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Volume 6, Issue 2: **Rheumatology**

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Foundation Years Journal

Foundation Years Journal is an international peer-viewed journal which seeks to be the pre-eminent journal in the field of patient safety and clinical practice for Foundation Years' doctors and educators. The Journal welcomes papers on any aspect of health care and medical education which will be of benefit to doctors in the Foundation training grade in the UK or international equivalents.

Publisher's Office

Abhishek Agrawal & Jack Westland
Managing Editors
123Doc Education
72 Harley Street
London
W1G 7HG
Tel: +44 (0)207 253 4363
Email: jack@123doc.com

Volume 6, Issue 2: Rheumatology

Foundation Years Journal is the ONLY journal for Foundation Years, doctors and educators, specifically written according to the MMC curriculum. It focuses on one or two medical specialties per month and each issue delivers practical and informative articles tailored to the needs of junior doctors. The Journal closely follows the Foundation Years syllabus to provide the best educational value for junior doctors. In addition to good clinical and acute care articles, assessment questions give junior doctors the chance to gauge their learning. Each issue provides comprehensive clinical cases for trainees as well as practical teaching assessments for educators. Readers will benefit from:

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Editorial For Rheumatology Issue Of Foundation Years Journal 2012

Many persons like to hold a book or journal in the hand. The ability to browse by turning pages, for those to annotate, who are prepared to deface paper copies to read without needing to find electronic apparatus to enable viewing (whether by computer, by Kindle device or otherwise), all are powerful stimuli to keep to conventional hard copy, paper publications. The feel of a book, the smell of the paper (maybe the binding), the colourful printing, and the variations in font and style all contribute to this sensual experience. However, paper copies become dated and cannot easily be amended except in loose-leaf form where they lose much of their aesthetic appeal. They are more expensive to produce at the point of the user. They decay with use, whether aided by fingers, thumbs or by mice, and they are bulky for publishers and readers to transport.

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Hence, this trends towards electronic publishing. Electronic journals have many advantages and can be accessed from computers worldwide. This journal offers all of these advantages and on this occasion brings to readers aspects of important neurological topics relevant to Foundation Years practitioners.

The neurosciences, of which, everyday clinical neurology forms a part, have made amazing progress over the last couple of decades. The interactions between laboratory and clinical research, and with clinical medicine that deals with illness in patients at its most elementary level, have contributed to these advances. However, sometimes research and cutting edge thinking from the laboratory is difficult to apply to some of the immediate clinical problems exhibited by patients. Common sense (whatever that is) and thinking is needed with acute problems and so is rapid decision making. Some of the topics covered in this issue deal with acute medicine, and neurology is now very much part of this since nearly one fifth of those admitted acutely have neurological problems, and others with less acute matters still get admitted to hospital. Papers published here express some of the most important points that Foundation Years doctors experience during their everyday duties, lessons they wish to share with others in order to help prevent mishaps.

Indeed, such practitioners are encouraged to submit to this journal. There is so much to be learned from our everyday activities and our patients are in many ways our best teachers, using their symptoms and signs to make us think. It is in many ways a moral imperative to share this information with others and to publish for the widest circulation. Specific lessons that may be drawn from the papers in this issue of the Foundation Years Journal, include epilepsy and the causes of blackouts together with some useful tips on the use of the EEG in diagnosis, an important supportive test in some patients. Stroke is now an emergency in more ways than previously (since more can be done), a brain attack that needs handling acutely and which can result from venous sinus thrombosis, two more areas covered in this journal. The techniques of lumbar puncture are still important although much that was investigated previously by this technique now is revealed by the increasingly complicated imaging processes that have become available.

Acute neuromuscular weakness is a further presenting feature that has many causes and this condition may be quite puzzling in many patients. Increasingly complicated drugs and drug regimes may lead to toxicity, an important cause of disability that can easily be overlooked; baclofen is a useful drug for spasticity and intoxication is disabling. Trigeminal neuralgia can be treated in many ways; not all being effective and a paper on this topic should help guide those who deal with its early manifestations.

And what of that imperative to publish? Here we are guided in the values of clinic letters and of the role of the doctor as educator. All very important stuff, hopefully interesting, certainly enlightening, and without doubt we hope a stimulus for readers to provide further papers dealing with the many topics in neurology that may perplex all of us including those working in the Foundation Years.

Christopher Gardner-Thorpe
Exeter, UK
cgardnerthorpe@doctors.org.uk

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Notice

CASE BASED DISCUSSION: MIXED CONNECTIVE TISSUE DISEASE

S Mukherjee and R Armstrong

Case Based Discussion:
Mixed Connective Tissue Disease
Patient Management.

Abstract

A 53-year old female with a previous history of non-specific arthralgia, myalgia and Raynaud's phenomenon was admitted with chest pain, dyspnoea and cough. She was found to have overlapping features of lupus, scleroderma and polymyositis along with raised inflammatory markers and anti-ribonucleoprotein antibodies. She was diagnosed as having Mixed Connective Tissue Disease and was started on immunosuppressive therapy with a good response. This case-based discussion describes the process of diagnosis and management of this patient.

Case History

A 53-year old Afro-Caribbean female was admitted with 2-week history of malaise accompanied by pleuritic chest pain, dyspnoea and cough productive of yellow sputum. She had also noticed recent intermittent leg swelling. She denied any calf pain or tenderness and had no risk factors for deep vein thrombosis (DVT). However, she reported feeling feverish and having intermittent sweats for a few months and had thought that these were menopausal. There was no significant past medical history apart from a Rheumatology referral five months previously with non-specific arthralgia, myalgia and possible Raynaud's phenomenon. The clinical examination and investigation results were unremarkable at that stage and therefore no definite diagnosis could be made.

On admission she was pyrexial with a temperature of 37.8° C. She had a pulse rate of 100/min, blood pressure 120/65 mm Hg, respiratory rate 22/min and oxygen saturation 98% on air. There was no clubbing or lymphadenopathy. She had percussion dullness and reduced breath sounds over the right lung base. Her heart sounds were normal. There was no calf tenderness or DVT clinically. She had a trace of protein and blood on urine dipstick testing. Blood tests showed normocytic anaemia with haemoglobin of 97 g/dl and MCV 85.1fL. Renal function was normal and liver function tests showed slightly elevated Alanine transaminase (ALT) of 63 iu/L and low albumin of 25 g/L. The C-reactive protein (CRP) was only marginally raised at 15 mg/L and her d-dimer was more than 5000 µg/L. ECG showed sinus rhythm with no acute changes but the chest x-ray revealed patchy consolidation in the right mid and lower zones along with a right-sided pleural effusion (Fig 1).

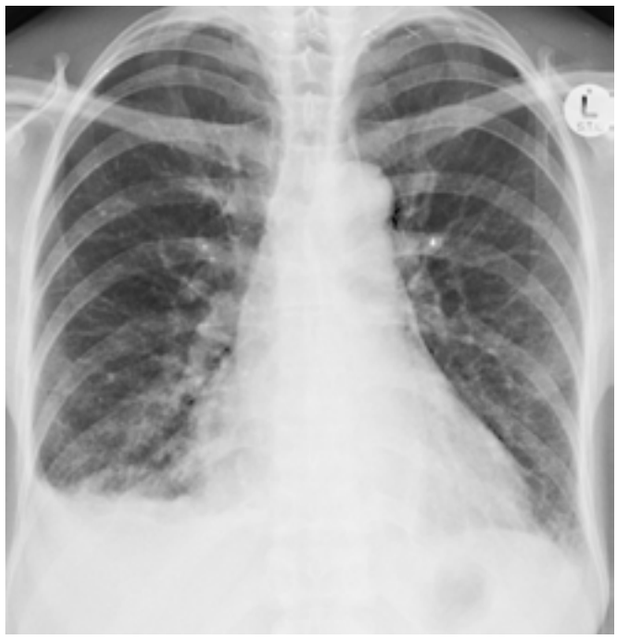

Fig 1 - Chest x-ray showing right-sided patchy consolidation and pleural effusion.

The Respiratory team diagnosed her as having pneumonia with a para-pneumonic pleural effusion but felt that pulmonary embolism (PE) needed to be excluded. An underlying autoimmune condition was also included in the differential diagnosis. She was started on intravenous antibiotics along with an oral non-steroidal anti-inflammatory drug. She was also given full dose enoxaparin and a CT pulmonary angiogram (CTPA) and autoimmune screen were requested. The CTPA showed no evidence of PE but there were bilateral pleural effusions, the right being larger (Fig 2). The enoxaparin was then reduced to a prophylactic dose and the antibiotics were continued. Pleural fluid analysis showed an exudative effusion with no microbial growth on culture. Although there was some initial improvement, the pleuritic pain persisted and on Day 7 she again developed a temperature of 39°C. The antibiotics were therefore stopped and further blood and urine cultures were sent along with a referral for a Rheumatology opinion.

CASE BASED DISCUSSION: MIXED CONNECTIVE TISSUE DISEASE

S Mukherjee and R Armstrong

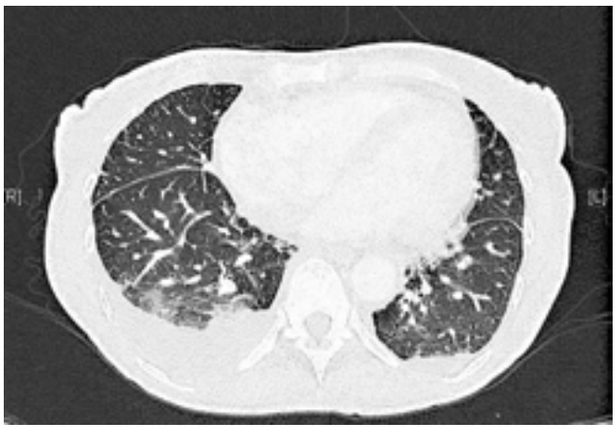

Fig 2 - CTPA showing bilateral pleural effusions, the right being larger.

