, J Harty

Abstract

Acute kidney injury (AKI) is a very common medical problem. It is expensive to manage, prolongs hospitalization and is associated with increased mortality. It can develop in both patients with pre-existing renal impairment and in those patients with normal baseline renal function. AKI poses problems for foundation doctors on a daily basis in maintaining fluid balance and managing acid-base and electrolyte abnormalities and can, if not addressed, lead to significant mortality.

AKI is a largely preventable condition causing a significant financial burden to the National Health Service (NHS), with more than £1.02 billion spent annually on the treatment of acute kidney injury in England alone (1).

A focus on making improvements in early recognition, risk-stratification, and prevention would help reduce the so-called 'predictable and avoidable AKIs', which number approximately 20% of all cases (2).

Using three case examples, we show that AKI is easily:

- Detected – *using simple laboratory tests and clinical assessment.*
- Managed – by reviewing offending medications, optimising volume status and blood pressure, and through the timely referral to nephrology where indicated.
- Prevented – *through identifying high-risk individuals and in acting promptly to prevent AKI and reduce its severity.*

Definition

AKI is defined as an acute deterioration in renal function, in a matter of hours to days, which is potentially reversible. This deterioration is reflected by:

- A rise in creatinine by >26umol/L
- A 1.5 fold/50% increase in serum creatinine; or
- A decrease in Urine output <0.5mL/kg/hr for at least 6 consecutive hours according to AKIN (3).

The AKIN classification (Stage 1, 2, 3) and the RIFLE criteria are commonly used to grade severity of acute kidney injury.

In the RIFLE criteria:

Risk = AKIN Stage 1; Injury = AKIN Stage 2; and Failure = AKIN Stage 3.

The RIFLE classification adds two additional outcomes to AKI; Loss and End Stage Renal Failure where the patient never regains independent renal function (3,4).

Kidney Disease Improving Global Outcomes (KDIGO) staging classification for AKI

Kidney Disease Improving Global Outcomes (KDIGO) staging classification for AKI		
Stage	Serum creatinine (Scr) criteria	Urine output criteria
1	Rise in Scr of 26 umol/L within 48 hrs Increase of 1.5 – 1.9 x baseline Scr within past 7 days	< 0.5 mL/Kg/hr for > 6 consecutive hours
2	Increase of 2 - 2.9 x baseline Scr	< 0.5 mL/Kg/hr for > 12 consecutive hours
3	Increase of 3 x baseline Scr or Scr ≥ 354 umol/L or Commenced on dialysis	
Additional RIFLE Criteria reflecting outcome of AKI		
Loss	Need for ongoing dialysis for > 4 weeks	
Failure	Need for ongoing dialysis for > 3 months	

Figure 1: KDIGO staging classification.

In 2009, the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) published a report into the care of patients who died with a diagnosis of AKI. They highlighted that management of these patients was of a poor standard (2).

- *Only 50% of AKI care was deemed good clinical care*
- *Risk factors for AKI were poorly identified*
- *60% of post-admission AKI was predictable*
- *21% of post-admission AKI was avoidable*
- *2/3 of patients had a significant progression of AKI before a diagnosis was made*

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In 2013, as a result of the NCPOD enquiry, the National Institute for Health and Care Excellence (NICE) highlighted AKI as a condition of importance. They published guidelines for management of AKI stating that with early recognition and careful attention to management of hydration and medication, 100,000 cases of AKI could be prevented and 42,000 deaths could be avoided annually (5).

Causes of AKI

AKI can be best understood by an anatomical classification, which reflects the pathophysiology behind disruption to renal function (6). Simply put, AKI can be:

- *Pre-renal – events compromising renal perfusion*
- *Renal – intrinsic damage to the kidney structure*
- *Post-Renal – obstruction to drainage of filtrate/urine*

Pre-renal

Pre-renal AKI accounts for the majority of all AKI. It occurs following hypo-perfusion of the kidneys. Patients with Chronic Kidney Disease (CKD) are more vulnerable to this form of renal injury. Renal hypo-perfusion reduces glomerular capillary pressure and subsequently causes a reduction in the production of a glomerular filtrate. Under these conditions, the glomerulus attempts to maintain a filtration pressure by dilating the afferent arteriole (via prostaglandin production) and constricting the efferent arteriole (via the action of renin).

Common causes of renal hypo-perfusion, and their mechanism, are listed below.

Table 1: Causes of renal hypo-perfusion.

Volume Depletion	Haemorrhage, Vomiting/Diarrhoea, Diuretics
Reduced Cardiac Output	Heart Failure, Myocardial Infarction
Systemic Vasodilation	Sepsis, Anaphylaxis, Drug overdose
Local renal hypo-perfusion	Nephrotoxins, renal artery stenosis

Renal

The most common cause of intrinsic renal damage is acute tubular necrosis (ATN), which can develop following a prolonged period of pre renal hypo-perfusion. In such a scenario, the renal tubules experience a reduction in blood flow from the glomerulus and, as a result of this, ischemic structural injury occurs.

Other intrinsic renal diseases are rare. However, it is extremely important for the foundation doctor to recognise these conditions in a timely manner as they often require specific management interventions by nephrologists. **These conditions should be considered after first ruling out both pre and post renal causes of acute kidney injury.** Examples of such intrinsic renal diseases include acute interstitial nephritis (affecting the interstitium), glomerulonephritis (affecting the glomerulus), and vasculitis (affecting blood vessels).

Post-Renal

Post-renal acute kidney injury refers to a deterioration in renal function caused by an obstruction anywhere along the urinary tract from the renal tubules to the urethra. Common scenarios, which may be encountered by foundation doctors, include ureteric/bladder calculi, benign prostatic hypertrophy and malignancy.

Sick Day Guidance

The majority of AKI begins in the community. Patients with CKD and patients receiving drugs that inhibit renal auto-regulation are at increased risk of AKI if they develop an illness associated with hypovolaemia and hypotension. There is a strong professional concensus that advice on sick day guidance should be given and this approach is advocated in the NICE AKI guideline (5) Such patients can be identified in Primary care, educated and issued with a Kidney Care card, detailing when and why to stop their medications, and for how long. These are typically available in the renal units in most hospitals. (7)

Figure 2A: Guidleines.

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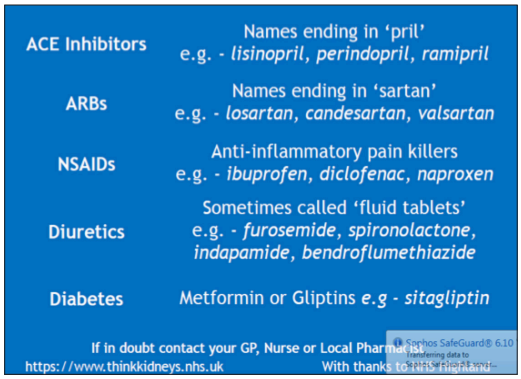

Figure 2B: Sick Day Rules Card.

However currently the evidence that supports this intervention in reducing overall patient harm is weak. Communicating the concept of a temporary cessation of medication to patient groups at risk of AKI has been found to be challenging. There is a strong concensus that such advice should be provided in a face to face consultation (7).

Assessment of AKI

Recognising high-risk patients, and identifying situations that predispose to AKI is a daily task for any Foundation Doctor. Thorough clinical assessment is paramount.

The initial history obtained from the patient can be used to identify any obvious acute events which may give rise to kidney injury e.g. infection, excessive losses, poor oral intake. A comprehensive drug history should be obtained, searching for serial offending medications such as diuretics, Angiotensin Converting Enzyme inhibitors (ACE-i) and Non-steroidal Anti-inflammatory drugs (NSAID's).

In addition, the foundation doctor should thoroughly assess the patients past medical history for evidence of diseases, which may cause a background of chronic kidney disease (CKD) e.g. vascular disease, diabetes mellitus and congestive heart failure.

Mean Arterial Pressure (MAP)
<65
Postural BP drop
Tachycardia
↓ Skin Turgor
Dry Mucous Membranes
Cold peripheries
Cap refill > 2s

Table 2: Signs of Hypovolaemia.

On examination, it is vital to assess the patients' fluid status promptly. AKI in the presence of hypotension is likely due to a pre-renal insult.

Along with hypotension, the patient may be septic and deterioration in other vital signs along with focal signs of infection in the chest or abdomen should be ruled out.

The presence of a palpable bladder on abdominal examination suggests a post renal obstruction.

A head to toe examination may reveal signs associated with vasculitis/ glomerulonephritis e.g. petechial rash, arthopathy.

Clinical assessment should also be directed to look for the complications of AKI, especially fluid overload.

↑BP
↑JVP
Tachycardia
↑RR
↓Oxygen Saturations

Table 3: Signs of Hypervolaemia.

Investigations

One useful tool in Northern Ireland to guide the set of investigations performed by the foundation doctor to seek the cause of AKI is the GAIN guidelines (8). There are also useful care bundles in place which can be found on the Think Kidneys Website (7).

Urea & Electrolytes (U&E):

Dictates the extent of AKI
A rise in creatinine will lag behind the development of an AKI
Equally a fall in creatinine will lag behind the recovery of renal function

Full Blood Picture (FBP)

A marked anaemia and thrombocytopenia can suggest sepsis or haemolytic uraemic syndrome (HUS).

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C-reactive protein (CRP)

↑ *White Cell Count and* ↑ *CRP indicate Sepsis,*
↑ *Platelet count and* ↑ *CRP indicate inflammation (vasculitis)*

Creatinine Kinase (CK)

Elevated in Rhabdomyolysis

Serum Calcium

Hypercalcaemia in the context of malignancy / myeloma

Urinary dipstick

Blood and protein suggests a glomerulonephritis/vasculitis.
Increased urinary specific gravity (>1.020) indicates a pre-renal cause of AKI.
Nitrites and leucocytes may suggest infection.

Renal Immunology Screen

Includes anti-glomerular basement membrane antibodies (anti-GBM) and anti-neutrophil cytoplasmic antibodies (ANCA). (Send this when no obvious cause for acute kidney injury,hypo-perfusion or obstruction)

Chest X-ray

May identify source of sepsis, signs of fluid

Ultrasound (US) Renal tracts

Indicates obstruction
Normal sized kidneys suggest AKI
Small Kidneys indicate CKD
Hydronephrosis with an empty bladder would illustrate an upper urinary tract obstruction.

CT Kidneys Ureter Bladder (KUB)

Confirm hydronephrosis
Localise the site of obstruction
In the setting of AKI a non-contrast CT is preferred unless there is clear indication to use contrast.

Prevention

Early recognition of risk factors for developing AKI is paramount to prevention. The first opportunity to identify the high-risk patients for junior doctors is typically during the clerking.

Some hospitals use pro forma to highlight patients most at risk of acute kidney injury who will require close monitoring throughout their stay in hospital. These Risk Assessments may help stratify those at increased risk to prompt early intervention and timely management of this costly condition. However at present they remain unvalidated. An example of a risk assessment is given below:

AKI RISK ASSESSMENT (All acute Medical Admissions > 65 Years)	
Risk Factor	**Score (circle each that applies)**
Co-Morbidity: ≥2 Of IHD, CHF, HTN, DM, COPD, Stroke/TIA, PVD	2
Baseline eGFR < 60 mls/min	2
Systolic BP < 100mm Hg	2
Receiving IV Fluids	2
Nephrotoxic Meds (ACE-I/ARB, NSAID's, diuretics)	1
****If ≥ 3 Complete MANAGEMENT IF IDENTIFIED AS AKI AT RISK****	☐

For the admitting doctor, it is important that in addition to recognising patients at risk of AKI, specific actions are undertaken to prevent either the development or worsening of AKI. An example of an action checklist is shown below:

MANAGEMENT IF IDENTIFIED AS AKI AT RISK	
Request daily U+E (for next 2 days)	☐
Ask nursing staff to record UO 6hrly & if <150ml/6hr alert medical staff	
Optimise BP and volume state (in context of patients normal BP)	
If BP < 120/80 Consider withholding BP meds (unless strongly indicated)	
Avoid nephrotoxins (unless strongly indicated)	

Management

Initial Management

The management of acute kidney injury should begin with a thorough ABCDE approach as often these are critically ill patients with multi-organ failure. Immediate priorities are correction of sepsis, hypoxia, treatment of life-threatening hyperkalaemia and restoration of blood pressure. Such patients require immediate access to senior help and HDU/ICU environment.

It is important to review all medicines and to stop those which interfere with renal auto-regulation e.g. NSAIDS, ACE inhibitors. The foundation doctor should also consider stopping medications which worsen hypotension including beta-blockers and diuretics and dose adjustment may be required for DOACs and some antibiotics.

PREVENTION & MANAGEMENT OF ACUTE KIDNEY INJURY (AKI)

C Nolan, C Brown, M Harty, J Harty

Pre-renal

· Treat dehydration: *In the case of shock/hypovolaemia, rapid fluid resuscitation with fluid boluses of crystalloid (0.9% saline or Hartmann's) is required to achieve a target MAP of ≥ 65 mmHg. NICE Guidelines (9) recommend a fluid bolus of 500ml of crystalloid over 15 mins repeated to an initial total of 2 litres if the patient still needs fluid resuscitation. If there are pre-existing signs of fluid overload (pulmonary oedema) or if fluid overload develops, fluid replacement should stop and senior help should be sought. Hartmann's should be avoided if serum potassium is >6mmol/L.*

· Optimise blood pressure: *If adequate blood pressure is not achieved or maintained, the foundation doctor should discuss with senior staff consideration of vasopressors in a critical care environment.*

· If despite correction of hydration and restoration of BP, the patient remains oliguric/anuric, progression to acute tubular necrosis must be considered. The patient should be protected from receiving excessive fluid. NICE guidelines (9) recommend prescribing less maintenance fluids for patients who have renal impairment and to seek senior help. One example of a fluid regime used in some renal centres is to continue IV fluids at a reduced rate of previous hours urine output + 30-50mls.

Renal

· If intrinsic renal disease other than ATN is suspected, the patient should be urgently referred to the nephrology service as specialised investigation (kidney biopsy) and treatments are often required.

- Vasculitis is managed with high dose steroids, cyclophosphamide, plasma exchange and Rituximab.
- Interstitial nephritis is managed with high dose steroids.
- HUS requires plasma exchange.

Post-renal

· When pre-renal causes have been excluded, post-renal causes should be at the forefront of the foundation doctors thinking as the second most common precipitant.
· An ultrasound of the renal tracts should be performed within 24hrs if no other cause of AKI is found hours (5).
· The typical patient is an elderly male with a history of Benign Prostatic Hypertrophy or prostate carcinoma. Here, in the presence of euvolaemia, AKI, and reduced urinary output, a bladder scan should be undertaken and a urinary catheter placed if there is evidence of urinary retention.
· If a high level of obstruction has been identified, refer to urology for further management.
· Where hydronephrosis is present despite an empty bladder the patient should be discussed urgently with the Radiology and Urology service as treatment may require either percutaneous nephrostomy drainage or retrograde insertion of ureteric stents.

When to refer to Nephrology

Less than 10% of patients require direct care by Nephrologists. Studies show that less than 4% of hospitalized patients with AKI require dialysis.

The Northern Ireland GAIN guidelines (8) recommend referral of the following groups of patients:

GAIN AKI referral guidelines.