On Rheumatology review she reported a 12-month history of myalgia, polyarthralgia and fatigue along with Raynaud's phenomenon. She also reported morning stiffness lasting for about one hour but none of her joints had been red, hot or swollen. There was some positional variation in her chest pain suggestive of pericarditis and she also mentioned exertional dyspnoea and presyncope raising the possibility of pulmonary hypertension. She denied any dysphagia. On examination there was no obvious synovitis but her wrists and fingers were slightly puffy and tender. There was no muscle tenderness or weakness and she did not have any rash or other features suggestive of a connective tissue disease. Her blood and urine cultures yielded no growth and there was no evidence of haematuria on urine microscopy. She had a lymphopenia of 0.7x109/L and there was a polyclonal hypergammaglobulinaemia with IgG of 32.9 g/L and IgM of 3.2 g/L. Additional investigations were suggested including serum creatinine kinase (CK), complement assay (C3 and C4), erythrocyte sedimentation rate (ESR), repeat CRP and an echocardiogram .

Her anti-nuclear antibody (ANA) screen subsequently came back as strongly positive along with a positive test for anti-ribonucleoprotein (RNP) antibodies. The Rheumatoid factor was also strongly positive at 2930 iu. Her complement levels and antibody to double-stranded DNA were normal but the CK was raised at 827 iu/L. Further blood tests showed significantly raised inflammatory markers with CRP of 124 mg/L and ESR of 86 mm/1st hr. The echocardiogram suggested pulmonary hypertension with an estimated pulmonary artery pressure of 45 mm Hg (normal up to 25 mm Hg). There was also a small pericardial effusion.

A diagnosis of mixed connective tissue disease (MCTD) was made and Prednisolone 30 mg daily was started with significant symptomatic improvement within 5 days. She remained afebrile and there was a fall in the inflammatory markers (CRP 23 mg/L, ESR 73 mm/1st hr). She was discharged home on a tapering dose of corticosteroid and Azathioprine was commenced as a steroid-sparing agent. She is currently undergoing outpatient follow-up in the Rheumatology and the Pulmonary Hypertension Clinics and she is progressing well. Her inflammatory markers have normalised and the CK remains only marginally raised. A repeat chest x-ray has also shown resolution of the pleural effusions (Fig 3).

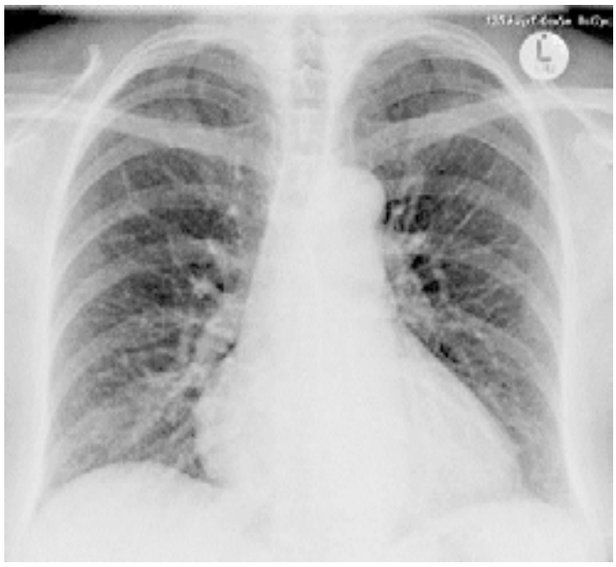

Fig 3 - Repeat chest x-ray showing resolution of pleural effusion.

Discussion: MCTD is an autoimmune connective tissue disorder characterised by clinical features seen in systemic lupus erythematosus (SLE), scleroderma and polymyositis (PM) in combination with anti-RNP antibodies.1 Females are nine times more commonly affected than males. MCTD is less common than systemic lupus erythematosus, but more common than systemic sclerosis or myositis and the disease does not appear to show the relative preponderance of Afro-Caribbeans that is seen in SLE.1, 2

The early clinical manifestations of MCTD are non-specific and consist of fatigue, general malaise, arthralgias, myalgias and low-grade fever. Patients also commonly give a history of Raynaud's phenomenon.1, 2 The simultaneous presence of overlap features usually seen in SLE, Scleroderma and PM is seldom seen in the early stage of the disease. The various clinical features related to these conditions appear gradually over time and may take several years to become fully apparent.3,4

CASE BASED DISCUSSION: MIXED CONNECTIVE TISSUE DISEASE

S Mukherjee and R Armstrong

The underlying connective tissue disease is often identified when screening tests reveal a positive ANA with positive anti-RNP antibodies. Patients commonly have swollen hands or puffy fingers. They may develop severe arthritis and more than 50 percent of MCTD patients are seropositive for rheumatoid factor.2 An inflammatory myopathy identical to PM can develop but non-specific myalgia is more common and in most patients there is no demonstrable weakness or significant elevation of muscle enzymes .2 Pleurisy and pericarditis occur in about 60 percent of patients.1 The lungs are also commonly affected with a wide spectrum of problems including interstitial lung disease and pulmonary hypertension and the latter is a major cause of death in MCTD.2 Disordered motility in the upper gastrointestinal tract is the commonest gastrointestinal problem. Severe renal and central nervous system disease are uncommon in MCTD.2 The most frequent laboratory findings are leucopenia, thrombocytopenia and hypergammaglobulinaemia along with raised inflammatory markers.1

Treatment usually involves the use of non-steroidal anti-inflammatory drugs, Hydroxychloroquine and low-dose corticosteroid for articular manifestations. High dose corticosteroid is used for features of SLE (e.g. pleurisy/pericarditis) and PM (e.g. myositis) and often patients need steroid sparing agents such as Azathioprine and Methotrexate. Intravenous Immunoglobulin is sometimes used when there is steroid resistance.2 The features of Scleroderma (e.g. pulmonary hypertension) are more difficult to treat and need specialised input.

This case illustrates the difficulties often faced when managing patients with connective tissue diseases like MCTD. Presenting features are often non-specific and the full clinical picture may only manifest over a prolonged period. The initial diagnosis of pneumonia with pleural effusion seemed the most likely at that stage and therefore the use of antibiotics was entirely appropriate. In fact, there may have been a degree of secondary infection that responded to the antibiotics. Similarly, PE was also a possibility and therefore anticoagulation was entirely appropriate until this had been excluded. The possibility of an underlying connective tissue disease was also considered on admission and she was appropriately referred to the Rheumatology team when there was a lack of satisfactory response to antibiotics. She displayed several features of MCTD. Apart from the usual non-specific presenting features like malaise, fatigue, arthralgia, myalgia and Raynaud's phenomenon, she had features of lupus (serositis) as well as features of scleroderma (pulmonary hypertension) and evidence of myositis (elevated CK). The raised ALT was also most likely related to muscle inflammation rather than liver disease and similarly the absence of red blood cells on urine microscopy suggests that the positive result for blood on urine dipstick testing may have been due to myositis induced myoglobinuria rather than true haematuria. Finally, she also had raised inflammatory markers and was subsequently found to have positive tests for ANA and anti-RNP antibodies. She was therefore appropriately diagnosed as having MCTD and was started on immunosuppressive therapy with a very good clinical response.

MCQs (Best of 5)

1. Patients with MCTD have clinical features commonly seen in
a) Systemic Lupus Erythematosus
b) Scleroderma
c) Myositis
d) all of the above
e) none of the above

2. Mixed Connective Tissue disease
a) is more common in females
b) is never seen in males
c) has equal sex distribution
d) is as common as SLE but less common than Scleroderma or myositis
e) is commoner in Afro-caribbeans similar to SLE

3. Patients with MCTD often have
a) positive Rheumatoid factor
b) positive anti-RNP antibodies
c) leucopenia and thrombocytopenia
d) hypergammaglobulinaemia
e) all of the above

4. Patients with MCTD commonly have
a) the simultaneous presence of overlap features of SLE, Scleroderma and PM from onset
b) pulmonary hypertension but this is not clinically significant
c) presence of severe renal and central nervous system disease
d) a history of Raynaud's phenomenon
e) all of the above

5. The following investigation results that were seen in the case of the patient discussed above could be suggestive of myositis:
a) raised CK and inflammatory markers
b) raised ALT
c) urine dipsitck positive for blood with no haematuria on microscopy
d) all of the above
e) none of the above

CASE BASED DISCUSSION: MIXED CONNECTIVE TISSUE DISEASE

S Mukherjee and R Armstrong

MCQ Answers and Teaching Notes

Answer 1: d

MCTD is an autoimmune connective tissue disorder characterised by clinical features seen in systemic lupus erythematosus (SLE), scleroderma and polymyositis (PM). The various clinical features related to these conditions appear gradually over time and may take several years to become fully apparent. The early clinical manifestations of MCTD are very non-specific with a wide differential diagnosis and therefore there is often a delay before the actual diagnosis is made. 3,4 Awareness of this condition as well as the other autoimmune connective tissue diseases is likely to ensure their inclusion in the initial differential diagnosis in such cases and therefore could potentially lead to an earlier diagnosis.