Referral Indication	Comments
Complications of AKI requiring dialysis	Refractory hyperkalaemia, pulmonary oedema. Severe metabolic acidosis due to kidney failure (pH < 7.2). Uraemic pericarditis and encephalopathy.
Suspicion of a diagnosis that may require specialty Nephrology treatment	For example; vasculitis, myeloma, interstitial nephritis or glomerulonephritis.
AKI occurring in patients with CKD	Stage 4 or 5 CKD (eGFR ≤ 30 mL/min/1.73m²)
AKI occurring in renal transplant patients	Complex interactions with immunosuppressive medications. Infection can provoke acute rejection.

Case 1

65-year-old man was admitted with a 3 day history of vomiting and diarrhoea. His BP was 88mmHg/60bpm 96. He was clinically dry. His abdomen was distended.

WCC 15 x 10^9/l, CRP 300mg/L, Creatinine 340umol/L (baseline creatinine 110umol/L, 3 months previously)

Lactate 6mmol/L.

Urine dipstick: Glucose 1+.

PmHx: Ischaemic heart disease, Myocardial infarction, Type 2 Diabetes Mellitus, Hypertension, Hyperlipidaemia, Smoker.

Drug Hx: Bisoprolol, ramipril, atorvastatin, metformin, gliclazide, amlodipine. His nephrotoxic medication was stopped.

He was fluid resuscitated with boluses of 0.9% Saline to a maximum volume of 2L over 2hrs. He was commenced on Tazocin and Gentamicin for sepsis.

Despite this his BP remained low (SBP < 100mmHg) and he remained oliguric (urine output 5ml/hr). He was commenced on noradrenaline targeting a MAP of 65mmHg.

His abdominal signs and failure to respond to fluids prompted a CT abdomen, this showed a perforated diverticulum requiring urgent surgery. Post operatively, with vasopressor support his urinary output recovered to > 30ml/hr. His renal function recovered after 1 week, eGFR > 60.

PREVENTION & MANAGEMENT OF ACUTE KIDNEY INJURY (AKI)

C Nolan, C Brown, M Harty, J Harty

Learning Points

• Sick day rules: encourage patients to carry a 'Sick Day Rules Card' to remind them of the medications they should avoid when they are unwell i.e. vomiting, diarrhoea, feverish. This should be directly discussed with the patient and carers.

• Sepsis with severe AKI should prompt a vigorous search for a treatable source. The presence of AKI should not be a barrier to the use of contrast in this search but always with careful thought to avoiding if possible contrast nephropathy.

• Early correction of hypotension with both fluids and vasopressors is essential in preventing "downstream" ischaemia to the renal tubules (ATN), which will delay recovery in renal function.

Case 2

70-year-old man was admitted with a 2 week history of cough, and general malaise.

Hb 108g/L, WCC 12 x10^{9}L, Platelets 550, CRP 200mg/L, eGFR 30 (Baseline >60) Urinalysis: 4+ Blood, 2+ protein x10^{9}L.

CXR showed some minor bilateral patchy infiltrates.

US KUB: Swollen and echo bright kidneys, but no obstruction.

He was not hypotensive or hypoxic. Despite treating a presumed chest infection and provision of IV fluids his renal function continued to deteriorate over the next 48 hrs.

Following discussion with Nephrology an urgent vasculitis screen was sent. This showed a cANCA: 160 and PR3> 8.

CT Chest: opacities within both hemi-thoraces, consistent with presumed pulmonary haemorrhage. He was transferred to the care of the nephrologists.

He was commenced on treatment for cANCA vasculitis, consisting of pulse IV methylprednisolone, Pulse UV cyclophosphamide and plasma exchange.

A subsequent renal biopsy showed focal and segmental necrotizing glomerulonephritis with crescents corresponding with a small vessel vasculitis. His renal function returned to baseline over the next 3 months.

Learning Points

• Deteriorating renal function in the absence of hypotension and in the setting of blood and protein positive dipstick should raise the possibility of intrinsic renal disease, in particular an acute glomerulonephritis or vasculitis.

• Urgent request for a vasculitis screen (ANCA and anti GBM antibodies), should be undertaken as a positive result will fundamentally alter the patients management.

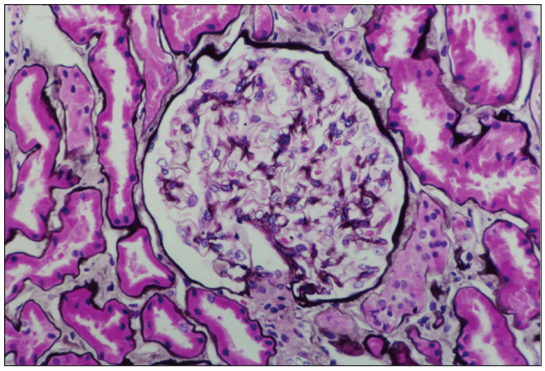

Figure 3A: Normal Glomerulus.

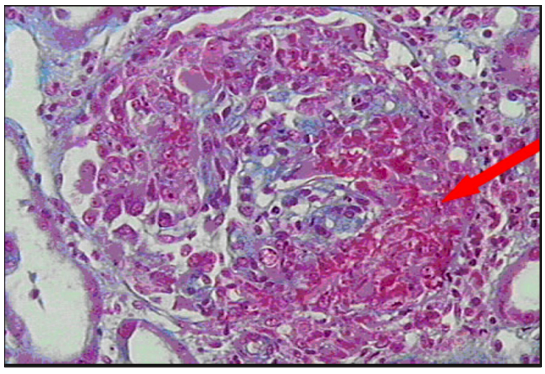

Fig 3B: Focal and Segmental Glomerulonephritis.

PREVENTION & MANAGEMENT OF ACUTE KIDNEY INJURY (AKI)

C Nolan, C Brown, M Harty, J Harty

Case 3

49-year-old female was admitted with vomiting and abdominal pain. She had noted RUQ pain for 3 months, which failed to resolve following a laparoscopic cholecystectomy.

eGFR 16, baseline of > 60 mls/min.

BP 180/90mmHg, no signs of significant dehydration.

She was on no potentially nephrotoxic medication.

Following IV fluids, her eGFR continued to deteriorate despite a urine output of 800mls/day. Urinalysis was negative for blood and protein.

Her US Abdomen showed mild bilateral hydronephrosis of questionable significance. The bladder was empty (catheterised). A non-contrast CT abdomen showed a similar mild-moderate bilateral hydronephrosis.

In light of her failure to improve renal function she had bilateral ureteric stents inserted which resulted in a marked diuresis (400mls/min) and a slight improvement in her GFR to 25. Her ureteric lumens were described as "tight" when advancing the stents. However, her renal function subsequently deteriorated with marked oliguria and she underwent bilateral nephrostomy insertion. Her eGFR has returned to >60 mls/min. A contrast CT scan has shown retroperitoneal fibrosis.

Learning Points

• In the absence of hypotension, nephrotoxic agents and a negative urine dipstick, urinary tract obstruction must be considered. Such patients may maintain a reasonable urine output in the initial phase of their ureteric obstruction.

• Bilateral hydronephrosis in the presence of an empty bladder, normal ureters and falling GFR, is suggestive of an obstruction between the level of the kidneys and the ureters.

• CT KUB will provide essential information, confirming both hydronephrosis and the site of obstruction.

• Rapid involvement of Radiology /Urology services is required where high level obstruction is identified/

Self Assessment

1. What is the target mean arterial pressure (MAP) in patients presenting with AKI of pre-renal aetiology?

2. What is the mechanism of ATN following a severe pre-renal AKI?

3. In patients presenting with AKI and evidence of dipstick blood and protein, what is the most important serological test to request?

4. Does the absence of oliguria (< 500mls/24hrs) despite hydronephrosis exclude urinary tract obstruction?

5. What is the next appropriate management step in patients who remain oliguric despite adequate and timely fluid resuscitation and restoration of blood pressure?

a. Continuation of IV fluid boluses

b. Commencement of vasopressors

c. IV loop diuretic

d. Restrictive fluid replacement

Answers

1. The target MAP is 65.

This level of Blood pressure should be adequate to maintain intra-glomerular pressure and maintain glomerular filtration in the presence of intact glomeruli and tubules. Older patients with established hypertension may require a higher MAP.

2. Prolonged hypotension from any cause will result in failure of glomerular auto-regulation and will lead to a fall in the intra-glomerular pressure.

This will cause a reduction in perfusion to the vasa-recta down stream from the glomeruli resulting in an ischaemic insult to the renal tubules.

3. This scenario may be consistent with an acute vasculitis, which is associated with the presence of Anti Neutrophil Cytoplasmic Auto-antibodies (ANCA) in over 90% of cases.

Anti-GBM antibodies should always be requested in tandem with ANCA as between 10 – 38% of patients with positive anti-GBM antibodies have positive ANCA serology.

PREVENTION & MANAGEMENT OF ACUTE KIDNEY INJURY (AKI)

C Nolan, C Brown, M Harty, J Harty

4. No – obstruction above the level of the bladder due to compression of the ureters in the retroperitoneal space can result in progressive AKI despite a urine output in excess of 500mls/24hs.

Where renal function fails to improve in the presence of bilateral hydronephrosis, measures to drain the renal pelvices should be undertaken (nephrostomy or retrograde ureteric stents).

5. D. This scenario is suggestive of ATN. In this case, further fluid challenges may result in volume overload and pulmonary oedema.

There is direct tubular damage compromising glomerular filtrate, which will not respond to a further increase in the MAP beyond 65mmHg using vasopressors. There is no evidence that IV diuretics result in a more rapid recovery in renal function in the euvolaemic patient. The correct answer is D, as having achieved clinical euvolaemia, further fluid replacement should match losses. NICE guidelines for IV fluids should be followed..

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BEHÇET'S SYNDROME

JE Peters, ASM Jawad

Abstract

Behçet's syndrome is a multisystem auto-inflammatory disease which causes oro-genital ulceration and other features including cutaneous, ocular, vascular, articular and neurological manifestations. It mainly affects young men of Mediterranean, Middle Eastern or Asian descent during their third or fourth decade. There is a strong genetic association with HLA-B51. Oral ulcers can usually be managed with topical treatment or colchicine. More serious manifestations such as eye disease, central nervous involvement or vasculitis require immunosuppressive therapy.

Case History

A 25 year-old Turkish male presents to the emergency department with a warm swollen right calf. He is diagnosed with a deep vein thrombosis (DVT) and anti-coagulated with warfarin. Two months later, he develops a painful red eye with blurring of vision. He is seen by an ophthalmologist who diagnoses pan-uveitis. On further enquiry he gives a long history of recurrent ulcers affecting his mouth and scrotum. A diagnosis of Behçet's syndrome is made. He is treated with azathioprine and oral corticosteroids. The warfarin is stopped.

What is Behçet's syndrome

Behçet's syndrome (pronounced "Beh-chets") is a rare inflammatory multi-system disease. It occurs primarily in patients from countries along the ancient Silk Route which extends from the Mediterranean Basin across Asia to Japan. Behçet's syndrome is most common in Turkey, where the prevalence is estimated to be between 110 and 420 per 100,000 (1,2). It is much rarer in the UK, with an estimated prevalence of between 0.64 and 5 per 100,000 (3,4).

The disease is characterised by vasculitis of veins and arteries of all sizes. It classically presents with orogenital ulceration, skin, eye, joint, brain and gut manifestations. A number of classification criteria exist to improve the accuracy of clinical phenotyping (Box 1). The 2014 International Criteria for Behçet's Disease are more sensitive than the 1990 International Study Group criteria (sensitivity 94.8% versus 85.0%, respectively), but are less specific (90.5% versus 96.0%) (5,6). Behçet's syndrome typically affects young men, although the male to female ratio differs between countries. Men are more frequently affected in the Middle East and Turkey, with male to female ratios 11:1 in Lebanon, 5.3:1 in Egypt, 3.8:1 in Israel, and 3.4:1 in Turkey. However, there is a slight female preponderance in Japan (male to female ratio 1:1.25) (7). Men tend to have more severe disease manifestations than women.

1990 International Study Group criteria for the diagnosis of Behçet's Syndrome

Recurrent oral ulceration (at least 3 times in one 12-month period) with at least two of:

- Typical eye lesions (uveitis, retinal vasculitis)
- Recurrent genital ulceration
- Typical skin lesions (erythema nodosum, pseudofolliculitis or papulopustular lesions, acneiform nodules in post-adolescent patients not on steroids)
- Positive pathergy test

2014 The International Criteria for Behçet's Disease

A score ≥4 indicates Behçet's

Sign/symptom	Points
Ocular lesions	*2*
Genital aphthosis	*2*
Oral aphthosis	*2*
Skin lesions	*1*
Neurological manifestations	*1*
Vascular manifestations	*1*
Positive pathergy test	*1**

**Pathergy test is optional and the primary scoring system does not include pathergy testing. However, where pathergy testing is conducted one extra point may be assigned for a positive result.*

Box 1: Classification criteria for Behçet's syndrome.

What causes Behçet's syndrome?

The aetiology is incompletely understood but multiple genetic factors play a role. *HLA B51* is the most significant genetic determinant of Behçet's syndrome, but genetic variants near other genes including *IL23R* and *IL10* also contribute to disease susceptibility (8,9). There is evidence to suggest that both the innate and adaptive immune systems are involved in pathogenesis, but the relative contribution of the latter remains controversial (10). Environmental factors are also important. There is circumstantial evidence to suggest that host commensal bacteria may trigger disease in a genetically susceptible individual.

BEHÇET'S SYNDROME

JE Peters, ASM Jawad

Clinical manifestations

Mucocutaneous

Oral ulceration is an almost universal feature of Behçet's syndrome. However, there are many other causes of oral ulceration (Table 1). Isolated oral ulceration without any of the other features described here is not Behçet's syndrome.

Differential diagnosis of oral ulceration:

- **Benign recurrent oral ulceration**
- **Lichen planus, mucous membrane pemphigoid**
- **Deficiencies (haematinics, B group vitamins)**
- **Gastrointestinal disease (coeliac, inflammatory bowel disease)**
- **Rheumatological (SLE, Reiter's, Behçet's)**
- **Infection (HSV, EBV, HIV)**
- **Neutropenia**
- **Squamous cell carcinoma**
- **Drugs e.g. methotrexate**

Table 1

Genital ulcers are commonly found on the scrotum in men and the vulva in women. The appearance of the ulcers is similar to the oral aphthae and they are usually painful. Scrotal scarring is rarely seen in conditions other than Behçet's. Ulceration of the penis is not typical of Behçet's and should raise suspicion of an alternative diagnosis such as genital herpes infection.

The skin is affected by papulopustular lesions in around 85% of patients. These are usually indistinguishable clinically and histologically from acne vulgaris. Erythema nodosum occurs in 50% of patients. Pathergy is an inappropriate excessive response to injury and is very suggestive of Behçet's. It can be assessed with skin prick testing (Figure 1). The frequency of the pathergy phenomenon in Behçet's syndrome patients varies considerably between cohorts. In Japan pathergy occurs in 44-75% of patients (3), but in the UK the pathergy test has low sensitivity (positive in ~10% of patients). Pathergy is thought to be a marker of disease severity and activity. The reaction is not confined to the skin, so caution should be taken with invasive procedures such as surgery, dentistry, and arterial angiograms (there is a risk of aneurysm formation at the puncture site). Patients may need peri-procedure steroid cover to suppress the pathergy reaction.

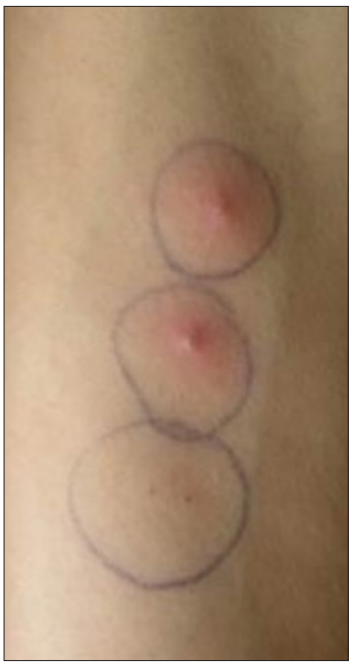

Figure 1: Skin prick testing demonstrating the pathergy reaction.

Ocular

Eye involvement is one of the most serious complications, and usually develops within 3 years of disease onset. It is more common and more severe in young men. It usually manifests as pan-uveitis (where there is inflammation in both the front and back of the eye). Retinal vein occlusion in the presence of inflammation should be considered due to Behçet's syndrome until proven otherwise. If uveitis is not identified promptly and treated appropriately, permanent visual loss can occur.

Vasculature

Behçet's syndrome can affect both arterial and venous vessels (variable vessel vasculitis), although it has a predilection for the latter. Vascular involvement affects 10–30% of patients, and is most frequently observed in young males. The most common manifestation is thrombophlebitis of the superficial or deep veins of the legs. Chronic recurrent deep vein thrombosis (DVT) of the legs may cause erythema, dermatitis, pigmentation or ulceration. Thrombosis leading to inferior or superior vena cava obstruction can occur (Figure 2). Dural sinus thrombosis results in symptoms and signs of raised intracranial pressure (headaches worse in the morning and when lying down, vomiting, and papilloedema). Axillary, brachial, hepatic and portal DVTs occur less frequently. The risk of thrombosis is greatest within two years of diagnosis, in patients less than 31 years of age, and in those with eye disease (11).

BEHÇET'S SYNDROME

JE Peters, ASM Jawad

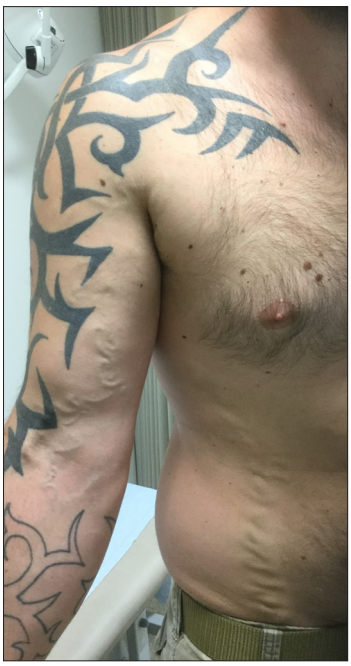

Figure 2: A patient with Behçet's syndrome with thromboses in the hepatic vein and the vena cava. Note the dilated superficial collateral veins on the arm and torso.

The pulmonary arteries share similar properties to veins. They are thin-walled structures which carry deoxygenated blood at low pressures compared to systemic arteries. In keeping with its predilection for veins, Behçet's syndrome may cause vasculitis of the pulmonary arteries resulting in either thrombosis or aneurysms. Both can present with haemoptysis. The combination of a DVT and a pulmonary artery aneurysm is known as the Hughes-Stovin syndrome. In this situation the clinician may be tricked into ascribing the haemoptysis to a pulmonary embolus and administering anticoagulants, which is likely to prove fatal.

Systemic arterial involvement is seen in 1.5-7.5%. Arteritis can affect anywhere in the arterial tree. It can result in aneurysmal dilatation or, less commonly, occlusive lesions. The abdominal aorta is the most frequently affected artery, followed by the iliac, femoral, popliteal, carotid and subclavian arteries in descending order.

Joints

Joint pain (arthralgia) is common. Frank arthritis (i.e. evidence of joint swelling) occurs in ~50%, typically involving the knees, ankles and wrists. Unlike rheumatoid arthritis, this is rarely erosive.

Neurological

Central nervous system involvement (CNS) occurs in 5-10% of patients (see Box 2).

- **Headache**
- **Venous sinus thrombosis**
- **Sterile meningoencephalitis**
- **Stroke syndromes (cortical, brainstem) - usually transient**
- **Inflammatory space-occupying lesion (may be mistaken for a neoplasm)**
- **Auditory and vestibular disturbance**
- **MRI brain may show subcortical small hyperintensities**

Box 2: Neurological manifestations of Behçet's syndrome.

Gastrointestinal

Ulceration can occur anywhere along the gastro-intestinal tract from mouth to anus. Symptoms include abdominal pain, weight loss and gastro-intestinal bleeding.

Differential diagnosis

Behçet's can be confused with Crohn's disease and multiple sclerosis (MS).

Distinguishing features:

1. Oral and gastrointestinal ulcers can occur in both Crohn's disease and Behçet's syndrome, but fistulas and perianal ulceration are strongly suggestive of Crohn's.

2. Uveitis in Crohn's disease is limited to the anterior chamber, whereas panuveitis is characteristic of Behçet's syndrome.

3. Optic neuritis is rare in Behçet's syndrome and suggests multiple sclerosis.

4. MRI lesions in multiple sclerosis are periventricular whereas in Behçet's syndrome they are situated in the basal ganglia and diencephalon.

BEHÇET'S SYNDROME

JE Peters, ASM Jawad

Investigations in Behçet's

The diagnosis of Behçet's syndrome is clinical. There is no diagnostic test. Investigations help exclude other causes. Findings in Behçet's syndrome may include:

- Modest ↑ WCC
- Modest ↑ CRP & ESR
- Modest ↑ immunoglobulins
- Usually no autoantibodies
- Complements normal
- *HLA B51* is not that helpful in clinical practice:
  - *20% prevalence in general population in Middle East*
  - *6% in Caucasians*
- Skin testing
  - *Pathergy is highly specific, but has a low sensitivity.*

Treatment

Pharmacological treatment needs to be tailored according to which organs are involved (Box 3). Oral ulcers can generally be managed with topical treatments.

Topical treatments

Triple mouth wash - betamethasone soluble tablets 0.5mg, doxycycline soluble tablets 100mg, nystatin oral suspension 100,000 units. Dissolve 1 tablet betamethasone and 1 tablet doxycycline in 10 ml water, and add 1 ml nystatin suspension. Rinse for 2 minutes before spitting out. Do not eat and drink for 1 hour after use.

Tip: *An asthma inhaler can be used to apply topical steroid to mouth ulcers.*

Corticosteroid ointments and creams (e.g. betamethasone) can be used for genital ulcers.

Steroid eye drops (e.g. prednisolone 1%, dexamethasone 0.1%) are useful for anterior uveitis, but penetrate the posterior segment poorly. Since there is frequently posterior uveitis in Behçet's syndrome, systemic immunosuppression is often required. Intra-ocular steroid injections can also be used for posterior uveitis. A short-acting mydriatic (e.g. tropicamide 1%) can prevent synechia formation and relieve pain from ciliary muscle spasm. Recently formed weak posterior adhesions can be broken up with intensive topical medications (e.g. atropine).

Box 3A: Drugs used to treat Behçet's disease.

Systemic treatments

Colchicine 1-2 mg/day is effective for arthritis, erythema nodosum, genital ulcers and oral ulcers in some patients. It may be more effective in females (12).

Corticosteroids are widely used, although erythema nodosum is the only manifestation for which there is controlled-trial evidence for their efficacy. Long-term steroid use results in serious morbidity including osteoporosis, hypertension, diabetes mellitus and immunosuppression. Every attempt should be made to use the lowest dose possible for the shortest time necessary.

Azathioprine 2.5 mg/kg daily is effective for both preserving vision in established eye disease and for preventing the development of eye disease (13, 14). It is also effective for thrombophlebitis, genital ulcers and arthritis. It reduces the incidence of venous thrombosis (14). Azathioprine has a slow onset of action.

Ciclosporine 3-5 mg/kg daily has a more rapid onset of action and is used in acute and severe ocular involvement.

Mycophenolate mofetil (MMF) has also been used.

Interferon may be used for eye and parenchymal CNS disease (15).

Thalidomide 100 mg/day is effective in mucocutaneous disease. It is rarely used because it may cause peripheral neuropathy. It can paradoxically exacerbate erythema nodosum (16).

Anti-TNF agents. Etanercept is effective in mucocutaneous disease and arthritis. Adalimumab and infliximab are effective in eye, central nervous system, vascular and gut disease.

Cyclophosphamide is used for life-threatening vasculitis.

Apremilast is an oral small-molecule drug phosphodiesterase-4 inhibitor which increases levels of intracellular cyclic AMP, particularly in immune cells, with consequent effects on several inflammatory pathways. It reduces pain and the number of ulcers at 12 weeks (17).

Alemtuzumab (Campath) is a monoclonal antibody directed against CD52 on the surface on lymphocytes and results in depletion of both B and T cells. Campath has been successfully used in Behçet's syndrome, but is reserved for severe and refractory cases (18, 19).

Box 3B: Drugs used to treat Behçet's disease.

BEHÇET'S SYNDROME

JE Peters, ASM Jawad

Potential future treatments

Tocilizumab is a monoclonal antibody targeting the IL6 receptor and is an effective treatment for rheumatoid arthritis. There are reports of the successful use of tocilizumab in Behçet's syndrome (20), but randomized clinical trials are required to evaluate the potential of this agent. Organising such trials is complex due to the rarity and heterogeneity of Behçet's syndrome.

Management of DVT in Behçet's syndrome

Deep vein thrombosis should be treated with immunosuppression to control the vessel wall inflammation. Decisions regarding anticoagulation pose significant management dilemmas in Behçet's (21). The EULAR 2008 guidelines do not recommend anticoagulation (22), although this recommendation does not have a strong evidence base.

A small non-randomised retrospective series found that patients managed with anticoagulation alone had a higher rate of re-thrombosis than those treated with either immunosuppression alone, or those treated with a combination of immunosuppression and anticoagulation (23). One argument against anticoagulation in Behçet's syndrome is that the reason for thrombosis is vessel wall inflammation, rather than increased coagulability as in most other causes of DVT (see Virchow's triad, Box 4). It is thought that DVTs in patients with Behçet's syndrome rarely embolise because they are firmly tethered to the inflamed vessel wall. Furthermore, patients with Behçet's are at higher risk of bleeding from aneurysms. However, in practice there may be arguments for anticoagulation; the diagnosis of Behçet's may not always be definite, there may coincidental reasons for thrombosis, and pulmonary emboli can occur (21). Our recommendation is to screen for aneurysms with non-invasive MR or CT angiography if considering anti-coagulation.

Three factors leading to thrombosis:

1. Hypercoagulability states (e.g. cancer, post-surgery, genetic mutations in clotting proteins)

2. Stasis (e.g. immobility following lower limb fracture)

3. Endothelial injury (e.g. vessel wall inflammation in Behçet's syndrome)

Box 4: Virchow's triad.

Prognosis

Behçet's syndrome tends to burn out with time. Serious morbidity such as visual loss or vascular involvement occurs early in the disease course, typically in young male patients. Unlike in classical systemic autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus, accelerated atherosclerosis does not occur in Behçet's syndrome.

Summary and take home messages

• Behçet's syndrome is a heterogeneous multisystem inflammatory disease which causes oro-genital ulceration and uveitis, mainly in young men.

• Ulcers causing scrotal scarring are virtually pathognomic for Behçet's syndrome.

• Eye involvement can lead to visual loss unless promptly treated.

• Retinal vein occlusion in the presence of inflammation should be considered due to Behçet's syndrome until proven otherwise.

• Vasculitis in Behçet's typically presents with venous thrombosis.

• Always consider a diagnosis of Behçet's in a young man with an unexplained superficial or deep venous thrombosis.

• Caution should be taken with surgery and invasive procedures such as angiography due to the pathergy reaction.

• Isolated oral ulceration without any of the other features described here is not Behçet's syndrome.

Multiple choice questions (single best answer)

Q1) In Behçet's syndrome:

1. Uveitis only affects the anterior chamber of the eye

2. Vasculitis predominantly affects the venous system

3. Deep vein thrombosis commonly embolise to the lung

4. Women are more commonly affected

5. Penile ulcers are typical

BEHÇET'S SYNDROME

JE Peters, ASM Jawad

Both anterior and posterior uveitis can occur in Behçet's syndrome; pan-uveitis where both anterior and posterior chambers of the eye are affected is typical. Vasculitis in Behçet's syndrome predominantly affects venules and veins, with arteries less frequently involved. Unlike typical deep vein thrombosis, deep vein thromboses in Behçet's syndrome are less likely to embolise because they are tethered to the inflamed wall of the vein. Behçet's syndrome predominantly affects young men. Ulcers occur on the scrotum not the penis.

Q2) In Behçet's syndrome:

1. HLA-B27 is strongly associated

2. Anti-nuclear antibodies are positive in most patients

3. Arthritis typically results in joint erosions

4. Aseptic meningitis can occur

5. Complement levels may be reduced

Behçet's syndrome is associated with HLA-B51. HLA-B27 is associated with ankylosing spondylitis. Anti-nuclear antibodies are positive in systemic lupus erythematosus (SLE), and not normally in Behçet's syndrome. The arthritis is Behçet's syndrome is typically non-erosive. Neurological manifestations including sterile meningitis can occur. Reduced complement levels are a feature of SLE and not Behçet's syndrome.

Q3) A patient with a known diagnosis of Behçet's syndrome presenting with haemoptysis out-of-hours to the emergency department:

1. Should be anticoagulated with low molecular weight heparin immediately

2. Needs an urgent CTPA even if there is no hypoxia or haemodynamic instability

3. Can be safely discharged if the haemoglobin is normal

4. Needs urgent bronchoscopy as the first-line investigation

5. Conventional angiography is the investigation of choice

Patients with Behçet's syndrome may develop haemoptysis either due to pulmonary emboli or pulmonary artery aneurysms. Anticoagulation in the context of the latter could prove fatal and should not be given until the presence of aneurysms has been excluded with an urgent CTPA. Given the need to distinguish pulmonary thrombosis from aneurysm, CTPA should be obtained urgently even if the patient is haemodynamically unstable. A normal haemoglobin does not exclude serious underlying pathology such as pulmonary artery aneurysm or PE, and so patients should not be discharged without imaging of the pulmonary vasculature. Bronchoscopy is not the first-line investigation. Invasive angiography is best avoided because of the risk of pathergy reactions at the site of arterial puncture. Non-invasive CT or MR angiography is preferable.

Q4) A 45 year old Caucasian woman presents with oral ulceration and abdominal symptoms

1. Behçet's syndrome is the most likely diagnosis

2. TTG testing is indicated

3. A negative pathergy test excludes a diagnosis of Behçet's syndrome

4. Normal upper GI endoscopy and colonoscopy rules out gastro-intestinal manifestations of Behçet's syndrome

5. She should be started on oral prednisolone

Behçet's disease typically affects young men with ancestry from countries along the old Silk Route. A middle-aged Caucasian woman presenting with oral ulcers is highly unlikely to have Behçet's. Coeliac disease can cause oral ulcers and abdominal symptoms and TTG testing should be performed.

Only 30-70% of Behçet's patients (depending on the population studied) have a positive pathergy test, and so a negative skin test does not exclude the diagnosis. Whilst in this case a diagnosis of Behçet's syndrome is highly unlikely, normal upper GI endoscopy and colonoscopy does not rule out gastro-intestinal manifestations of Behçet's. If clinical suspicion is high, investigation of the small bowel with, for example, capsule endoscopy, may be indicated. Prednisolone should not be started without establishing a diagnosis.