Answer 2: a

Females are nine times more commonly affected by MCTD than males. It is 4 times less common than systemic lupus erythematosus, but more common than systemic sclerosis or myositis and the disease does not appear to show the relative preponderance of Afro-Caribbeans that is seen in SLE.1, 2

Answer 3: e

Patients with MCTD commonly have positive ANA and anti-RNP antibodies. In contrast to SLE, the Complement levels in MCTD are usually normal or high and the tests for anti-Smith (Sm) and anti-double stranded DNA (dsDNA) antibodies are negative. Rheumatoid factor is found in more than 50 percent of patients with MCTD and its presence does not mean that the patient also has Rheumatoid arthritis. 1, 2 Patients commonly have swollen hands and/or puffy fingers and some may develop severe arthritis. Joint involvement in MCTD is more common and frequently more severe than in classic SLE. X-rays of hands often show deforming but non-erosive changes suggestive of Jaccoud's arthropathy as seen in patients with SLE and joint erosions are seen in rare cases. The most frequent laboratory findings are leucopenia, thrombocytopenia and hypergammaglobulinaemia. along with raised inflammatory markers.1

Answer 4: d

Patients with MCTD commonly have a history of Raynaud's phenomenon. The early clinical manifestations of MCTD are non-specific and consist of fatigue, general malaise, arthralgias, myalgias and low-grade fever. The simultaneous presence of overlap features usually seen in SLE, Scleroderma and PM is seldom seen in the early stage of the disease. 3,4 Severe renal and central nervous system disease are uncommon in MCTD but the lungs are commonly affected in this condition with a wide spectrum of problems including pleuritis, pleural effusions, interstitial lung disease and pulmonary hypertension. The latter often occurs insidiously and is also a major cause of death in MCTD. 2

Answer 5: d

The patient had muscle pain and stiffness along with raised CK and inflammatory markers suggestive of myositis. Interestingly, there were also other possible clues at the time of her admission to suggest this possibility. The raised ALT was most likely due to muscle inflammation and not related to liver disease. Similarly the absence of red blood cells on urine microscopy suggests that the positive result for blood on urine dipstick testing may have been due to myoglobinuria rather than true haematuria. Both of these phenomena are commonly encountered in patients with myositis and could potentially help in early diagnosis.

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Sandeep Mukherjee
Rheumatology Department, Southampton
University Hospitals NHS Trust, Southampton

Ray Armstrong
Rheumatology Department, Southampton
University Hospitals NHS Trust, Southampton

CLINICAL PROBLEMS WITH BIOLOGIC THERAPIES

O Farooqui and H Tahir

Clinical Problems with Biologic Therapies. Good Clinical Care.

A 32 year old female with rheumatoid arthritis presents with a two day history of abdominal pain, dysuria and fever. She feels lethargic, nauseated and is unable to tolerate anything orally.

What questions form part of your initial assessment?

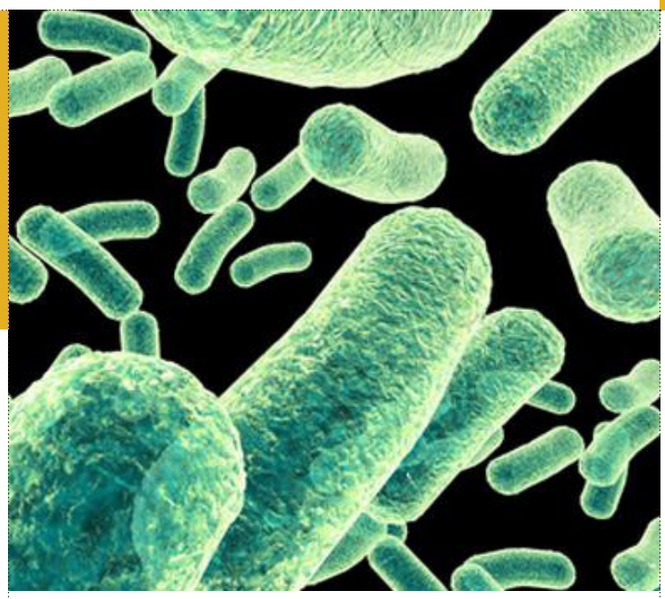
Regarding abdominal pain:
- onset/location/nature/timing pattern
- upper GI symptoms
- lower GI symptoms
- dietary indiscretion/travel
- urinary symptoms
- gynaecological symptoms
- trauma history

Regarding fevers:
- other infective symptoms
- history of rigors
- history of recurrent infections (?diabetes)
- history of similar episodes
- review headache/neck stiffness
- rash/weight loss/anorexia
- any features of autoimmune disease
- any features of thyrotoxicosis

Additional enquiry regarding:
- joint symptoms
- frequency/nature of RA flares
- present treatment/compliance

Other relevant questions:
- relevant past medical history
- smoking/alcohol/family history
- drug history (?NSAIDs/steroids)
- allergy/ recreational drug history
- sexual/pregnancy history
- normal functional level

The patient tells you she is on weekly Etanercept and methotrexate which has successfully controlled her RA for two years. She has not had previous infections whilst on this treatment.



On examination, what would you look for?

Assess for:

- observations: temperature, pulse, BP, RR, OD saturations

- evidence of delirium

- fluid status? dehydrated

- abdominal tenderness: check epigastrium (PUD), right hypochondrium (PUD, cholecystitis), flank (pyelonephritis), iliac fossa (appendicitis, diverticulitis, ectopic preg), suprapubic (cystitis)

- source of infection:
- signs of skin/joint infection
- signs of pneumonia
- signs of UTI
- signs of endocarditis
- signs of meningeal irritation

- signs of joint inflammation:
- warmth
- swelling
- tenderness
- Ðrange of movement/ Ðfunctional impairment

- also check for:
- blood sugar (?ketoacidosis), rash (?infection)

Examination reveals a regular pulse of 100 but normal BP. She is not confused or dehydrated. There is left flank and suprapubic tenderness but no evidence of inflammatory arthritis. Systemic examination is otherwise unremarkable.

CLINICAL PROBLEMS WITH BIOLOGIC THERAPIES

O Farooqui and H Tahir

Clinical Problems with Biologic Therapies. Good Clinical Care.

What investigations would you organise?

Bedside: urine dipstick
urine Ð-hCG
electrocardiogram

Bloods/urine:

Hb	arterial blood gas	urine MCS
WCC/neutrophils	urea+electrolytes	
ESR/CRP	liver function tests	
blood cultures	amylase	

Imaging: chest X-ray
abdominal/pelvic ultrasound

Initial results reveal: WCC 18 (neutrophilia 16), CRP 95, ESR 50; blood gases/ chest X-ray are normal. Urine dipstick shows leucocytes/nitrites+++ but no blood/protein. Urine pregnancy testing is negative.

She is treated with intravenous antibiotics for acute left-sided pyelonephritis. Subsequent ultrasound and blood cultures are normal. Urine culture grows E.coli.

How else would you manage this patient?

1. Stop both Etanercept and methotrexate as these are both immunosuppresants and the patient has a serious infection (ie. required admission for IV antibiotics)

2. Start intravenous fluids/antiemetics

3. In-patient rheumatology review as the patient is on biologic therapy for RA

She makes an uneventful recovery after 48 hours of intravenous antibiotics. She is discharged home after three days.

What must you ensure on discharge?

1. Early follow-up in rheumatology outpatients (within 2 weeks)

2. Patient to complete the necessary two-week course of antibiotics for pyelonephritis

This case highlights how a serious infection requiring admission is complicated by the patient's use of immunosuppressive drugs for a separate problem - her RA. These are not uncommon in patients on biologics and with the increasing use of such agents in the management of inflammatory arthritis, all doctors need to be aware of how best to deal with patients in similar clinical scenarios.

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder that principally attacks synovial joints but can affect many other tissues. Inflammation is orchestrated by signalling molecules called cytokines including tumor necrosis factor (TNF). In the rheumatoid synovium, though the cytokine expression is heterogeneous, TNF is abundant[1] and its role in potentiating synovitis is now known to be one of the drivers for systemic inflammation seen in RA. If unchecked, this can lead to joint destruction (see fig.1).[2]

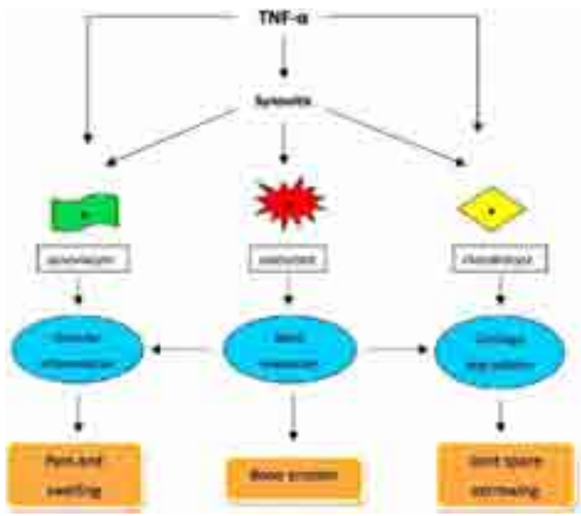


Figure 1. Mechanisms of TNF-mediated joint damage (reproduced with permission, Magnani A et al, 2005)

CLINICAL PROBLEMS WITH BIOLOGIC THERAPIES

O Farooqui and H Tahir

Biologics are genetically-engineered drugs that work by either selectively blocking the effects of cytokines or interfering with their immunologic effectors downstream. The development of TNF inhibitors therefore represents one of the most significant therapeutic advances in the treatment of RA in the last decade.

Currently, the four commonly used anti-TNF agents licensed in the UK for RA treatment are Etanercept (soluble TNF receptor), Infliximab, Adalimumab and Certolizumab (all anti-TNF monoclonal antibodies). Most recently a fifth agent, Golimumab, also a monoclonal antibody, has been licensed in the UK for RA. All these drugs are regularly administered subcutaneously whilst Infliximab, an infusion, is an option when closer patient supervision is warranted eg. concerns over compliance or inability to self-inject. Biologics targeting different immunological pathways are now also licensed for RA (see fig.2): Rituximab is an anti-CD20 antibody, Abatacept a T-cell co-stimulation inhibitor, Anakinra an anti-IL 1 molecule and Tocilizumab an anti-IL 6 antibody.[3] These drugs are beyond the scope of this article.