Q5) In the treatment of Behçet's syndrome:

1. Methotrexate is used for arthritis

2. Azathioprine is used for eye disease

3. Anti-TNF is first-line treatment

4. Posterior uveitis can be managed with steroid eye drops

5. DVT should be managed with anticoagulation without immunosuppression

BEHÇET'S SYNDROME

JE Peters, ASM Jawad

Methotrexate is used in rheumatoid arthritis. It can cause oral ulceration and is not recommended in Behçet's syndrome. Azathioprine is used for ocular manifestations. Anti-TNF is effective, but in the UK is reserved for severe or refractory cases. Steroid eye drops can be used for anterior uveitis, but posterior uveitis requires systemic therapy or intra-ocular steroid injection. A small retrospective study found that DVT recurrence was higher in those treated with warfarin without immunosuppression. EULAR guidelines recommend the use of immunosuppression in Behçet's syndrome patients with thrombosis.

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MYELOFIBROSIS SECONDARY TO SYSTEMIC LUPUS ERYTHREMATOUS

S Pathare

Abstract

We report a rare case of myelofibrosis secondary to Systemic Lupus Erythrematous (SLE), in a 35 year old lady, who presented with a three week history of fever, night sweats, a non productive cough and pancytopaenia. Treatment with immunosuppressive therapy led to complete regeneration of the bone marrow and improved haematological and clinical status.

Case Report

A 35-year old Nepali lady, with known SLE as per the ACR criteria (diagnosed in 2004 with a positive ANA 1:640 and DsDNA) on hydroxychloroquine was admitted in 2006 with a 3 week history of fever, night sweats and a non productive cough. She gave no history of weight loss, but had traveled to Nepal, 2 months prior to admission. On examination she was pyrexial with a soft pan systolic murmur and raised erythrematous papules were noted across palms of both her hands. Respiratory, abdominal, neurological and musculo-skeletal examination were unremarkable.

On admission, her full blood count showed a pancytopenia (Hb 8.7 g/dL, platelet count 80x109/L, and WBC of 2.5x10^9/L). She had elevated CRP (29 mg/L) and ESR (119 mm/1st hr). Ferritin was 695 µg/L. C3 was low, 0.14 g/L (0.75-1.65) and C4 levels were also low- 0.04 g/L (0.14-0.54). ANA titer was 1:640, ds DNA 198.4, with positive RNP, Ro, and Smith antibodies. However lupus anticoagulant was negative and IgG and IgM anticardiolipin antibodies were weakly positive.

During her admission she had a generalized tonic-clonic seizure. CT and MRI of the brain were unremarkable and her CSF report showed a raised protein of 1.75 g/L (0.2-0.4), a low glucose value of 2.7 mmol/L (paired plasma glucose 5.7 mmol/L). CSF cultures, including a test for acid fast bacilli, showed no growth and hence the seizure was deemed secondary to inflammatory meningitis.

Urinalysis showed microscopic haematuria and proteinura (0.31 grams in a 24 hour collection) and coliforms were grown on urine culture which was treated appropriately with antibiotics. Multiple blood and sputum cultures showed no growth. EBV, parvovirus B19, Chlamydia, Coxiella, enterovirus, HIV 1 and 2 antibodies were not detected. Blood film was negative for malarial parasites.

A trans-oesophageal echocardiogram did not show any valvular abnormality or lesions. Hence the soft systolic murmur was felt to be a flow murmur. The palmar rash was felt to be cutaneous manifestation of SLE (biopsy was done as rash improved with treatment). Initial chest x-ray revealed prominent hilar lymph nodes, and a follow up HRCT of the thorax showed multiple axillary and mediastinal lymph node enlargement with a small left pleural effusion. Ultrasound of abdomen was unremarkable.

As a result of the findings and recent travel, anti-tuberculous therapy was started empirically. Bronchial lavage and sputum were then cultured and an axillary lymph node biopsy was performed. Cultures showed no mycobacterium growth and biopsy revealed non-specific reactive hyperplasia. A bone marrow biopsy was eventually performed which showed disorganized marrow with increased dysplastic megakaryocytes along with fibrosis and reticulin formation consistent with myelofibrosis.

Our initial suspicion of subacute bacterial endocarditis and tuberculosis was ruled out by the negative investigations and anti-tuberculosis therapy was discontinued. In view of her pancytopenia and marrow biopsy, a diagnosis of myelofibrosis was made and she was commenced on prednisolone 50 mg daily. She was also commenced on mycophenolate mofetil on a gradual increasing regime upto 1g twice daily.

On discharge her blood count abnormalities were improving on mycophenolate and a reducing steroid regime and she was asymptomatic.

Blood Tests	Before hospital admission 16/09/2005	Admission with Myelofibrosis		28/4/2006 During treatment	08/01/2007 1 year after treatment
		28/02/06	16/03/06		
Haemoglobin (g/dL)	11.4	9.9	8.7	11.3	12.5
White-cell count (x10^9/L)	4.7	2.1	2.5	5.1	4.1
Neutrophils (x10^9/L)	3.0	1.9	1.9	3.6	2.5
Lymphocytes (x10^9/L)	1.2	0.4	0.4	1.2	1.1
Platelets (x10^9/L)	199	94	80	300	305

Table 1

Discussion

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disorder associated with microvascular inflammation with the generation of auto-antibodies. Haematological abnormalities are common in SLE (2). Anaemia is the commonest abnormality occurring in more than 50% of cases, and is usually due to anaemia of chronic disease although autoimmune haemolytic anaemia occurs in 15% of cases. Leucopenia is also common as a result of anti-leucocyte antibodies. Pancytopenia however is an uncommon finding in these patients (1, 3).

MYELOFIBROSIS SECONDARY TO SYSTEMIC LUPUS ERYTHREMATOUS

S Pathare

Anaemia
Leucopenia
Neutropenia
Lymphopenia
Thrombocytopenia
Autoimmune haemolytic anaemia
Thrombotic thrombocytopenic purpura
Myelofibrosis

Table 2: Haematological manifestations of SLE.

Myelofibrosis is a rare, but a well recognised complication of SLE, which usually develops within a period of three months to 9 years from the onset of SLE. Myelofibrosis is characterised by an increased deposition of collagen, fibronectin and laminin within the bone marrow. (4, 7) Blood smear in Myelofibrosis will be abnormal with low cell counts, tear drop red cells, nucleated red blood cells and immature white blood cells and increased count of basophils may be seen.

It is often associated with various malignant diseases, as well as chronic infections, especially HIV and tuberculosis (6-8). Leishmaniasis, which is prevalent in Nepal, may be associated with pancytopenia and mimic clinical features of a flare of SLE (9).

Rarely myelofibrosis has been linked with autoimmune diseases such as SLE and systemic sclerosis (3, 4, 6, and 8). As it is a rare association, diagnosis may be difficult at times in these patients due to varied clinical presentation. As a result, a thorough diagnostic work-up is usually performed before a diagnosis of myelofibrosis is made in patients with SLE.

Primary Myelofibrosis
Chronic Myelogenous Leukemia
Hairy cell Leukemia
Essential thrombocytosis
Myelodysplastic syndrome
Polycythemia Vera
Granulomatous disorders– Histoplasmosis, Tuberculosis

Table 3: Differential diagnosis of Myelofibrosis.

In SLE the pathological mechanism of myelofibrosis remains unknown, though it may be an extension of the basic lesion, vasculitis, within the bone marrow as the target organ, as its improvement with autoimmune disease control supports this possibility (5).

Paquette et al. reported a series of eight patients and a review of nine other patients having myelofibrosis with systemic lupus erythematosus; twelve of the 17 were steroid responsive. Blood count abnormalities resolved with steroid treatment in 70-90% of patients with myelofibrosis and autoimmune disease and 30% had regression of bone marrow fibrosis (8, 10). Intravenous immunoglobulin therapy and the use of colony stimulating factors have also been used in extreme cases of bone marrow suppression in SLE (11,12).

Conclusion

SLE is a multi-system disease with varied clinical presentation. Myelofibrosis is a rare but well known association which can present as pyrexia of unknown origin in these patients. It is therefore important to include this in the differential diagnosis for patients with SLE and pancytopenia.

Multiple choice questions

1. Which of the following may cause haematological abnormalities in Systemic lupus erythematosus?

a. Active disease affecting bone marrow

b. Immunosuppressive drugs like Azathioprine

c. Infection

d. All of the above.

2. Which of the following infections typically results in pancytopenia?

a. Influenza

b. Streptococcus viridans

c. Leishmaniasis

d. Chlamydia trachomatis

MYELOFIBROSIS SECONDARY TO SYSTEMIC LUPUS ERYTHREMATOUS

S Pathare

3. Myelofibrosis is a rare manifestation of SLE, which of the following should be considered in differential diagnosis of Myelofibrosis?

a. Tuberculosis

b. Polycythemia Vera

c. Myelodysplastic syndrome

d. All of the above

4. Which of the following is not seen on peripheral blood smear in myelofibrosis?

a. Tear–drop red blood cells

b. Nucleated red blood cells

c. Increased basophil count

d. Sickle cells

5. Which of the following medication is commonly used to treat Pancytopenia in SLE?

a. Oral Prednisolone

b. IV Methylprednisolone

c. Intravenous immunoglobulins

d. All of above

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SYSTEMIC SCLEROSIS: MULTIPLE ORGAN PRESENTATIONS & MANAGEMENT

CM Lwin, CJ Edwards

Abstract

Systemic sclerosis (Scleroderma) is a multisystem disease that typically causes thickening of skin in the fingers but can lead to interstitial lung disease, pulmonary hypertension, various forms of gastrointestinal conditions, cardiac involvement and renal crisis. Musculoskeletal and vascular presentations are common and may precede the onset of organ involvement by many years.

This article describes three cases with different presentations of systemic sclerosis. The first case developed pulmonary fibrosis and pulmonary hypertension leading to cor-pulmonalae. The second case presented with myocarditis and cardiac fibrosis complicated by sustained ventricular tachycardia that needed implantation of a cardioverter defibrillator device.

The third lady developed malabsorption as a result of intestinal failure 17 years after the diagnosis of systemic sclerosis and needed total parenteral nutrition. The manifestations of systemic sclerosis are briefly described. The current treatment approach including general measures and that needed for specific organ involvement is described.

Case History 1

A 48 year-old lady presented with progressive breathlessness on exertion for one year. She had also developed bilateral pedal oedema over the past few months. Her exercise tolerance was reduced to 100 meters. She complained of a non-productive cough for many months but there was neither chest pain nor syncopal attack.

There was a background history of systemic sclerosis that began at the age of 38 years with digital calcinosis and Raynaud's phenomenon and a anti-nuclear and anti-centromere antibodies. Microstomia had also progressively developed over the years.

On examination, she appeared breathless at rest. There was no clubbing. There were cutaneous signs of scleroderma with sub-cutaneous calcinosis at the tip of left middle finger, distal sclerodactyly below the proximal inter-phalangial joint and multiple telangiectasia on her hands and face. Heart sounds were dual with a split second sound and loud pulmonary component. Her JVP was elevated. There were a few end-inspiratory bibasal crackles in both lungs and mild peripheral oedema.

Oxygen saturations at rest on room air were 88-90%. A six-minute walk test demonstrated she walked for 100 metres with an oxygen saturation nadir of 79%.

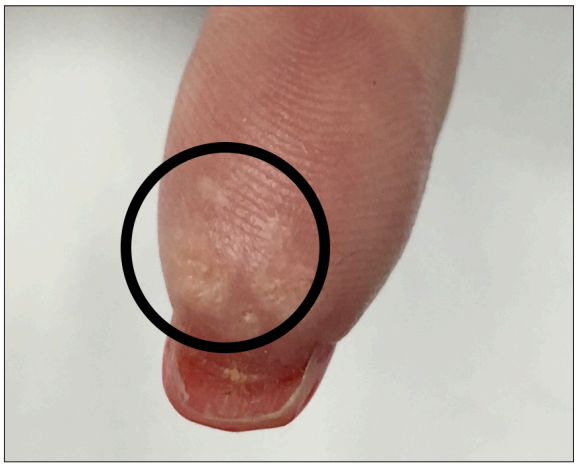

Figure 1: Sub-cutaneous calcinosis at the tip of left middle finger (circled).

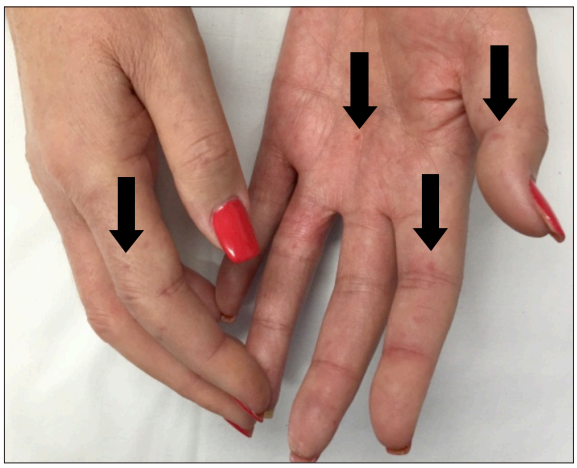

Figure 2: Small telangiectasia on hands (see arrows).

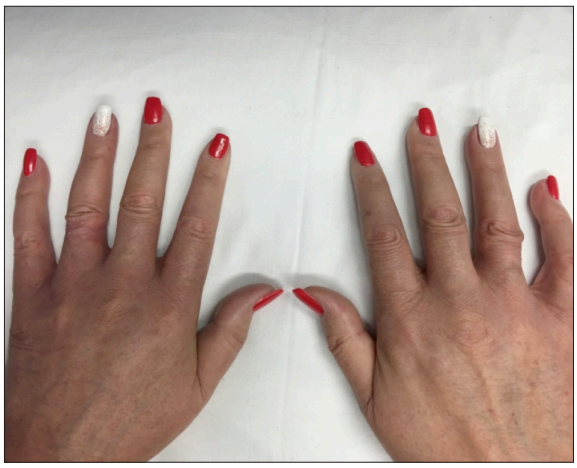

Figure 3: Mild sclerodactyly distal to proximal inter-phalangeal joints.

SYSTEMIC SCLEROSIS: MULTIPLE ORGAN PRESENTATIONS & MANAGEMENT

CM Lwin, CJ Edwards

The Investigations

Capillary Blood Gas on Oxygen 3L/min:

pH	*7.47 (7.35 – 7.45) High*
pCO_2	*5.43 (4.27 – 6.4 kPa)*
pO_2	*10.52 (11 – 14.4 kPa) Low*
$cHCO_3$	*29.7 (21 – 28 mmol/L) High*
BE	*6.0 (-2.0 – 2.0 mmol/L) High*
cSO_2	*96.3% (95 – 99%)*

The blood gas analysis demonstrated a pattern of respiratory alkalosis, which is not uncommon in pulmonary fibrosis.

Pulmonary function demonstrated a restrictive picture with an FEV1/FVC of 1.07/1.31. This gives an FEV1 37% and FVC 36% predicted. Her gas transfer (TLCO) was markedly reduced at 28% predicted and kCO was 64%.

Chest x ray demonstrated increased pulmonary interstitial markings and cardiomegaly.