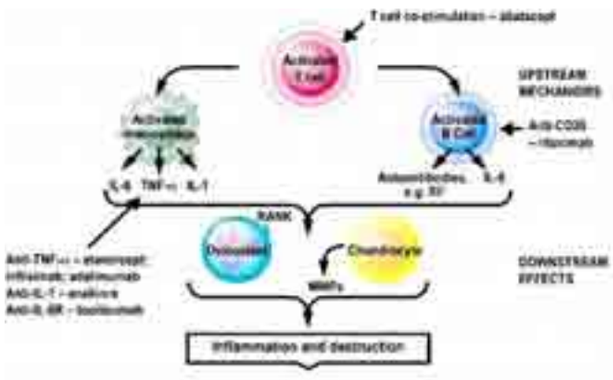
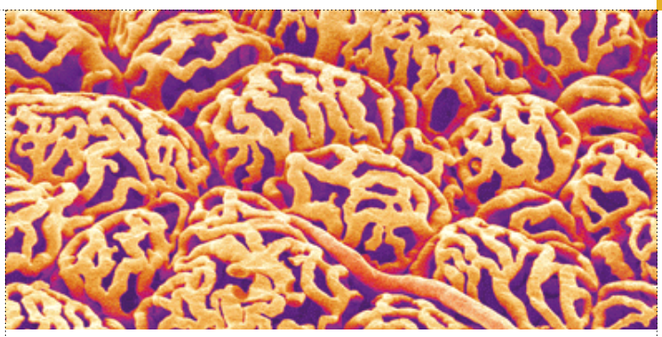


Figure 2. RA immunopathogenesis showing biologic therapy targets (reproduced with permission, Birbara C, 2008)

As relatively new drugs and in view of TNF's role in combating infection, preventing tumorigenesis and 'immune surveillance', there have been justified concerns regarding the long-term safety of these agents. The British Society for Rheumatology Biologics Register (BSRBR) - a collaboration between the BSR, University of Manchester and pharmaceutical companies – was therefore set up in 2001 to follow up patients long-term for this very reason; other European countries have similar registries. To date, at least 4000 patients each on all TNF-inhibitors (Certolizumab registration ongoing) have provided a wealth of data on their safety profile. The author aims to review this and provide guidance to doctors encountering common clinical scenarios in patients on these therapies.



Safety Profile

1. Infection Risk: a) Non-mycobacterial

Serious infection (requiring admission/parenteral antibiotics or causing death) risk in RA patients is twice that of the general population and RA severity independently increases this risk.Ð This is further increased on anti –TNF therapy, particularly in the first six months of treatment.Ð Anti-TNF agents should be discontinued/not initiated during active infection and only recommenced after clinical resolution. Caution is advised in patients with chronic leg ulcers, septic arthritis within the previous year, recurrent chest infection, indwelling catheter, hypogammaglobulinaemia and bronchiectasis.Ð As these agents can mask the signs of infection, clinicians must assume a high index of suspicion and investigate thoroughly for any infective nidus.

Infection risk is similar between the biologics and overall is not significantly higher compared to patients on conventional DMARDs. However, the incidence of serious skin/soft tissue infection and septic arthritis appears to be increased in anti-TNF treated patients;Ð clinicians thus need to be vigilant in assessing for these. Other opportunistic infections reported include fungal (candidosis, aspergillosis), atypical mycobacterial and viral (hepatitis B) infections.

b) M. tuberculosis

There is now a well-known and established increased risk of TB associated with anti-TNF therapy.Ð National guidelines recommend all patients be screened for mycobacterial infection though recent French data analysis shows pre-treatment tuberculin skin testing positivity as low as 33% in confirmed cases. Chemoprophylaxis prior to anti-TNF commencement should be considered in those with potentially latent disease (previous history, abnormal chest film) as per British Thoracic Society guidelines.Ð Close monitoring should continue in any patient for at least 6 months after biologic cessation (for whatever reason) in view of their prolonged elimination phase.Ð Newer tests for latent TB (Quantiferon and T-spot) remain unvalidated.

BSRBR data found the risk of latent TB reactivation to be higher with Infliximab and Adalimumab compared to Etanercept with nearly half of Infliximab-associated cases occurring much sooner (within first 90 days of treatment) compared to Etanercept (10%).Ð One possible explanation is that both monoclonal therapies inhibit T-cell activation and interferon-Ð production whilst Etanercept does not. Both TNF and interferon-Ð can protect against TB. Lastly, TB with TNF-inhibitors has a higher likelihood of dissemination or involving extrapulmonary sites thereby necessitating considerable vigilance on the clinician's part.

CLINICAL PROBLEMS WITH BIOLOGIC THERAPIES

O Farooqui and H Tahir

Clinical Problems with Biologic Therapies. Good Clinical Care.

2. Malignancy

TNF plays a crucial role in the body's defence against tumorigenesis yet no convincing evidence exists of an overall increased risk of de novo malignancy with anti-TNF therapy over and above that expected for the RA population.Ð These findings mirror results from Swedish registries. Presently, biologics are cautioned against in those treated for malignancy in the previous 10 years or those with pre-malignant conditions like Barrett's oesophagus.

There is emerging evidence of a non-significant but increased risk of non-melanotic skin cancer in anti-TNF treated patients with no previous dermatological malignancy. Factors increasing this risk include previous malignancy and biologic treatment duration (particularly Infliximab).Ð The higher lymphoma incidence associated with RA is well-established and increases with disease severity. However, evidence suggesting higher than expected rates in anti-TNF treated patients remains inconclusive; it is unclear whether this reflects the inherent increased risk in RA patients or from the therapy itself. Studies in the USA and Sweden have similarly failed to show any increased risk. Treatment should always be stopped when malignancy is confirmed.

3. Demyelination

This is reported with all three agents affecting diverse parts of the central and peripheral nervous systems. Clinical presentations include optic neuritis, hemiparesis, transverse myelitis, Guillain-Barré syndrome and peripheral neuropathy. Though causality remains unclear, many reports indicate partial/complete improvement on treatment withdrawal. Biologics should not be used where a clear history of demyelination exists and must be withdrawn when it is confirmed.

4. Heart disease

TNF-inhibitors are relatively contraindicated in cardiac failure and should be discontinued if this develops or worsens on treatment. Interestingly, current data suggests a potential beneficial effect of TNF-inhibitors on cardiovascular events (myocardial infarction, stroke) but firm conclusions cannot yet be drawn.

5. Mortality

Compared with patients on standard DMARD therapy, treatment with anti-TNF therapies is not associated with increased mortality.Ð

6. Miscellaneous

a) Haematological

Neutropenia is reported with all three agents but in many cases there have been co-prescribed drugs with potential for marrow toxicity. Anti-TNF-associated pancytopenia/aplastic anaemia is reported but very rare.Ð Full blood counts should be monitored.

b) Lupus-like disease/vasculitis

ANA formation has been reported with all three agents and is thought to explain the mild disease seen; 'full-blown' lupus-like disease is rare.Ð Skin rash (vasculitis) is the commonest symptom which typically resolves on drug discontinuation. There are no reports of nephritis or neuropsychiatric involvement. Treatment should be stopped if autoimmune disease develops.

c) Psoriasis

Various reports indicate an increased incidence of psoriasis in patients on TNF-inhibitors despite NICE having now having approved these very drugs for its treatment.Ð Data shows Adalimumab-treated patients to have the highest incidence with anti-TNF-induced psoriasis far more likely to be the pustular type affecting the palms/soles (palmoplantar) than classical plaque disease.Ð Drug cessation with additional conventional psoriatic treatments usually induces remission.

d) Uveitis

Anterior uveitis is a common spondyloarthritic extra-articular feature. Several case reports now show uveitis developing with all three agents despite their reported use in resistant uveitis. Most cases of treatment-associated disease in one study occured with Etanercept though in many of these patients, the underlying clinical diagnosis was unknown thus casting doubt on the apparent causality.

CLINICAL PROBLEMS WITH BIOLOGIC THERAPIES

O Farooqui and H Tahir

Clinical scenarios

1. Coexistent infection

As described, TNF-inhibitors are associated with a small but significant increase in serious infections, particularly in the first 6 months. Some evidence supports infections becoming more severe if patients continue with anti-TNF therapyÐ so patients should omit these until clinical resolution occurs. This is particularly the case in RA patients, many of whom already have a high background infection risk eg. bronchiectasis, glucocorticoid use.

Present guidelines suggest patients developing TB-related symptoms on anti-TNF therapy should receive full anti-mycobacterial treatment but may continue biologic treatment if clinically indicated.

2. Perioperative

Withholding TNF-inhibitors is generally recommended, particularly prior to prosthetic joint surgery, to allow optimal healing and reduce post-operative infection risk.Ð Though drug elimination varies, current advice is to stop treatment for a duration of 3-5 half-lives pre-operativelyÐ depending on the agent. The half-life is 8-9 days for Infliximab, 3-4 days for Etanercept and 15 days for Adalimumab. Treatment can be restarted once infection is excluded and wound healing deemed satisfactory (usually 10-14 days post-operatively). Current data is conflicting on the risk of increased infection where treatment is continued.

3. Pregnancy

The safety of TNF-inhibitors has not been established in pregnancy/lactation.Ð Precautions against pregnancy are advised where either/both partners are on anti-TNF therapies. Therapeutic continuation may still be considered in patients wishing to conceive and where drug cessation poses a high relapse risk. This qualification also applies to women who conceive whilst on treatment. Whilst various reports suggest some anti-TNF-related pregnancy complications, others reassuringly show normal outcomes despite continuous treatment. Present human studies are insufficient to guarantee safety.Ð Non-biologic DMARDs known to be safe in pregnancy remain an alternative. The pros and cons of breastfeeding whilst on therapy needs to be considered on an individual basis but is thought to pose little risk.

4. Immunization

Data on immunization whilst on biologics is limited so BSR recommendation mirrors that for patients on non-biologic immunosuppressants. Subjects should have both the influenza (including outbreak-specific vaccines eg. Swine flu) and pneumococcal immunization despite the known attenuated responses seen on TNF-inhibitors (ideally prior to treatment).Ð Attenuated live vaccines whose effects whilst on anti-TNF remain unknown are not recommended.

Hepatitis B vaccination is recommended for all at-risk unvaccinated adults, ideally prior to biologic commencement.

MCQs

True or false?

1. A female diagnosed with breast cancer 5 years ago cannot be treated with anti-TNF therapy (T/F)
2. HIV infection is an absolute contraindication to anti-TNF therapy (T/F)
3. Patients on anti-TNF therapy and concomitant methotrexate should stop both during active infection (T/F)
4. Upper respiratory tract infections require temporary cessation of anti-TNF therapy (T/F)
5. Chicken-pox vaccination is safe in patients on anti-TNF therapy (T/F)

Answers

1. True. Any patient with a previous history of malignancy within the previous 10 years should not be given biologic therapy
2. False. Evidence actually suggests anti-TNF treatment is well-tolerated as long as patients are established on HIV treatment with no apparent adverse clinical events (eg.ÐCD4, Ðviral load) being attributable to the former
3. True. Methotrexate is also an immunosuppressant and like ant-TNF should only be restarted once the infection has clinically resolved
4. False. Minor infections (eg.viral URTI) can be treated without interrupting anti-TNF therapy
5. False. This is a live, attenuated vaccine and therefore should not be administered

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Authors

Omar Farooqui BSc MB MRCP (UK)
Specialist Registrar, Rheumatology/GIM
University College Hospital, London

Hasan Tahir BSc, MB BS, D Sports Ex-Med, MFSEM, FRCP
Consultant Physician and Rheumatologist
Whipps Cross University Hospital, London

A CATASTROPHE OF CLOTS

L Nadarajah, O Farooqui and H Tahir

A Catastrophe of Clots.
Patient Management.

Abstract

Antiphospholipid Syndrome (APS) is characterised by venous and arterial thrombosis with recurrent foetal loss in women. Uncontrolled thrombosis can have devastating consequences, particularly since APS is under-recognised and under-diagnosed. We present the case of Mrs X, a 29 year old lady with APS who presents with worsening dyspnoea. Her case raised numerous clinical challenges with the development of possible neoplastic-driven events, pulmonary hypertension and massive haemoptysis.

Case based discussion

A 29 year old Asian female with a confirmed diagnosis of APS presents to you in A&E with dyspnoea.

On history-taking, what questions would you ask as part of your initial assessment?

Relating to dyspnoea:

- onset

Associated symptoms:

- cough
- haemoptysis
- chest pain - ?exertional/pleuritic
- wheeze
- fever
- anorexia/weight loss
- ankle swelling/orthopnoea
- normal exercise tolerance

Other:

- travel
- surgery
- contraceptive pill
- smoking

Relating to APS:

- previous miscarriages (?gestation)
- previous deep vein thrombosis /pulmonary embolism

She reports having worsening dyspnoea over a 2 week period and a decline in exercise tolerance to 25 metres. History also reveals that she has had recurrent pulmonary emboli and deep vein thrombosis and is on lifelong Warfarin. She denies having any other symptoms.
What are your differentials?

- pulmonary embolism (PE)
- pulmonary hypertension (PAH)
- lower respiratory tract infection

How would you investigate her?

Laboratory tests:

- full blood count
- electrolytes
- liver function tests
- coagulation
- D-Dimer
- CRP
- Arterial blood gas (ABG)
- blood film

Radiology & specialist investigations

- chest X-ray
- ECG
- CT pulmonary angiography (CTPA)
- echocardiogram

Initial investigations revealed an elevated D-Dimer (1.2) and hypoxia on ABG (PaOÐ 8.2kPa). INR was 3.6 and was therefore within therapeutic range. A normal CRP and chest X-ray made infection an unlikely diagnosis. ECG showed sinus tachycardia. A high clinical suspicion of a further thromboembolic event prompted a CTPA which confirmed bilateral pulmonary emboli but also showed a suspicious hilar mass. A normal ultrasound Doppler of the lower limbs precluded the need for a caval filter. Echocardiogram identified severe pulmonary hypertension with pulmonary artery systolic pressures of 135mmHg (normal 15-30mmHg).

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At this stage her problems were the following:

1. Recurrent thrombotic events despite therapeutic anticoagulation
2. A suspicious hilar mass
3. Severe PAH

How would you manage her?

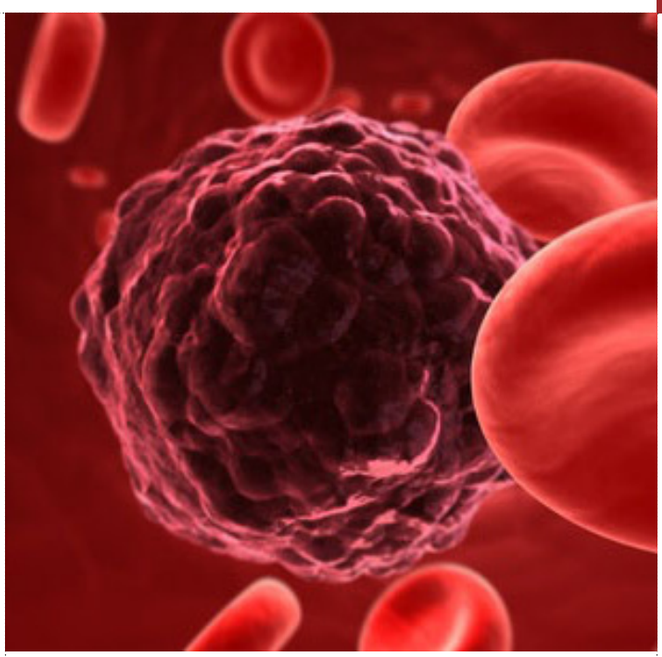
1. Discussion with the haematologists - for venous or arterial thromboembolism therapeutic INR is normally between 2-3; however in APS patients with recurrent arterial/venous events this should lie between 3-4. Our patient was within the therapeutic range yet still presented with a PE. This is described as 'warfarin resistance'. The exact mechanism by which this occurs remains unclear. Patients with malignancy can also present in a similar way.[1] Anticoagulation for this group of patients involves lifelong therapeutic low molecular weight Heparin (LMWH) and daily Aspirin. She was therefore started on Enoxaparin 1.5mg/kg daily and once daily dose of Aspirin 75mg.

2. Investigation of the hilar mass with a biopsy was felt to be contraindicated due to the severe PAH. General anaesthesia/intubation would impose a high risk of right sided heart failure which in turn could lead to systemic hypotension and subsequent cardiac arrest.Ð A PET (positron emission tomography) scan was used as a second line investigation. This form of nuclear imaging uses a radioactive glucose analogue, FDG-PET, to pick up metabolically active tissues. Tumours are usually metabolically active and therefore have a high uptake of FDG-PET. Results of our patient's PET scan revealed a 'cold mass' – a metabolically inactive mass making malignancy/ infection less likely.

3. Her severe PAH was discussed with the cardiologists. This led to the initiation of Siladenfil which augments the vasodilatory effects of nitric oxide, leading to a decrease in pulmonary arterial resistance and pressure.[1]Ð Other medication that may have been intiated for the treatement of her PAH include endothelium antagonists, i.e Bosentan or Ambrisentan.[11] She was also referred to the cardiothoracic surgeons for consideration of endarterectomy.
She symptomatically improve, however following successful discharge she re-presented within a few weeks with haemoptysis. On arrival she was haemodynamically stable and alert. She then had a further episode of massive haemoptysis of 2 litres. She became haemodynamically compromised with a BP 88/56, tachycardia 105, and saturations of 88% on 15 litres OÐ.

Massive haemoptysis is a medical emergency and is defined as haemoptysis of greater than 600ml.

Initial management should follow the Advanced Life Support (ALS) 'ABCDE' algorithm.



- Airway protection - early anaesthetic involvement for intubation
- High flow oxygen
- Assessment of hemodynamic stability- IV colloids, blood transfusion
- Urgent fibre-optic bronchoscopy to locate the source of bleeding
- CT Angiography and embolisation

Differential diagnosis at this stage included:

- Massive pulmonary embolus
- Severe PAH
- Pulmonary arteriovenous malformation
- Catastrophic antiphospholipid syndrome
- Over anticoagulation with enoxaparin

She was transfused 6 units of bloods, intubated and ventilated, and was then transferred to a tertiary intensive care unit for CT angiography. Blood tests showed significant renal and liver impairment culminating in multi-organ failure. Neither CT–Angiography nor bronchoscopy could locate the source of the bleeding. Appropriate organ support was given and she was also treated with corticosteroids and IV immunoglobulins to cover the possibility of Catastrophic APS. IV Iloprost was used to lower her pulmonary artery systolic pressure. Over anticoagulation with enoxaparin was thought to be an unlikely differential as she was not underweight and blood tests prior to admission showed normal renal function. Unfortunately she did not respond and died within 48 hours of presentation.