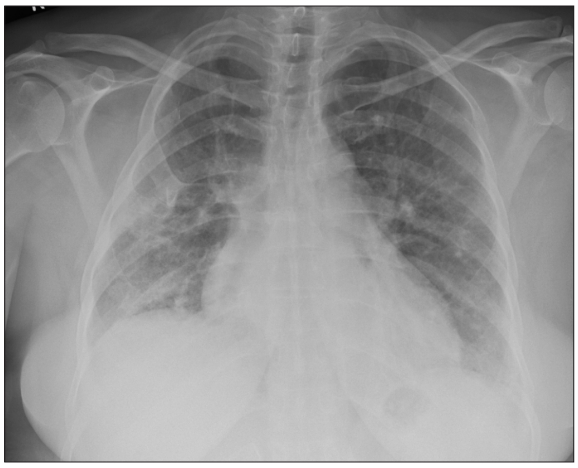

Figure 4: Chest x ray showing increased interstitial markings (mainly in the lung bases) and cardiomegaly.

High resolution CT (HRCT) scan of the chest showed lower zone changes typical of non-specific interstitial pneumonia (NSIP) showing ground glass with fine reticulations predominantly within the bases.

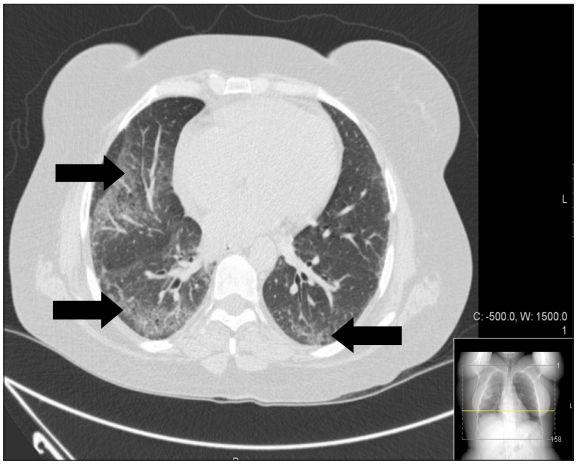

Figure 5: HRCT Chest showing interstitial changes (arrowed).

24-hour tape demonstrated sinus rhythm only.

The echocardiogram reported a severely dilated right ventricle with severe impairment overall and severe tricuspid regurgitation. Estimated right ventricular systolic pressure was 92-103mmHg + right atrial pressure 10-15mmHg. Right atrium was severely dilated. Left ventricle had a small cavity size with preserved function. Visual ejection fraction was 55-60% with grade 1 diastolic dysfunction.

Right heart catherization was reported to show severe pulmonary hypertension with low pulmonary capillary wedge pressure. There was a mean right atrial pressure of 6 mmHg and 73% saturation; right ventricle pressure of 107/22, mean 35 mmHg, pulmonary artery pressure 92/33 mean 57mmHg and 77% saturations, pulmonary capillary wedge pressure 7 mmHg, cardiac output 5.1L/min, cardiac index 2.4, systemic vascular resistance 1693 (800 - 1200 dynes · sec/cm^5), pulmonary vascular resistance 817(<250 dynes · sec/cm^5).

She was treated with Mycophenolate Mofetil, a course of intravenous Cyclophosphosphamide 500 mg every 2 weeks on 3 occasions, Prednisolone 15 mg per day on a tapering regime, diuretics, Rivaroxaban and Bosentan that was later switched to Ambrisentan and then to Macitentan.

To summarize, this patient with systemic sclerosis presented with interstitial lung disease and pulmonary hypertension complicated by right heart failure.

SYSTEMIC SCLEROSIS: MULTIPLE ORGAN PRESENTATIONS & MANAGEMENT

CM Lwin, CJ Edwards

Case History 2

A 45-year-old gentleman presented with progressive weakness of his proximal muscles and difficulty in swallowing. This was preceded by a history of Raynaud's phenomenon for 2 years. Examination revealed sclerodactyly affecting his hands up to forearm and microstomia. CK was raised to more than 12000 U/L (normal 40 - 320).

Although he did not have cardiac symptoms, the ECG was abnormal showing marked first-degree heart block with a PR interval of 255 ms. and an atypical left bundle branch block pattern with QRS duration of 148 ms. He was positive for anti- signal recognition particle (anti-SRP) antibody which is associated with connective tissue diseases and particularly severe inflammatory myositis.

Echocardiogram showed a dilated left ventricle at 6.8 cm with general dyskinetic wall motion. The ejection fraction was approximately 45 to 50%. Cardiac MRI showed mild left ventricular impairment but with quite extensive myocardial scar and oedema involving the papillary muscles in the right ventricular free wall and septum. There was also scarring over the inferolateral wall. Cardiac catheter showed normal coronary arteries. His troponin was raised at 1.45 micrograms/L (less than 0.07).

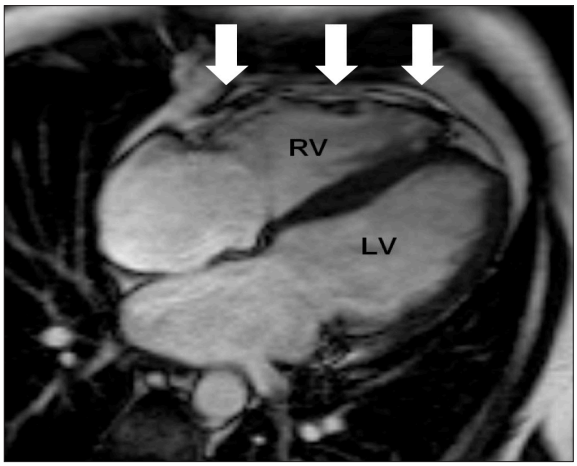

Figure 6: Cardiac MRI showing extensive myocardial scar and oedema in right ventricular wall (arrowed).

He was diagnosed as having systemic sclerosis/myositis overlap with myocarditis and cardiomyopathy. He was treated initially with Methotrexate 15 mg per week, Rituximab 1 gram iv at day 0 and 14 to induce remission and Prednisolone starting at 30 mg per day with a tapering regime. Two years later, he developed sustained ventricular tachycardia that needed an implantable cardioverter defibrillator device.

Case History 3

A lady was diagnosed as having systemic sclerosis at the age of 43 years when she presented with Raynaud's phenomenon, skin tightening and positive anti-centromere antibodies. Seventeen years later, at the age of 60, she started to develop abdominal distension, recurrent small bowel bacterial over-growth and alternating diarrhoea and constipation. The disease course was complicated by development of intestinal pneumatosis and recurrent spontaneous pneumoperitonium that needed needle aspiration.

The CT of the abdomen demonstrated dilated bowel loops with intestinal pneumatosis and pneumoperitoneum.

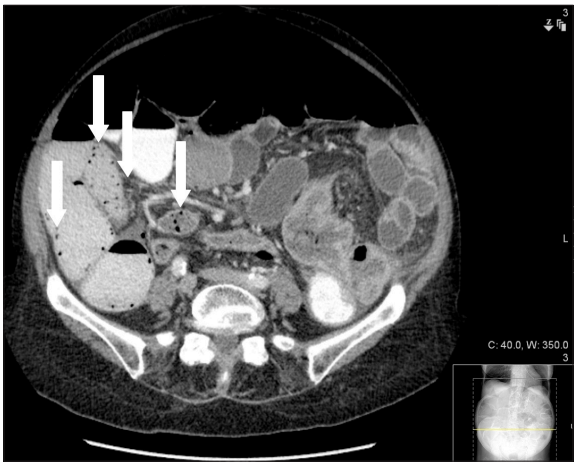

Figure 7: CT Abdomen showing multiple pneumatosis in intestinal walls (Arrows – intestinal pneumatosis).

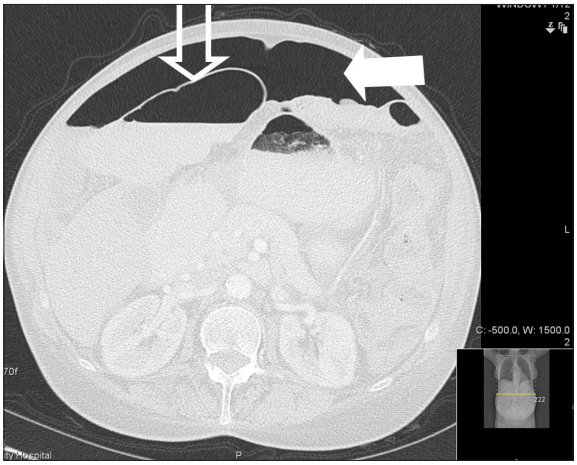

Figure 8: CT Abdomen showing dilated intestine (open arrow) and pneumoperitoneum (closed arrow).

SYSTEMIC SCLEROSIS: MULTIPLE ORGAN PRESENTATIONS & MANAGEMENT

CM Lwin, CJ Edwards

Chest x ray did not show lung or cardiac pathology but confirmed the presence of dilated bowel loops.

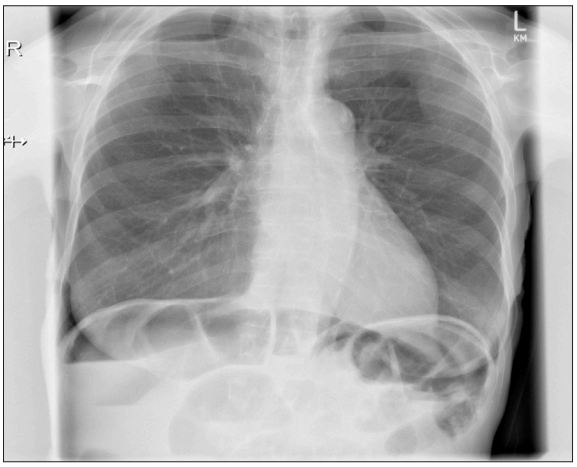

Figure 9: Chest x ray showing dilated bowel loops.

She struggled with diarrhoea, weight loss and malabsorption. Then she went on to develop generalized oedema due to low serum albumin. She has also developed osteoporosis and anaemia. She had received total parenteral nutrition intermittently.

She had been on intermittent rotating courses of antibiotic therapy that includes Co-amoxiclav, Metronidazole and Cephelexin for the treatment of bacterial overgrowth. She has not been started on any disease modifying medication. This case represents a case of systemic sclerosis with intestinal failure.

Discussion

Systemic sclerosis (scleroderma) is a chronic disorder characterized by diffuse fibrosis of the skin and internal organs. Symptoms usually appear in the third to fifth decades, and women are affected two to three times as frequently as men. It can present in a number of organ systems and diagnosis is often delayed.

Two forms of scleroderma are generally recognized: limited cutaneous (in 80% of patients) and diffuse cutaneous (in 20%). Overlap syndromes may also be seen in association with other autoimmune conditions such as polymyositis. Sine Scleroderma is a rare condition in which there are internal organ complications without classical features of the disease.

Autoantibodies are detected in 95% of patients at the diagnosis. 85-99% of patients have a positive anti-nuclear antibody. Anti-centromere antibodies are found in 20 – 40 % of the patients and majority of them have the limited cutaneous type. This form is associated with higher risk of pulmonary hypertension and gastrointestinal symptoms. Anti- Scl 70 which is also known as anti-topoisomerase I is detected in 15 - 20% of the patients and is mostly associated with diffuse cutaneous disease and pulmonary fibrosis. Anti-Scl 70 and anti-centromere antibodies are mutually exclusive.

Other less prevalent auto-antibodies are anti-RNP antibody, anti-polymyositis/scleroderma (anti-PM/Scl) antibody, anti-Ro antibody, anti-phospholipid antibodies,anti-fibrillin-1 antibody, anti-U3-RNP antibody, anti-RNA polymerase antibody and anti-U1-RNP antibody.

The disease involves skin and musculoskeletal system in many cases. When there is internal organ involvement, it can progress to organ or multi-organ end stage failure. The following describes the manifestations in various organ systems.

Vascular Manifestations

Raynaud's phenomenon often represents the earliest and most common feature. Fingertip ulcers and digital pulp atrophy may follow Raynaud's phenomenon and chronic digital ischaemia. Although Raynaud's phenomenon is common in the general population, when it presents later in adult life or with ulceration, it warrants investigations for an autoimmune condition such as scleroderma. Nailfold capillaroscopy may differentiate between primary and secondary Raynaud's phenomenon. Digital gangrene is a rare but is a severe manifestation in a few cases.

Skin and Musculoskeletal Manifestations

Arthralgia is among the most common symptoms. Synovitis is found in approximately 16% of the patients affected by this condition. Tendon friction rubs have been detected in up to 11%.

Cutaneous disease can manifest initially as non- pitting subcutaneous oedema. With time the skin becomes thickened and hidebound, with loss of normal folds. Small telangiectasia can be seen on the face, hands and chest in long standing disease. Pigmentation and depigmentation are characteristic. Subcutaneous calcification may be seen in fingertips, feet, knees and legs and predominates at sites of repetitive stress or pressure.

Osseous resorption and acro-osteolysis occurs in about 20% of the patients. Myopathy can be mild, non-progressive with minor proximal weakness and normal or slight elevation of creatine kinase. This form of mild myopathy is common and seen on 80% of the patients. The overlap between inflammatory myopathy and systemic sclerosis is less frequent with a prevalence of about 5%.

Gastrointestinal Involvement

Approximately 90% of patients suffer from some gastrointestinal symptoms. Dysphagia, gastroparesis and symptoms of reflux due to oesophageal dysfunction are common and result from abnormalities in motility and later from fibrosis. Watermelon stomach or gastric antral vascular ectasia is a rare gastric complication. Fibrosis and atrophy of the gastrointestinal tract causes hypomotility, gut dilatation, strictures, intestinal pneumatosis, bacterial overgrowth and malabsorption. Large- mouthed diverticuli may occur in the jejunum, ileum, and colon.

SYSTEMIC SCLEROSIS: MULTIPLE ORGAN PRESENTATIONS & MANAGEMENT

CM Lwin, CJ Edwards

Lung Involvement

Lung involvement is a leading cause of morbidity and mortality. Non-specific interstitial pneumonia (NSIP) is the most common histological pattern although usual interstitial pneumonia (UIP) can be present.

Pulmonary Arterial Hypertension (PAH)

This represents a serious and life-threatening condition and is found in 9% of the patients. It tends to occur late, often in the second decade of the disease. It can also develop secondary to interstitial lung disease. The diagnosis of PAH is often missed until it is advanced. Screening for this with an annual trans-thoracic echocardiogram is recommended.

Cardiac Involvement

The heart is often sub-clinically affected by fibrosis involving both the myocardium and the conducting system in a patchy distribution.

Kidney Involvement

Kidney involvement can cause scleroderma renal crisis characterized by abrupt onset of high blood pressure and kidney failure associated with micro-angiopathic haemolytic anaemia, thrombocytopenia and oliguria. This can be aggravated by high-dose corticosteroid use.

Management

Overall Treatment

There is no therapy proven to prevent disease progression. However, Methotrexate has shown some beneficial effects on skin thickening and intravenous Cyclophosphamide in lung involvement. For severe cases, intense immunosuppression followed by autologous stem cell transplantation has been shown to improve skin scores and stabilize lung function and pulmonary pressure at the cost of 17% of initial procedure related mortality.

Digital Vasculopathy

Raynaud's symptoms are initially managed with standard medical treatment including calcium channel blockers, ACE inhibitors, Losartan and Fluoxetine. When there is associated digital ulceration, a phosphodiesterase inhibitor, Sildenafil 25mg three times per day (tds) increasing to 50mg tds can be successful.