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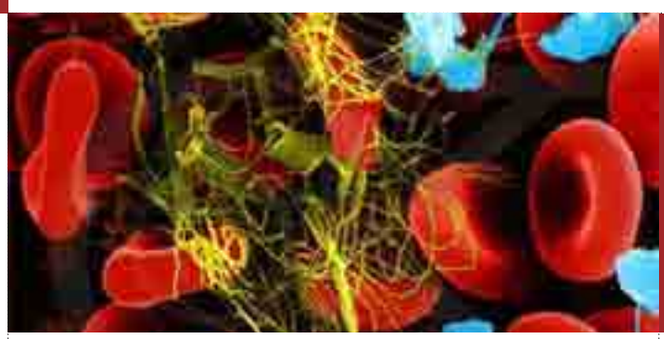

A Catastrophe of Clots.
Patient Management.

Antiphospholipid syndrome

APS is characterised by venous and arterial thrombosis with recurrent foetal loss in women. Uncontrolled thrombosis can have devastating consequences, particularly since APS is under-recognised and under-diagnosed. Therefore APS must be considered in younger patients presenting with vascular thrombosis (arterial or venous) or females with recurrent miscarriages.
APS is considered present when one clinical and one laboratory criterion are met using the following:

- **Clinical:** one episode of arterial/venous thrombosis or pregnancy loss (imaging/histology are essential).

- **Laboratory:** antiphospholipid (aPL) antibody, either anticardiolipin (aCL), lupus anticoagulant (LA) or anti-Ð2-glycoprotein-1 (Ð2-GP1) presence in significant titre. Positivity must be present on two separate occasions three months apartÐ, as transient positivity occurs in some infections.

Approximately 50% of cases occur in isolation, primary APS. The remaining cases are associated with other autoimmune diseases (SLE, Sjogren's, scleroderma, rheumatoid arthritis), and are therefore labelled as secondary APS. An acute APS variant, catastrophic APS (Asherson's syndrome), is characterised by chronological vaso-occlusive events typically affecting the brain, kidneys, lung and skin causing a widespread thrombotic microangiopathy and multiorgan failure.

Mechanism of action

The three antiphospholipid (aPL) antibodies, directed against membrane phospholipids, are: anticardiolipin (aCL), lupus anticoagulant (LA) and anti-Ð2-glycoprotein-1 (Ð2-GP1). Found in 1-5% of the healthy population, their prevalence increases with age, certain infections (eg. HIV, hepatitis C) and drugs (phenytoin, propranolol, amoxicillin).

aPL antibodies augment a pro-coagulatory cascade by increasing platelet aggregation, provoking endothelial cell dysfunction and possibly inhibiting anticoagulation factors. These processes attract other pro-inflammatory cells eventually causing endothelial cell damage and ultimately thrombosis (figure 1).[3]

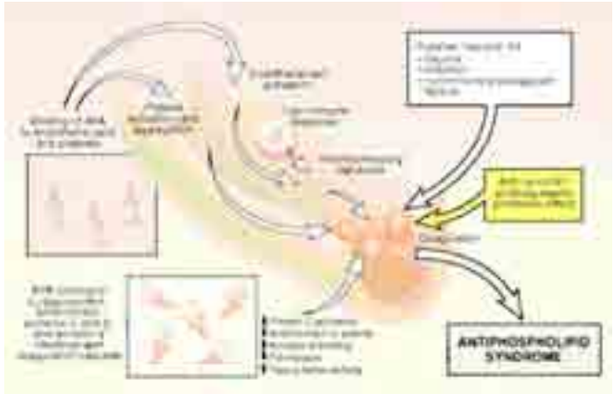

Figure 1. Putative mechanisms in APS

Patients positive for all three antibodies have a potentially greater risk of vascular events and pregnancy morbidity. Factors like smoking and oral contraceptive use additively increase this risk.

Clinical Presentation

Although aPL antibody prevalence is 1-5%, only a minority will develop APS. The syndrome's clinical diversity means that first presentation can be to a variety of specialists (figure 4).[2]

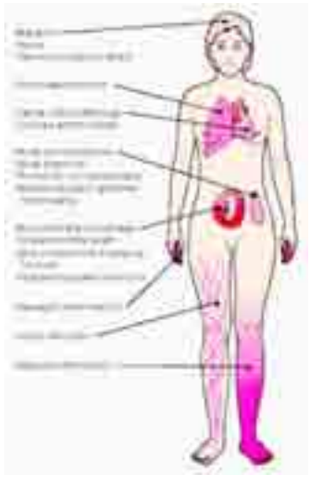

Figure 2. APS: clinical manifestations

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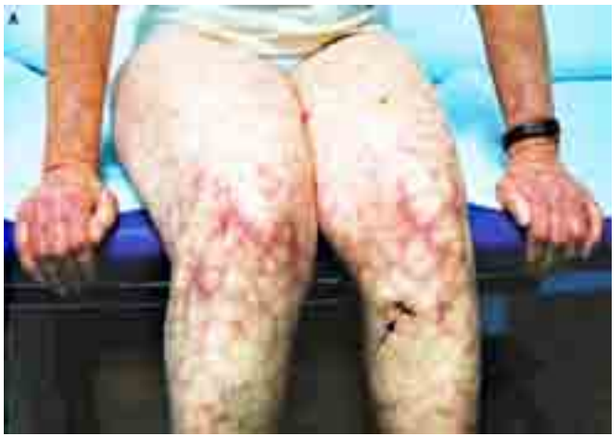

Figure 3. Livedo reticularis

In a cohort of 1000 patientsÐ, the commonest presentations were DVT (39%) and PE (14%). The commonest arterial events in the cohort were stroke (20%) and transient ischaemic attack (11%). Notably, the risk of recurrent events is consistent for both venous (70%) and arterial thromboses (90%).[2]

Who to Suspect

Clinical suspicion of APS must be context-dependent; aPL antibody testing is advised in the following:

Thrombosis:

- Arterial event <50
- Unprovoked venous event <50
- Recurrent thrombosis (arterial or venous)
- Unusual venous thrombosis (eg. axillary, cerebral)
- Both arterial and venous thromboses

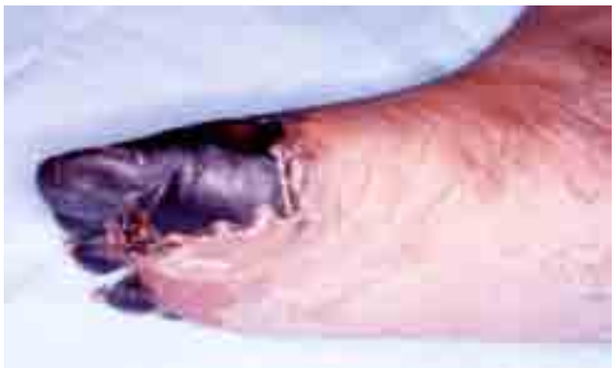

Figure 4. Peripheral thrombosis causing ischaemia and necrosis

Obstetric patients:

- ≥1 unexplained foetal loss (>10/40)
- ≥3 spontaneous miscarriages (<10/40) - chromosomal abnormality remains commonest cause
- Early/severe pre-eclampsia
- Unexplained intrauterine growth retardation

Lupus patients:

- At diagnosis
- Before pregnancy, surgery or hormone treatment
- Whenever new neurological/thrombotic/obstetric event

Treatment

Antiplatelet and anticoagulant therapies reduce the risk of recurrent thromboembolism and remain the mainstay of treatment. Management depends on the event sustained.

In an unprovoked venous thrombosis (no reversible factors e.g. surgery, pregnancy) or thromboembolism with persistent aPL antibody, lifelong anticoagulation is recommended. In APS-related stroke, indefinite Aspirin or Warfarin is advised with comparable rates of recurrent events and bleeding risks.[2] Guidelines recommend that patients with recurrent thrombosis while anticoagulated require a target INR of 3.5 (3-4).

No evidence presently exists for the primary prevention or thromboprophylaxis in asymptomatic seropositive individuals; this applies to pregnant women without clinical symptoms[2].

Women with previous APS-related obstetric morbidity pose a more complex problem. By and large, Aspirin ± unfractionated Heparin (LMWH) before and LMWH or Warfarin after delivery provide the mainstay of treatment.

Important Points

1) Early recognition of APS prevents later disabling morbidity and possibly death.

2) Check all three aPL antibodies, where possible, before anticoagulation commencement (this interferes with assay). Anticoagulation, where indicated, must never be delayed for such testing.

3) Refer to specialists early, especially pregnant women.

4) Address other vascular risk factors like smoking, cholesterol, obesity and hormone treatment.

5) APS represents a disease continuum with many clinical manifestationsÐ so patients must not be evaluated and managed as one disorder with a predictable outcome. Multidisciplinary management may involve a rheumatologist, dermatologist, haematologist, neurologist, nephrologist, cardiologist or obstetrician.

A CATASTROPHE OF CLOTS

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MCQs

True or false?

1. Catastrophic APS (CAPS) occurs in 10% of patients?
2. A definitive diagnosis of (CAPS) requires three or more organ/tissue/system involvement?
3. Malignancy can give rise to aPL positivity?
4. All APS patients with a previous thrombotic event need anticoagulation?
5. LMWH should be commenced as soon as the urine Ð-hcG is positive?

A Catastrophe of Clots.
Patient Management.

Answers

1. False. CAPS accounts for <1% of APS cases. An international registry of CAPS patients is available online documenting the entire clinical, laboratory and therapeutic data of around 300 patients.
2. True. Other essential criteria include the development of manifestations simultaneously or in less than one week along with the histopathological and laboratory confirmation as for APS.
3. True. These include many solid tumours, haematological malignancies and paraproteinaemias.
4. False. Where the initial thrombotic event is 'triggered' by a drug (OCP) or trauma, long-term anticoagulation may not be necessary. 'Trigger' avoidance, possibly along with aspirin, may suffice for future thromboprophylaxis.
5. False. Aspirin should be commenced as soon as the urine pregnancy test is positive; LMWH self-injection should start once a foetal heartbeat is confirmed.