Intravenous prostanoids (usually Iloprost) are considered if Sildenafil fails to control the progression. It is administered in courses, up to a frequency of once every 6-8 weeks. Combination treatment with intravenous prostanoid and Sildenafil is effective in some patients who do not respond to either treatment alone. A dual endothelin receptor antagonist Bosentan can be considered after failure of the above treatments. (1)

Skin Involvement

Methotrexate and Mycophenolate mofetil are used for treatment of skin manifestations. (2)

Interstitial Lung Disease

Intravenous Cyclophosphamide has been shown to improve lung function tests, dyspnoea score and quality of life. (3)

Pulmonary Arterial Hypertension

a. Conventional Medical Therapies

Calcium Channel Blockers help decrease blood pressure although are only appropriate for a few patients demonstrating a favourable response to vasodilator testing at the time of heart catheterization.

Digoxin may be used to improve contractile function.

Diuretics are particularly useful for patients with fluid overload.

Warfarin helps prevent thrombosis in the pulmonary circulation.

Ambulatory oxygen may be considered when there is evidence of symptomatic benefit and correctable desaturation on exercise.

b. Endothelin Receptor Antagonists

Bosentan improves dyspnoea and functional class. It has beneficial effects on some haemodynamic measures in pulmonary arterial hypertension (PAH). It is strongly considered for treatment of PAH. (4, 5)

Ambrisentan and Macitentan are newer medications, which have also proven to be beneficial in the treatment of PAH. Liver function should be closely monitored in patients receiving this class of medications.

c. Prostanoids

Iloprost and Epoprostanol are intravenous forms that can be used as continuous infusions. These have shown beneficial haemodynamic effects and recommended for severe cases of PAH. (6)

Treprostinil can be administered either intravenously or subcutaneously.

Ventavis is an inhaled solution form of Iloprost indicated for treating PAH.

Beraprost is an orally active prostacyclin analogue. It has shown an improvement in exercise capacity that unfortunately persists only up to 3–6 months.

SYSTEMIC SCLEROSIS: MULTIPLE ORGAN PRESENTATIONS & MANAGEMENT

CM Lwin, CJ Edwards

d. Phosphodiesterase Inhibitors

Sildenafil can be used for the treatment of PAH patients in WHO functional classes II, III and IV. It has been shown to significantly improve the 6-minute walk test result, functional class and haemodynamics over a 12-week period. (7)

At present, sildenafil should be considered in patients in whom Bosentan has been ineffective, or cannot be used for safety reasons.

Tadanafil is also recommended for the treatment of PAH.

Scleroderma renal crisis

Angiotensin-converting enzyme (ACE) inhibitors should be used in the treatment of scleroderma renal crisis although it is still not known if they can prevent this complication. Low dose ACE inhibitors are often used in patients to reduce the future risks of this complication. As corticosteroids can be associated with precipitation of renal crisis, doses of Prednisolone more than 20 mg daily are best avoided.

Gastrointestinal Involvement

Modification of life style is the sensible approach to control symptoms of reflux. Promotility agents, H2 receptor blockers and proton pump inhibitors are prescribed to treat reflux and oesophageal strictures. Broad-spectrum antibiotics are used to treat bacterial overgrowth caused by slow transit. Treatment with Octreotide can stimulate bowel function in early phase.

Best of Five Questions and Answers

1. What autoantibodies are commonly associated with systemic sclerosis?

a. Anti-CCP antibody

b. Anti-Ach receptor antibody

c. Anti- Scl 70 antibody

d. Anti- RNP antibody

e. Anti- Histone antibody

2. What feature is not usually seen is systemic sclerosis?

a. Sub-cutaneous calcinosis

b. Pulp atrophy

c. Microstomia

d. Telangiectasia

e. Nail pitting

3. What is the major cause of mortality in systemic sclerosis?

a. Myocardial infarction

b. Pulmonary hypertension

c. Interstitial lung disease

d. Renal Failure

e. Hepatic Failure

4. What medication is not used in the treatment of digital ulceration secondary to Raynaud's phenomenon?

a. Bosentan

b. Iloprost

c. Sildenafil

d. Bisoprolol

e. Nifedipine

5. All of the following features about generalised systemic sclerosis are true except

a. Raynaud's phenomenon can be seen years before skin changes.

b. Immunosuppression can reverse intestinal involvement.

c. Hyperpigmentation and hypopigmentation often co-exist.

d. Liver failure is reported in patients receiving endothelin antagonists.

e. Neurological complications are rare.

SYSTEMIC SCLEROSIS: MULTIPLE ORGAN PRESENTATIONS & MANAGEMENT

CM Lwin, CJ Edwards

Answers

1. c

Among the antibodies described in the question, Anti- Scl 70 antibody is more commonly associated with systemic sclerosis although anti-nuclear antibody is the most common antibody. Anti-RNP and anti-histone antibodies can also be seen but to a much lesser extent. Anti-CCP antibody is detected in patients with rheumatoid arthritis and anti-Ach R antibody in myasthenia gravis.

2. e

Sub-cutaneous calcinosis, pulp atrophy, microstomia and telangiectasia are common clinical findings in systemic sclerosis. Nail pitting is a characteristic feature of Psoriasis.

3. c

Interstitial lung disease is the major cause of morbidity and mortality in patients with systemic sclerosis although the rest of the conditions can still be the cause of mortality in some patients.

4. d

Bisoprolol is a beta blocker that can lead to vasoconstriction aggravating Raynaud's symptoms and subsequent digital ulcerations.

5. b

Intestinal failure once established is not reversible by any kind of treatment. To date, there is no proven immunosuppressive medication to retard the process. Treatment is only supportive.

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THE MANAGEMENT OF GOUT IN PATIENTS WITH MULTIPLE CO-MORBIDITIES

S Ellis, H Lennard-Jones, A Hepburn

Abstract

Gout is a crystal arthropathy associated with hyperuricaemia and is the most common form of inflammatory arthritis in middle-aged men. It most often presents with an acute synovitis in one or more peripheral joints, particularly those in the lower limb. More chronic presentations may also be seen. There are numerous factors that may precipitate acute attacks of gout.

Here we describe a case of a 79-year old gentleman whose acute flares of chronic tophaceous gout most likely resulted from a concurrent illness (chronic lymphatic leukaemia). Management was complicated by concurrent anticoagulation with warfarin and difficulty tolerating optimal doses of urate-lowering therapy. We review the case history and investigations, and discuss the challenges of the management of gout in patients with several co-morbidities.

Case History

A 79-year old gentleman was referred to the rheumatology outpatient clinic by his GP with a two-week history of pain and swelling in the second and third toes of his right foot (Figure 1). He had similar but slightly less severe symptoms in the third and fourth toes on the left. There was no history of injury.

He had a background of recurrent attacks of acute gout since his 40s, predominantly affecting the ankles, mid-tarsal joints, great toes and wrists, which had been managed with colchicine or diclofenac. He had not received urate-lowering therapy (ULT), such as allopurinol, previously. His past medical history included chronic lymphatic leukaemia (CLL), atrial fibrillation (for which he was anticoagulated with warfarin), a previous right rotator cuff repair, hypertension (treated with ramipril and doxazosin) and retinal vasculitis.

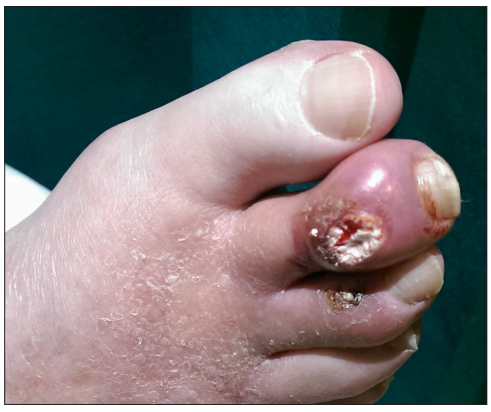

Figure 1: Tophaceous deposits in lesser toes of right foot. Note de-squamation of skin surrounding affected toes, a common sign as an acute flare of gout settles.

At presentation, his total white cell count was 46.2 x 10^9/l (reference range 4-10), of which 41.1 were lymphocytes. His ESR was 27mm/hr with a CRP of 183mg/l (reference range 0-10). His serum urate (sUA) was 448umol/l (reference range 140-360). He had normal renal function with a creatinine of 104umol/l (reference range 60-120). Plain radiographs demonstrated juxta-articular erosions in the symptomatic toes (Figure 2).

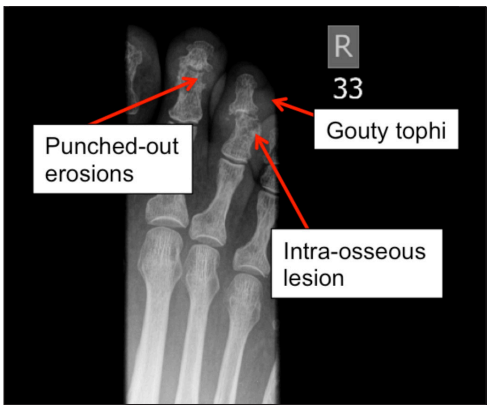

Figure 2: Radiological findings of gout in the patient's right foot.

He was commenced on allopurinol 100mg once daily and prednisolone 10mg once daily, reducing to 5mg once daily after two weeks, as prophylaxis against a further flare during initiation of ULT. Prednisolone was chosen, as the patient had previously been unable to tolerate anymore than a few days of colchicine.

At his next review appointment one month later his symptoms were settling and the repeat sUA was 330umol/l and CRP of only 4mg/l. The dose of allopurinol was further increased to 300mg once daily to aim for a target sUA of <300umol/l. NSAIDs were avoided as he was taking warfarin. Prednisolone was continued for the first 6 months of ULT.

Nine months after his initial presentation he re-presented with pain and swelling in his left ankle. On examination there was warmth and erythema medially, with swelling and tenderness over the Achilles tendon. His most recent sUA, measured approximately one month previously, was 277umol/l. Plain radiographs of the ankle showed normal appearances.

A subsequent MRI scan, performed with gadolinium contrast, demonstrated synovitis in the mid- and hindfoot and chronic Achilles tendinopathy. After confirming an INR of <2.5 to minimise the risk of haemarthrosis, the ankle was injected with corticosteroid (methylprednisolone acetate 40mg, with 1ml of 1% lignocaine) and prednisolone was recommenced at a dose of 25mg once daily for seven days (without tapering). Unfortunately despite this, symptoms failed to improve but eventually settled following an intramuscular injection of 120mg methylprednisolone.

During this time his CLL underwent transformation (total white cell count 108.9 x 10^9/l, lymphocytes 106.7). His whole body CT scan confirmed widespread lymphadenopathy (Figure 3). He was reviewed by his haematologist and was due to start systemic chemotherapy with chlorambucil and obinutuzumab (an anti-CD20 monoclonal antibody).

THE MANAGEMENT OF GOUT IN PATIENTS WITH MULTIPLE CO-MORBIDITIES

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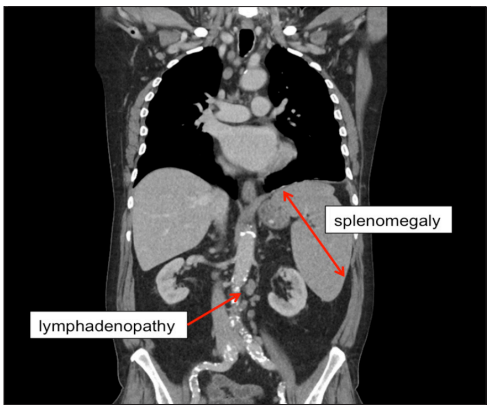

Figure 3: Coronal section from whole body CT scan demonstrating CLL-associated lymphadenopathy and splenomegaly.

The patient's chronic tophaceous gout remained difficult to control with a flare affecting the right knee. This was further complicated by a ruptured Baker's cyst. At this stage his sUA was 311umol/l. The patient had been struggling to tolerate allopurinol and asked to try an alternative form of ULT. He was therefore changed to febuxostat 80mg once daily.

Although febuxostat proved effective (the repeat sUA being 236umol/l), he also found this drug difficult to tolerate. He therefore returned to allopurinol 300mg once daily. At his most recent review he was receiving RCVP chemotherapy for the CLL, his total white cell count falling to 4.0x109/l. His most recent sUA level was 307umol/l. He had experienced no further attacks of gout, and a considerable improvement was seen in the appearance of his toes (Figure 4).

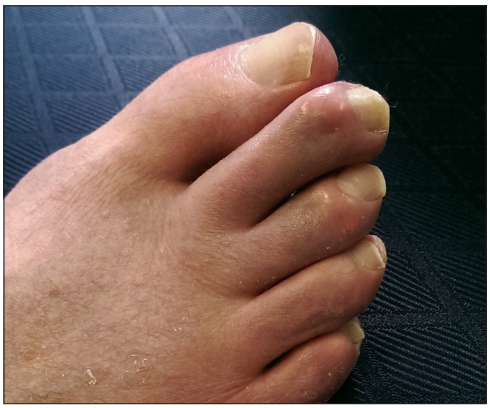

Figure 4: Partial resolution of tophi in lesser toes of right foot. Subcutaneous tophi are still just visible in third toe.

Discussion

The management of gout in patients with multiple co-morbidities is challenging and often associated with a poor long-term prognosis. The disease affects approximately 1-2% of the UK; however, the standard of management of these patients remains inadequate even though the disease has been recognised since antiquity and its pathophysiology is well described.

Hippocrates provided some of the earliest descriptions of gout in the 5th century BC, describing it as the "unwalkable disease" (1). Gout is an inflammatory reaction to high sUA levels and the deposition of monosodium urate (MSU) crystals within tissues and joints (2). An acute attack is often precipitated by a specific event such as trauma, excess alcohol or drugs that affect sUA levels.

Concomitant illnesses associated with a high nucleic acid turnover, such as lymphoproliferative disorders, also increase the likelihood of an acute attack. High sUA levels within joints stimulate vascular endothelial cells, resulting in vasodilation and increased permeability to leukocytes. This causes macrophages and recruited monocytes to produce pro-inflammatory cytokines, causing localised joint pain (2). The causes of hyperuricemia are given in Table 1.

Increased purine synthesis	Decreased purine excretion
Excessive purine intake	Primary/idiopathic hyperuricaemia
Increased purine nucleotide turnover e.g. psoriasis, lympho- & myeloproliferative disease	Ketoacidosis & lactic acidosis
Accelerated ATP degradation e.g. glycogen storage diseases, hypoxia	Drugs e.g. diuretics, ciclosporin, pyrazinamide
Accelerated purine nucleotide synthesis e.g. Lesch-Nyhan syndrome	Toxins e.g. lead, ethanol
	Chronic kidney disease

Table 1: Causes of hyperuricaemia.

Patients with gout frequently have several comorbidities, including hypertension, renal impairment and metabolic syndrome (Table 2). Hypertension is the most common comorbidity in patients with gout (3). This is in part due to its association with chronic renal failure and metabolic syndrome. Furthermore, impaired renal function due to hypertension or metabolic syndrome causes reduced uric acid filtration and hyperuricaemia, which further perpetuates the disease.

Hyperuricaemia	Centripetal obesity
Hypertension	Hyperlipidaemia
Insulin resistance / type 2 diabetes	Accelerated atherosclerosis

Table 2: Features of the metabolic syndrome.

Management of hypertension in patients with gout is complex. Loop and thiazide diuretics impair renal function and increase sUA levels (4). However, the angiotensin II receptor antagonist losartan and the calcium channel blocker amlodipine have been found to reduce sUA levels and improve outcomes (5, 6). Losartan is often contraindicated in patients with renal impairment.

Acute gout

The management of gout includes treating acute attacks and long-term sUA lowering therapy to prevent recurrence. An acute attack of gout is extremely painful; therefore, treatment is initiated immediately following diagnosis (7). Management is dependent on oral non-steroidal anti-inflammatory drugs (NSAIDs), colchicine or joint aspiration and injection of corticosteroid (8, 9).

Opioid analgesics may also be used as adjuncts but they are not as effective as colchicine or NSAIDs in the management of acute gout. They should be used with caution in the elderly in particular. Affected joints should be rested, elevated and ice packs applied.

THE MANAGEMENT OF GOUT IN PATIENTS WITH MULTIPLE CO-MORBIDITIES

S Ellis, H Lennard-Jones, A Hepburn

NSAIDs are very effective in reducing inflammation. However, their use has to be restricted in many clinical situations. For example, they should be avoided in patients who are anticoagulated or have chronic kidney disease (10-12). NSAIDs also have multiple drug interactions, which is of particular importance in patients with co-existing renal and cardiac disease. The combination of an NSAID with diuretics and ACE inhibitors is of particular concern.

In this situation, the lowest dose for the shortest possible duration should be prescribed. Naproxen has the most favourable cardiovascular profile in this respect. Other important co-morbidities to remember include active peptic ulcer disease (increased bleeding risk), congestive cardiac failure (risk of decompensation) and asthma (although true sensitivity to NSAIDs is rare). The COX-2 inhibitor etoricoxib is also licensed for the treatment of acute gout; however, this class of anti-inflammatory has been associated with an increased risk of myocardial infarction.

Colchicine is commonly used for the short-term management of pain and inflammation during an acute attack. It is useful if NSAIDs are contraindicated but it can cause severe diarrhoea. Indeed, it is sometimes forgotten that patients with acute and chronic gout may be very immobile and debilitated, thus a severe bout of diarrhoea is the last thing they want in this situation! Colchicine is also limited in patients with impaired renal function (13). Toxicity is more common in patients with an eGFR of <60ml/min, thus doses of 0.5mg to 1mg tds are often sufficient, for 3-5 days. Drug interactions can also occur via the CYP3A4 pathway. Common examples of interactions include verapamil, diltiazem and clarithromycin.

Intra-articular injection of corticosteroids is also effective in managing an acute flare. However, it is amenable only in individuals with one or two joints affected (8, 9). In patients who are systemically unwell, arthrocentesis should be strongly considered to rule out a septic arthritis (8, 9). However, both conditions can co-exist. The simple manoeuvre of arthrocentesis itself can be very helpful, by reducing intra-articular pressure.

Oral prednisolone 25-35mg once daily for 5 days (or intramuscular methylprednisolone 120mg) is another suitable alternative. Corticosteroids can be very useful in the management of gout in patients with multiple co-morbidities. However, their use in patients with diabetes may lead to an increase in blood sugars. If in doubt, discuss the use of corticosteroids in acute gout with a rheumatologist.

Prevention of recurrence

The long-term management of gout is aimed at reducing sUA levels to less than 360 µmol/l, to reduce the formation of MSU crystals and prevent further attacks (8). First line management is via reduction of uric acid production by xanthine oxidase inhibitors (XOI), such as allopurinol and febuxostat (14, 15). However, there is also a role for increasing uric acid excretion by uricosurics (16), and the conversion of uric acid to the water-soluble allantoin by recombinant uricases (pegloticase and rasburicase) (17).

These therapeutic options are synergetic and can be used in combination. Non-pharmacological management via lifestyle modification and diet advice also have a very important role in preventing further acute flares of gout (8, 9).

Urate lowering therapy (ULT) should be commenced in patients experiencing two or more acute attacks per year. Other indications include chronic tophaceous gout, recurrent urate stones, erosive change in radiographs, renal impairment and a continued need for diuretics e.g. congestive cardiac failure. ULT usually involves allopurinol 100mg once daily. The dose should be increased in 100mg increments every 2-3 weeks according to tolerability and sUA. The typical maintenance dose is 300mg daily, with a maximum dose of 900mg daily.

Allopurinol can be used safely in renal impairment; however, the dose should rarely exceed 300mg daily [18]. The dose may have to be reduced in patients with more advanced renal failure (e.g. 100mg alternate days). Of particular note, allopurinol is associated with the rare but life-threatening allopurinol hypersensitivity syndrome (AHS). However, gradual introduction of allopurinol and close monitoring of sUA concentrations can limit side effects in patients with renal impairment.

Febuxostat 80-120mg once daily is an alternative to allopurinol. The National Institute for Health and Care Excellence (NICE) has approved it for use in patients with hyperuricaemia and gout who are unable to tolerate or who are resistant to treatment with allopurinol. Febuxostat can be used safely in renal impairment, down to an eGFR of 30ml/min. However, clinical trials have indicated an increased risk of cardiac events, so this drug should also be used with caution in patients with known cardiovascular disease. This has led to restriction of its use in the management of hyperuricaemia, given the high incidence of cardiovascular disease in patients with gout.

Uricosuric drugs are alternative agents for patients who are intolerant or resistant to allopurinol or febuxostat. These include probenecid, sulphinpyrazone and benzbromarone. Referral to a rheumatologist is recommended for patients in whom these drugs are being considered. Uricosuric drugs are prescribed in the UK on an individual patient basis and can be difficult for pharmacists to obtain.

Benzbromarone 50-200mg once daily is highly effective; however, it has to be imported from abroad and may be associated with hepatotoxicity. Benzbromarone is effective down to an eGFR of 20ml/min, thus it can be useful in fairly advanced renal impairment. Patients should be advised to increase their fluid intake whilst taking them (>2 litres per day). This can become an issue in the elderly or patients with congestive cardiac failure. In addition, uricosuric drugs should be avoided in patients with renal calculi.

Uricolytic drugs such as pegloticase are reserved for resistant cases and prescribed only in secondary care. They are not currently approved by NICE for use in the UK, but remain an attractive option in patients with severe tophaceous gout. Exacerbations of cardiac failure have been observed, so pegloticase is best avoided in such patients.

THE MANAGEMENT OF GOUT IN PATIENTS WITH MULTIPLE CO-MORBIDITIES

S Ellis, H Lennard-Jones, A Hepburn

Colchicine 0.5mg bd should be co-prescribed upon initiation of ULT and continued for 3-6months. If colchicine is not tolerated, then an NSAID or COX-2 inhibitor should be used e.g. naproxen 500mg once daily or meloxicam 7.5mg once daily. Co-prescription of a proton-pump inhibitor should also be strongly considered for gastroprotection. Very occasionally, colchicine 0.5-1mg daily is used for long-term prophylaxis in patients unable to tolerate or are resistance to standard forms of ULT.

Patients who are overweight or obese should be advised to gradually lose weight to achieve an ideal BMI. Crash diets and those high in protein should be avoided. Beneficial foods include: skimmed milk, low fat yogurt, soybeans and cherries. The intake of foods high in purines such as offal, shellfish, nuts and yeast extract should be restricted. Carbonated soft drinks containing fructose should be avoided. Interestingly coffee has a mild uricosuric effect, as does vitamin C.

In patients with hypertriglyceridaemia, consider use of fenofibrate due to its mild uricosuric effect. In patients with cardiovascular disease, low dose aspirin (75-150mg once daily) prescribed for cardioprophylaxis can be continued. Higher doses of aspirin (>600mg daily) interfere with uric acid excretion and should be avoided.

Finally, a group of patients that can be particularly challenging to manage are those with solid-organ transplants. One of the key contributing factors in this group is hyperuricaemia induced by ciclosporin (and to a lesser extent, tacrolimus). Gout is seen in up to 28% of these patients. Drug interactions are a particular issue, notably between XOIs and azathioprine. This can result in myelosuppression. XOIs should therefore be avoided in patients receiving allopurinol in this situation, and indeed when used as a steroid-sparing drug in autoimmune diseases such as lupus.

In summary, patients with gout often have multiple comorbidities that complicate management and contribute to long-term adverse outcomes. Treatment of acute gout and prevention of recurrence is complicated by patient comorbidities. Indeed, they can perpetuate further flares and complicate management if they are not addressed during treatment. However, several treatment options exist for managing gout in these patients and preventing disease recurrence.

Best of 5 MCQs

1. An 80 year old gentlemen presents to the acute medical unit with an acutely swollen right knee. He is apyrexial but tachycardic. The patient has a background of ischaemic heart disease, hypertension and type 2 diabetes mellitus, thus he is currently on aspirin, a calcium channel blocker, a thiazide diuretic, statin and metformin. You suspect a diagnosis of gout. What is your next step in the management of this patient?

a) Do an X-ray of the affected joint, stop the aspirin and the calcium channel blocker.
b) Check sUA levels, stop the metformin and the thiazide diuretic.
c) Do an ECG, stop the thiazide diuretic and statin.
d) Perform a knee aspirate and consider stopping thiazide diuretic.
e) Check the patient's glucose levels, stop the metformin and calcium channel blocker.

2. A 50-year old gentleman with a background of recurrent acute flares of gout has presented to accident and emergency with an acutely swollen left knee. He has a background of gastric ulcers, and is currently on allopurinol. How do you manage the patient's medication during the acute flare?

a) Stop allopurinol. Start the patient on colchicine.
b) Continue the allopurinol. Start the patient on colchicine.
c) Stop allopurinol. Start the patient on indomethacin with a proton pump inhibitor.
d) Continue allopurinol. Start the patient on oral corticosteroids.
e) Stop allopurinol. Start febuxostat.

3. What is the mechanism of action of colchicine?

a) Binds to tubulin and inhibits microtubule polymerisation.
b) Competitive inhibition of dihydrofolate reductase (DHFR).
c) Purine analogue.
d) Inhibits the enzyme topoisomerase.
e) Thymidylate synthase inhibitor.

4. A 40-year old patient presents to the acute medical unit with an acutely swollen left elbow. On examination, the olecranon is swollen, painful and erythematous. He has a background of a cadaveric renal transplant and anti-rejection therapy includes azathioprine. You perform an aspirate, which is negative on Gram staining but shows negatively birefingent needle-shaped crystals. The sUA level is 400 µmol/l. What is the most appropriate long-term management option for this patient's gout if he has further flares?

a) Start the patient on corticosteroids and NSAIDs during the acute flare. Initiate allopurinol once the flare settles.
b) Start the patient on colchicine during the acute flare. Initiate allopurinol once the flare settles.
c) Start the patient on colchicine. Provide lifestyle modification advice only for long-term management and consider non-xanthine oxidase ULT.
d) Start the patient on colchicine and febuxostat during the acute flare. Continue febuxostat long-term.
e) Provide lifestyle modification advice. Start the patient on allopurinol once the flare settles.

5. A 75-year old patient presents to A&E with an acute flare of gout. He is known to have chronic kidney diease. Which of the following are correct with regards to prescribing colchicine in this patient?

a) If his eGFR is 40 mL/minute/1.73 m^2, then he can have 500 micrograms of colchicine 2–4 times a day until his symptoms are relieved.
b) If his eGFR is 15, then he should not receive colchicine.
c) If his eGFR is between 35 to 50 mL/minute/1.73 m^2, then he can receive 500 micrograms 2–4 times a day until his symptoms are relieved.
d) If his eGFR is 60 mL/minute/1.73 m2, then he requires 250 micrograms of colchicine once daily until his symptoms are relieved.
e) If his eGFR is 9, then he should not receive colchicine.

THE MANAGEMENT OF GOUT IN PATIENTS WITH MULTIPLE CO-MORBIDITIES

S Ellis, H Lennard-Jones, A Hepburn

Answers

1. D: *The diagnosis of gout is based on the clinical history and examination. Investigations are often of limited use initially as sUA levels and X-rays can be normal during an acute attack. However, it is important to exclude septic arthritis in this patient as he is systemically unwell with a tachycardia. Thus, the patient should have a knee aspirate. If this is technically difficult, ultrasound guidance can be used.. In addition, the patient's risk factors for developing gout should be addressed. This includes consideration of stopping drugs that can raise serum urate, such as thiazide diuretics.*

2. B: *If a patient is already established on allopurinol (or febuxostat), it is important to not stop it during an acute flare of gout. You can give the patient an NSAID, corticosteroid or colchicine. In this question, the patient has a history of gastric ulcers thus an NSAID or steroid would not be advised due to the risk of gastritis. You should also advise the patient to return if symptoms worsen, or do not improve after 3–4 days.*

3. A: *Colchicine stops mitosis by acting on microtubules. In addition, it has anti-inflammatory effects by inhibiting neutrophil motility and activity.*

4. C: *Azathioprine is a purine analogue that is commonly used in patients with ANCA-associated vasculitis, Crohn's, lupus and renal transplantation. Allopurinol interferes with azathioprine degradation, which exacerbates its toxity. This can risk the development of pancytopaenia in the patient.*

5. E: *Colchicine should not be used in patients who have severe renal impairment, with an eGFR less than 10 mL/minute/1.73 m^2. If the eGFR is between 10–50 mL/minute/1.73 m^2 then the dose of colchicine can be reduced or the dose interval increased.*

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A CASE REPORT OF WHIPPLE'S DISEASE - THE DIAGNOSTIC CHALLENGE OF A SYSTEMIC DISEASE

L Phelan, N Burr, N Scott, A O'Connor, S Dass, S Savic, C Donnellan

Abstract

Infection with Tropheryma Whipplei (Whipple's disease) can provide a diagnostic challenge, given its low prevalence, multisystem involvement and varied clinical presentations. Although typically thought of as a GI disease, the presenting complaint is usually arthralgia.

We present a case of a 59 year old gentleman with a 9-year history of intermittent, migratory polyarthralgia and raised inflammatory markers who developed gastrointestinal malabsorption and weight loss and was admitted to hospital acutely. As part of a series of diagnostic investigations, oesophago-gastro-duodenoscopy was performed which showed duodenal lymphangiectasia. Periodic Acid Schiff staining of the duodenal biopsy and subsequent Polymerase Chain Reaction (PCR) testing ultimately diagnosed Whipple's disease.

Clinical suspicion for Whipple's disease should be raised in any patients who develop GI, or systemic symptoms when commencing immunosuppressive therapy, to try and avoid diagnostic delay and prevent the development of complications in this treatable condition.

Keywords

Whipple's disease, Tropheryma Whipplei.

Introduction

Case Presentation

A 59-year-old Caucasian man presented to Accident and Emergency with a two-week history of loose stools, non-specific abdominal pain, reduced appetite and unintentional weight loss of 12.5kg in the preceding three months.

He had an extensive past medical history and had been under the care of the Rheumatologists and Immunologists for the previous 9 years. Initially, he had been referred from Primary Care with a provisional diagnosis of polymyalgia rheumatica (PMR) with upper limb pain, stiffness and reduced range of shoulder movement. After Rheumatological review the clinical picture was more in keeping with osteoarthritis due to the symptom pattern, degenerative changes on x-rays and further corroborated by the fact that he had never responded to corticosteroids.

His symptoms progressed over time to a more widespread polyarthralgia with subsequent development of bilateral panuvetitis, despite no clinical evidence of an inflammatory arthritis. He had a persistently raised C-reactive protein (CRP) of between 26-134g/L (normal range <10mg/L) and a plasma viscosity (PV) of 1.89 mPa.s (normal range 1.50-1.72 mPa.s).

His autoimmune screen, creatinine kinase, myeloma screen, Human leukocyte antigen-B27, antinuclear antibodies, Immunoglobulins, anti-neutrophil cytoplasmic antibodies, serum immunology, serology for HIV and blood film were all normal or negative. Radiographs of his cervical spine showed degenerative changes only. The raised CRP prompted further investigations whilst under Rheumatology review.