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Authors

Luxme Nadarajah BSc, MB BS
Core medical trainee, Rheumatology/General Medicine
Whipps Cross University Hospital, London

Omar Farooqui BSc MB MRCP
Specialist Registrar, Rheumatology/General Medicine
University College Hospital, London

Hasan Tahir BSc, MB BS, D Sports-Ex Med, MFSEM, FRCP
Consultant Physician in Acute Medicine and Rheumatology
Whipps Cross University Hospital, Londo

WEAKNESS AND WHEEZING IN A YOUNG WOMAN

K Sanyal, K Moss and N Sofat

Weakness and wheezing in a young woman.
Patient Management.

Abstract

A 32-year old Asian woman presented with a 2-week history of weakness and tingling in her right arm and leg. She also reported a rash over her right leg. She had a past medical history of asthma. Clinical examination revealed an erythematous rash over her lower leg. On chest auscultation she had fine bibasal inspiratory crackles. Blood results showed raised inflammatory markers, a peripheral blood eosinophilia and a negative ANCA. A high resolution CT chest showed ground glass shadowing consistent with interstitial lung disease. A biopsy of the skin rash demonstrated eosinophilic vasculitis. Based on these findings, a diagnosis of Churg-Strauss vasculitis was made. The patient responded well to intravenous corticosteroid and cyclophosphamide therapy with rapid resolution of her vasculitis.

Case History

A 32-year old female presented with new onset weakness and a tingling sensation in her right arm, hand and leg. She also described a red, painful area over her right shin. She had a past medical history of asthma which was well controlled on salbutamol inhalers used as required.

On examination, her vital signs were normal. She had a 3 x 4 cm maculopapular rash over her right shin. She had a normal cranial nerve examination. Power was reduced in her right leg to 4/5 but she had normal tone, reflexes, co-ordination and sensation in all 4 limbs. Auscultation of the lung bases revealed fine bibasal inspiratory crackles.

Results of investigations are summarized in Table 1 below:

Hb	9.2 g/dl (12.0 – 16.0)	
White cell count	6.9 x 10^9 /L (4.0-11.0)	
Eosinophils	1.7 X 10^9 /L (0.1 – 0.8)	
Rheumatoid Factor	< 20 IU/ml (0 – 20)	
ANA	Negative	
ANCA	Negative	
C3	2.1 g/l (0.75 – 1.65)	
C4	0.42 g/l (0.14 – 0.54)	
IgG	10.6 g/l (6.0 – 16.1)	
IgA	3.10 g/l (0.8 – 2.8)	
IgM	1.0 g/l (0.5 – 1.9)	
Anticardiolipin IgG	Negative	
GBM antibodies	3 U/ml (0 – 10)	
β2 microglobulin	1.6 mg /l (1.2 – 2.4)	
Hepatitis B /C	Not detected	
Borrelia IgG and IgM	Negative	
ESR	89 mm/hr	(0-20 mm/hr)
CRP	101 mg/L	(<10)
Urinalysis: protein ++ , Blood: nil, Bilirubin: nil, scanty casts		

Table 1. Summary of patient results

A chest radiograph was performed and showed diffuse reticulonodular shadowing at the mid and lower zones of both lung fields (Figure 1). A CT scan of the chest/abdomen/pelvis was performed. Diffuse ground glass shadowing was observed throughout both lungs predominantly in the mid and lower zones (Figure 2). Bronchoalveolar lavage culture showed no evidence of TB, fungi or viruses. Electromyography revealed axonal degeneration involving the sciatic nerve on the right side. Punch biopsy of the left leg showed a vasculitis with eosinophilic infiltration. Renal tract ultrasound demonstrated normal sized, unobstructed kidneys, both showing increased echogenicity consistent with a vasculitic process.

WEAKNESS AND WHEEZING IN A YOUNG WOMAN

K Sanyal, K Moss and N Sofat

Weakness and wheezing in a young woman. Patient Management.Patient Management.

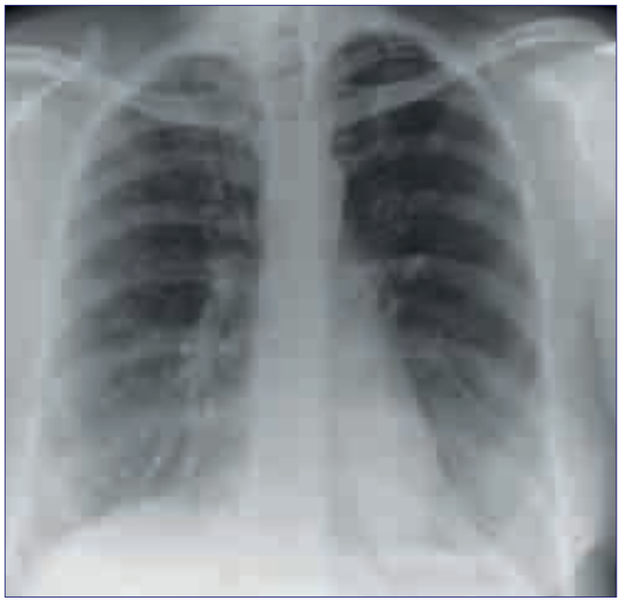


Figure 1. Chest radiograph of patient showing reticulonodular shadowing in the mid- and lower- zones bilaterally

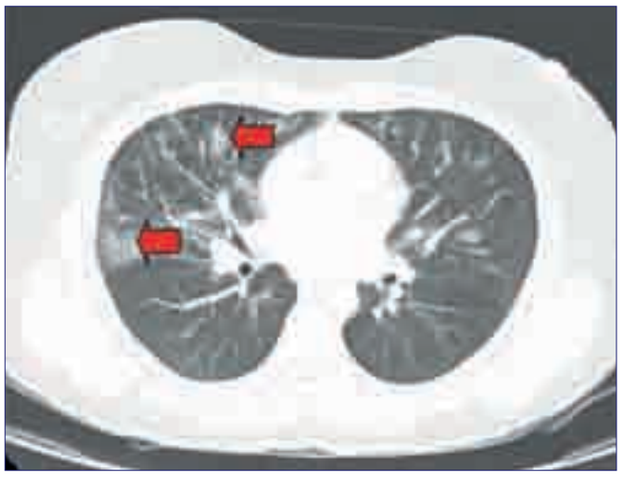


Figure 2. High resolution CT chest of the patient revealing ground glass opacification (red arrows)

Diagnosis

Based on the patient's peripheral blood eosinophilia, peripheral nerve involvement and the skin biopsy results, a diagnosis of eosinophilic vasculitis, or Churg-Strauss syndrome, was made.

Case-Based Discussion

The patient was given 3 doses of pulsed intravenous methylprednisolone 1g each over 3 days for treatment of her active vasculitis.

Two days after receiving the third dose of methylprednisolone, she developed acute onset chest pain and shortness of breath. Her ECG was normal. Due to the rapid onset of her symptoms, she underwent urgent computed tomographic pulmonary angiography (CTPA). Her CTPA showed substantial bilateral pulmonary emboli, shown in Figure 3. The pulmonary emboli were likely to be part of an acute vasculitic process. She was therefore commenced on warfarin and pulsed intravenous cyclophosphamide therapy to suppress the active vasculitic process.

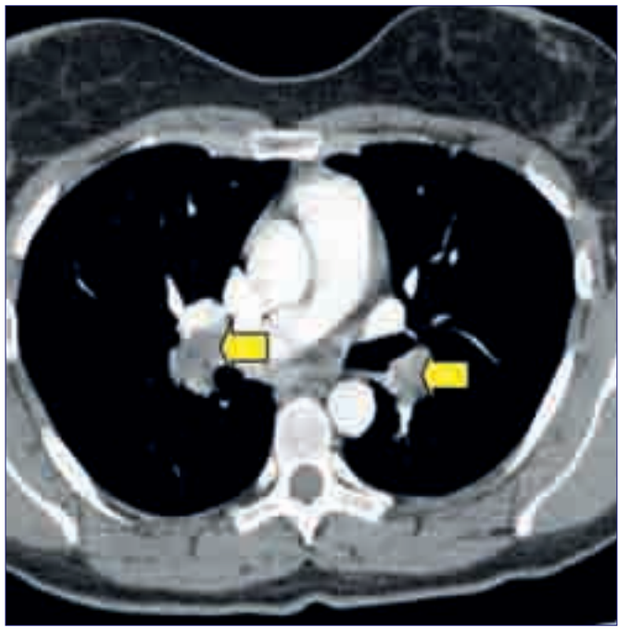


Figure 3. CT pulmonary angiogram of patient showing bilateral pulmonary emboli with filling defects (yellow arrows)

WEAKNESS AND WHEEZING IN A YOUNG WOMAN

K Sanyal, K Moss and N Sofat

Following 6 infusions of intravenous cyclophosphamide, long-term oral azathioprine 100 mg twice daily was instituted and she continued on a reducing dose of oral prednisolone 4 mg daily. Six months after her initial diagnosis, she was clinically in remission with improvement of her weakness, resolution of her skin rash and no further shortness of breath. Following treatment, her eosinophil count returned to normal.

Our patient was ANCA negative on repeated serology tests. Her peripheral blood eosinophilia was notably high at more than 3 times the normal level. Our case showed typical features of pulmonary involvement, mononeuropathy, renal vasculitis and hypereosinophilia characterised in Churg-Strauss syndrome. This is often observed in individuals with a previous history of asthma and/or allergic rhinitis.

Churg-Strauss syndrome is a rare disease. In 1990 the American College of Rheumatology (ACR) proposed six criteria for classification1. The presence of 4 or more criteria yields a sensitivity of 85% and a specificity of 99.7%. For classification purposes, patients should have at least four of the following six criteria, which include 1. Asthma 2. Eosinophilia more than 10% in the peripheral blood 3. paranasal sinusitis 4. pulmonary infiltrates (may be transient) 5. histological proof of vasculitis with extravascular eosiniphils 6. Mononeuritis multiplex or polyneuropathy.