A CT scan of his chest, abdomen and pelvis demonstrated no significant abnormality. CT, MRI and MR-venogram of his head were all normal. A PET-CT scan incidentally identified a rectal polyp. This was excised endoscopically and was identified as a tubular villous adenoma with a focus of adenocarcinoma with no local or distant involvement and not deemed to be relevant to his other symptoms. Despite numerous investigations and follow-up with the Rheumatology and Immunology departments, the cause of his raised inflammatory markers remained unclear.

His other past medical history included gallstones, congenital pyloric stenosis and osteoarthritis. He had a 45 pack year smoking history, was abstinent from alcohol at the time of presentation but previously had drank to excess. He lived with his wife, worked as a truck driver and had not worked in the agricultural industry.

On examination, he was pale with a prolonged capillary refill time, his abdomen was soft and non-tender and he had a petechial rash on his lower limbs. Otherwise, examination was unremarkable.

He was admitted under the care of the Gastroenterology team. Initial blood results showed an acute kidney injury (creatinine 118 mg/L, normal range 64-104) microcytic anaemia, Hb 88g/L (normal range 135-180g/L) and hypoalbuminaemia, 20g/L (normal range 33-48g/L). A repeat CT scan of his chest, abdomen and pelvis demonstrated no evidence of primary or metastatic malignancy and only degenerative changes in his cervical spine and sub-pleural emphysematous changes in his lungs.

A flexible sigmoidoscopy had limited views, due to solid stool, but showed no recurrence of his adenocarcinoma. Oesophago-gastro-duodenoscopy (OGD) demonstrated a small, sliding hiatus hernia, Los Angeles grade B oesophagitis, duodenitis with intestinal lymphangiectasia in the second part of the duodenum (Image 1).

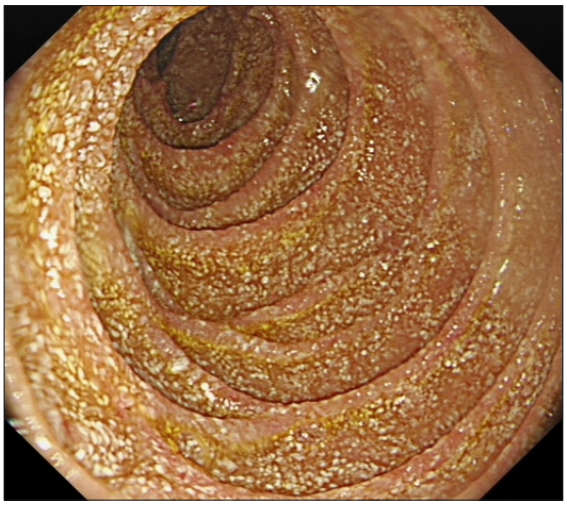

Image 1: Intestinal lymphangiectasia in the second part of the duodenum seen on upper GI endoscopy.

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Duodenal biopsies were taken which demonstrated partial villous atrophy with foamy histiocyte infiltration. Subsequent Periodic Acid Schiff staining was performed due to the suspicion of Whipple's disease (Image 2). Whipple's disease was then confirmed when PCR of the samples was positive for Trophyeryma Whipplei.

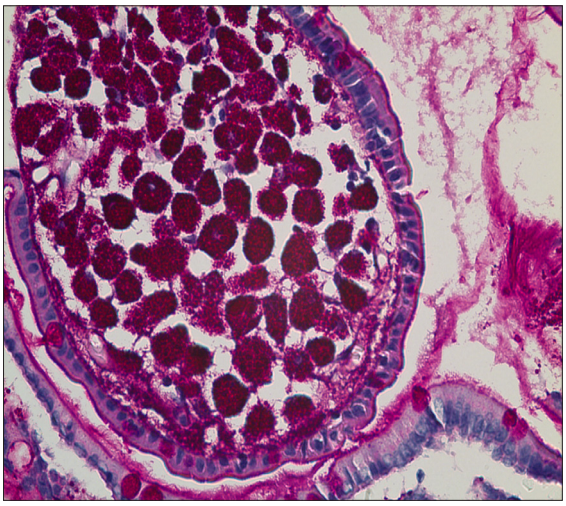

Image 2: Biopsy from the second part of the duodenum after Periodic Acid Schiff staining. Magnification X 100.

In the interim between the biopsy and its result the patient continued to lose weight despite nasogastric feeding and so started parenteral nutrition. He was reviewed by the psychiatric team who commenced anti-depressants for his low mood but apart from this he developed no further symptoms.

After the diagnosis of Whipple's disease was confirmed, he was commenced on intravenous benzylpenicillin. After improvement of his malabsorption symptoms, he was converted to oral doxycycline but continued on parenteral nutrition until he was able to meet his nutritional requirements orally/enterally.

Transoesophageal echocardiogram to investigate for cardiac Whipple's involvement showed severe left ventricular impairment with some focal calcification of the mitral valve leaflets but no vegetations. After cardiology review he was commenced on the beta-blocker bisoprolol and diuretic furosemide.

At the time of writing he is recovering well and gaining weight, continuing on oral doxycycline and hydroxychloroquine.

Discussion

Whipple's Disease is a rare chronic infection with less than 1,000 reported cases and an estimated incidence of less than 1 in 1,000,000. It is caused by the Gram positive microorganism, T. Whipplei. It is present naturally within our environment, but only rarely causes Whipple's disease.(1)

Typically, the disease affects middle aged men of European heritage, and can present with a wide spectrum of clinical features as the organism can invade various sites.(2) It is interesting to note that there is minimal inflammatory response in the affected tissues, which has led to the hypotheses that an underlying host immune deficiency or secondary down-regulation of the immune system by T. Whipplei is involved in the pathogenesis of this disease.(3)

The cardinal symptoms of classic Whipple's Disease are arthralgia, weight loss, diarrhoea and abdominal pain. Typically, arthralgia is the initial complaint, and was the predominant clinical feature in 78% of patients in a case series of 113 patients.(3) It can precede other symptoms of Whipple's disease by several years and up to 50% of patients are misdiagnosed as having seronegative inflammatory arthritis, as was the case in our patient.(3)

The symptoms are typically worse after starting immunosuppressive treatment in the form of corticosteroids or immunomodulators.(3) At the time of diagnosis, 76% of patients have gastrointestinal symptoms; typically, with diarrhoea and colicky abdominal pain. Eventually patients can progress to a severe wasting syndrome presenting with weight loss.
Neurological involvement tends to occur late in the natural history of the disease. Other systemic features can include; endocarditis, uveitis, symptoms related to pleuropulmonary disease, lymphadenopathy and skin hyper-pigmentation.(2)

Whipple's Disease is difficult to diagnose due to the variety and non-specific nature of the presenting symptoms which can develop over many years. The index of clinical suspicion should be raised in patients who do not improve, or develop further systemic symptoms, particularly after initiation of corticosteroids or immunomodulators for their inflammatory arthralgia.

Initial investigations of patients with Whipple's disease often show anaemia and a raised CRP. In those with gastrointestinal symptoms the most reliable method of diagnosis is an OGD with duodenal biopsies.(4) Only 26% of patients have an abnormal macroscopic appearance at OGD, with 10% having duodenitis and 11% having characteristic findings of Whipple's disease i.e. ectatic lymph vessels, clumsy or dilated villi and prominent/discrete oedema.(4) Duodenal biopsies should undergo Periodic Acid-Schiff (PAS) staining and PCR, the latter of which has a 97% sensitivity and 100% specificity when testing for T Whipplei.(5) If duodenal biopsy results are negative and the clinical suspicion remains high, further clinically directed samples, such as synovial fluid, CSF or lymph nodes, should be taken and sent for PCR testing.

The optimal antibiotic regimen to treat Whipple's Disease is uncertain. In Vitro testing of cell cultures has indicated that doxycycline, macrolides, ketolides, aminoglycosides, penicillin, rifampicin, teicoplanin, chloramphenicol and trimethoprim-sulfamethoxazole (TMP-SMX) can have activity against the bacterium.(7) Typical regimes have included a 2-4 week induction with penicillin or ceftriaxone followed by oral TMP-SMX for 12 months.(8) A prospective randomised controlled trial of different treatment regimens is ongoing.

A CASE REPORT OF WHIPPLE'S DISEASE - THE DIAGNOSTIC CHALLENGE OF A SYSTEMIC DISEASE

L Phelan, N Burr, N Scott, A O'Connor, S Dass, S Savic, C Donnellan

Relapse following treatment often presents with central nervous system involvement, which is thought to be secondary to inadequate initial management. Therefore, antibiotic choice should be tailored to an agent that is active against T. Whipplei and one that also crosses the blood brain barrier to ensure the risk of relapse is minimised.

Typically, patients tend to show a major improvement 7-21 days following the onset of antibiotic treatment. There are no clear guidelines to suggest how patients with Whipple's disease should be monitored, although some advocate yearly gastroscopy with biopsies to look for the organism, for the initial five years following diagnosis. Studies suggest that 17-35% of patients will relapse;(8) however it is believed that some of these have immune reconstitution inflammatory syndrome, in which patients develop a high fever and symptoms after commencing antibiotics. (9)

This case illustrates the complex diagnostic challenge that Whipple's disease can pose for clinicians given its broad spectrum of presenting features and low incidence. Our patient did not develop GI symptoms until late on in the disease course which delayed his diagnostic OGD. His case highlights the multisystem involvement of Whipple's as he had musculoskeletal, ophthalmic and GI symptoms.

His musculoskeletal symptoms were initially very non-specific and without clinical evidence of an inflammatory arthritis, which is more typically seen in this condition. Whipple's disease should be considered in patients with persistent raised inflammatory markers and a migratory polyarthralgia, whom fail to respond to immunosuppressive treatments, or develop new systemic symptoms. OGD with duodenal biopsies is a relatively safe, readily available test that is useful in confirming the diagnosis.

Whipple's Disease - Multiple Choice Questions

1. What type of organism causes Whipple's Disease?

a. Protozoa.
b. Gram-positive bacterium.
c. Fungi.
d. Gram-negative bacterium.
e. Virus.

2. What is the typical initial presenting complaint in Whipple's Disease?

a. Diarrhoea.
b. Arthralgia.
c. Abdominal pain.
d. Weight loss.
e. Low mood.

3. What is the most reliable method of diagnosis of Whipple's disease in patients presenting with diarrhoea, weight loss and abdominal pain?

a. Colonoscopy and biopsy.
b. PET- CT.
c. MRI.
d. OGD and duodenal biopsy.
e. Blood serum sampling.

4. Which one of the following is the most important in the management of Whipple's Disease?

a. Surgical intervention.
b. Total parenteral nutrition.
c. Symptomatic management.
d. Antibiotics.
e. Gluten free diet.

5. Which of the following are associated with Whipple's Disease?

a. Skin hyperpigmentation.
b. Uveitis.
c. Lymphadenopathy.
d. Endocarditis.
e. All of the above.

Answers

1. Answer - b

Trophyeryma whipplei is a Gram positive microorganism which is present naturally in the environment.(1) There is evidence that the infection can be transmitted by direct contact but this rarely causes Whipple's disease.

It is thought that T. whipplei causes some down regulation of the host immune response to cause Whipple's disease after infection as there is minimal inflammatory response to the infection in immunocompetent patients.

2. Answer - b

Arthralgia is the initial complaint and patients can often be misdiagnosed with seronegative inflammatory arthritis as the arthralgia can precede the other systemic symptoms by a number of years.(3)

Corticosteroids or immunomodulators can worsen the patient's symptoms and therefore Whipple's disease should be considered in patients with a migratory polyarthalgia with raised inflammatory markers whom fail to respond to immunosuppressive therapies or develop new systemic symptoms such as diarrhoea and abdominal pain.(3)

A CASE REPORT OF WHIPPLE'S DISEASE - THE DIAGNOSTIC CHALLENGE OF A SYSTEMIC DISEASE

L Phelan, N Burr, N Scott, A O'Connor, S Dass, S Savic, C Donnellan

3. Answer - d

In those with gastrointestinal symptoms the most reliable method of diagnosis is an OGD with duodenal biopsies. 26% of patients have an abnormal macroscopic appearance at OGD, with 10% having duodenitis and 11% having characteristic findings of Whipple's disease i.e. ectatic lymph vessels, clumsy or dilated villi and prominent/discrete oedema.(4)

Duodenal biopsies should undergo Periodic Acid-Schiff (PAS) staining and PCR, the latter of which has a 97% sensitivity and 100% specificity when testing for T. Whipplei.(5)

4. Answer - d

Patients with Whipple's disease should be treated with antibiotics. A typical regimen would include a 2-4 week induction with penicillin or ceftriaxone followed by a prolonged course of oral antibiotics, trimethoprim-sulfamethoxazole for 12 months.(8)

The optimal antibiotic regimen is currently uncertain, however a prospective randomised controlled trial of different treatment regimens is ongoing.

5. Answer - e

Whipple's disease can be difficult to diagnose due to the variety and nature of presenting symptoms which can develop over a number of years. The cardinal symptoms of classic Whipple's Disease are arthralgia, weight loss, diarrhoea and abdominal pain, with the initial complaint often being of arthralgia.(3)

At the time of diagnosis patients typically have gastrointestinal symptoms, but patients may experience a wide range of systemic complaints such as endocarditis, uveitis, symptoms related to pleuropulmonary disease, lymphadenopathy, skin hyperpigmentation and neurological involvement.

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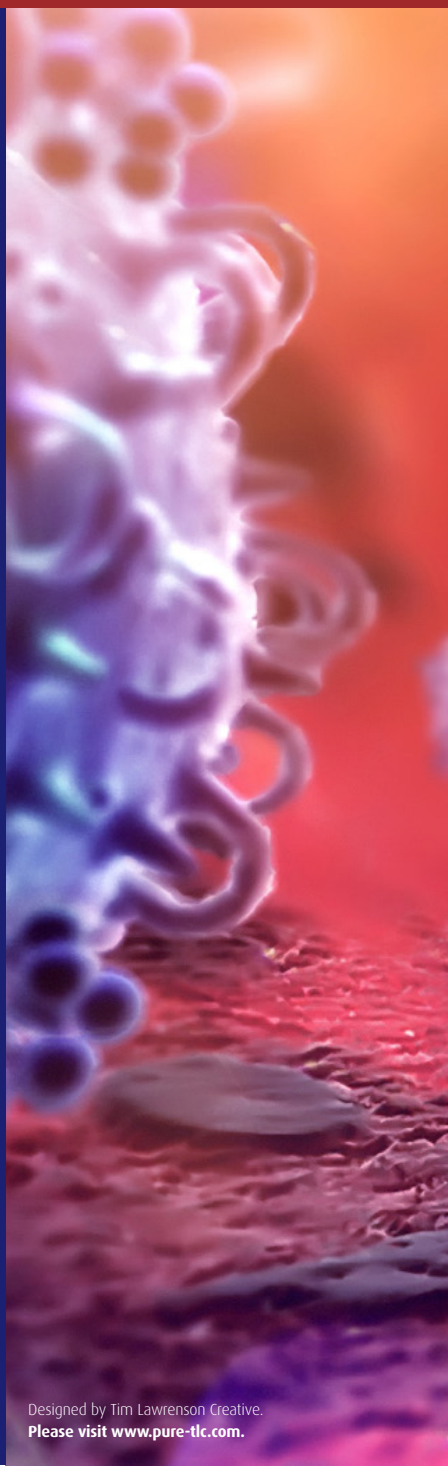

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