Churg-Strauss syndrome is considered to be part of a spectrum of ANCA-associated vasculitides. However, ANCA are not detected in many patients and it is probable that several phenotypes of the diseases co-exist. The vasculitic process in Churg-Strauss syndrome can be divided into three mechanisms that are implicated at different stages of the disease:

1. Involvement of Th2 lymphocytes (pathogenesis of asthma)

2. Pathological eosinophilic infiltration of tissues

3. Pathogenic role of ANCA directed against myeloperoxidase (MPO) in the development of vasculitis lesions.

The precipitating factors that are implicated are diverse and include: inhaled allergens, vaccinations, desensitization, drugs or infections (parasitic or bacterial). This is often followed by a massive expansion of eosinophils. Histologically, patients demonstrate angiitis and extravascular necrotising granulomas, usually with an eosinophilic infiltrate. The vasculitis may be granulomatous or non-granulomatous and typically involves both arteries and veins. Extra-pulmonary lesions are more commonly found in the gastrointestinal tract, spleen and heart than in the kidney.

Anaemia and elevated ESR/CRP, as observed in our case, are high in most of patients. Eosinophilia is constant and usually higher than 10% of normal 2, 3. There is an association with P-ANCA directed against myeloperoxidase (MPO). Rheumatoid factor is positive in up to 40% of patients. Our patient had an eosinophil count of 2 x 109 / L, negative P-ANCA and rheumatoid factor. Monitoring myeloperoxidase antibodies are a useful marker of disease activity and a good predictor of ANCA associated vasculitis4.

Churg-Strauss syndrome is associated with a number of complications, some of which are observed with other vasculitides e.g. Wegener's granulomatosus and others which are more likely to be observed in Churg-Strauss syndrome e.g. cardiac involvement5. A comparison of the complications observed in Churg-Strauss and Wegener's granulomatosus is shown in Table 2.

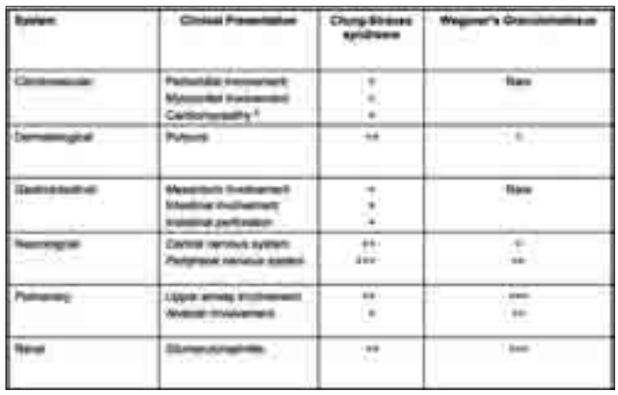


Table 2. Comparison of organ involvement observed in Churg-Strauss compared with Wegener's granulomatosus

Table adapted from Klippel and Dieppe, Rheumatology, Elsevier, 1997

Considerations for treatment

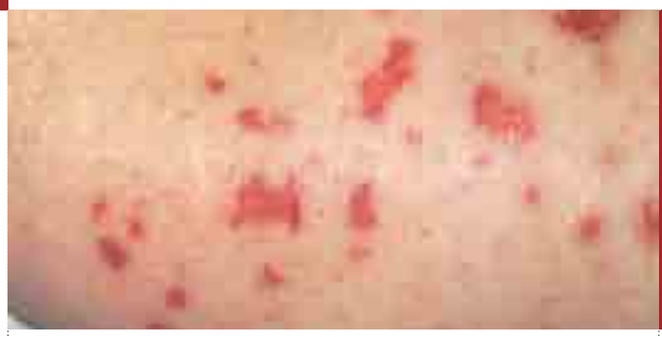
A typical management regime for Churg Strauss syndrome is high dose corticosteroid therapy at 1mg/kg /day. In cases of rapid onset of vasculitis, methylprednisolone pulses are usually given at 15 mg/kg intravenously for 60 minutes repeated for 1- 3 days, as was the case with our patient.

Oral or intravenous cyclophosphamide is part of first line therapy when one or more features of severity are observed. Based on prospective studies, it has been shown that 3 – 6 months of cyclophosphamide is sufficient for remission. Therapeutic trials are limited due to the rarity of cases, but have demonstrated that both glucocorticoid alone and glucocorticoid with cyclophosphamide are efficacious 6.

Intravenous immunoglobulin has also been used in ANCA-related vasculitis. Plasma exchange does not appear to improve vasculitis survival but is considered as second line for Churgh-Strauss refractory to conventional therapy. Our patient responded to intravenous cyclophosphamide followed by the oral immunosuppressive agent azathioprine. Rituximab is also a safe treatment in patients intolerant to the conventional medications7.

WEAKNESS AND WHEEZING IN A YOUNG WOMAN

K Sanyal, K Moss and N Sofat



Weakness and wheezing in a young woman.
Patient Management.Patient Management.

Multiple Choice Questions

1. What is the aetiology of the peripheral nerve lesions in Churg-Strauss syndrome?

a) Alcohol toxicity
b) Infection
c) Vitamin B12 deficiency
d) Vasculitis
e) Granuloma formation

2. Which of the following is associated with a high eosinophil count and pulmonary infiltrates:

a) Wegner's Granulomatosis
b) Microscopic Polyangitis
c) Churg-Strauss Syndrome
d) Polyarteritis Nodosa
e) Systemic lupus erythematosus

Answers

Answer: D.

Peripheral nervous system involvement is due to active vasculitis and is a prominent feature of Churg-Strauss syndrome.

Answer: C.

Churg-Strauss syndrome can presents with both high a eosinophil count and pulmonary infiltrates. Pulmonary infiltrates may occur in the prodromal phase, vasculitic phase or both. Pulmonary involvement can occur with or without renal involvement.

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Author

Kaushik Sanyal
Specialist Registrar in Rheumatology
Department of Rheumatology
St George's Hospital NHS Trust
Blackshaw Road
London SW17 OQT

Katie Moss
Consultant Rheumatologist
Department of Rheumatology
St George's Hospital NHS Trust
Blackshaw Road
London SW17 OQT

Corresponding author

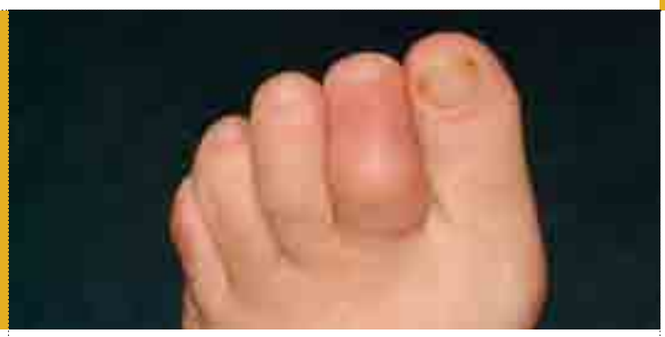
Nidhi Sofat
Consultant Rheumatologist and Clinical Senior Lecturer
Department of Rheumatology
St George's Hospital NHS Trust
Blackshaw Road
London SW17 OQT

Email: nsofat@sgul.ac.uk

DACTYLITIS

LD Williamson and L Williamson

Dactylitis.
Good Clinical Care.



Introduction

Dactylitis or 'sausage-like digits' is the inflammation of a finger or toe, affecting any of the structures within a digit. It can occur in patients of all ages and can be overlooked during routine history and examination. It is important to be aware that dactylitis is often part of a systemic disease, and may be the presenting feature. Using an illustrative case, this article discusses the common, important causes of dactylitis.

Case

A 17 year old Caucasian male attended the emergency department with a 6 week history of pain and swelling of his left second toe. He had suffered from three similar short-lived episodes during the previous two years. He was otherwise healthy, with no history of trauma, no recent travel, and no sexual history. He had no systemic symptoms, in particular no gastrointestinal or genitourinary symptoms. He had no significant past history and no family history of arthritis, colitis, iritis or tuberculosis. His father had psoriasis.

On examination he was apyrexial with normal pulse and blood pressure. Examination of skin, hair, nails, chest, abdomen and musculoskeletal system was normal apart from a dactylitis of the right second toe.

Blood tests revealed a mild microcytic anaemia (Hb 11.2 g/dL, MCV 74 fl) and a raised CRP of 16. Renal and liver function tests were normal and rheumatoid factor and tissue transglutaminase antibody tests were negative. His chest radiograph was normal.

He was prescribed Ibuprofen and Paracetamol and sent home for outpatient rheumatology review.

Six weeks later he was admitted to hospital with a four day history of severe abdominal pain and vomiting. He underwent a laparotomy where he was found to have a 50cm segment of inflamed ileum. Histology of the segment confirmed Crohn's disease.

Discussion

In this case, dactylitis is the presenting feature of enteropathic arthritis. The low-grade microcytic anaemia and raised inflammatory response in an otherwise healthy young man should alert the clinician to a search for an underlying cause. The microcytic anaemia in this case could be caused by malabsorption of iron, inadequate diet or chronic blood loss secondary to pre-clinical Crohn's disease.

The most common cause of dactylitis in the UK is as part of a seronegative inflammatory arthritis spectrum (enteropathic arthritis, reactive arthritis, psoriatic arthritis and ankylosing spondylitis). It is important to take a travel history and sexual history when considering reactive arthritis. The family history of psoriasis in this case points towards a diagnosis of possible psoriatic arthritis (PsA). Dactylitis has recently been included in the classification criteria for PsA (CASPAR) and affects up to 50% of PsA patients during their lifetime. The CASPAR criteria can be used to diagnose PsA in patients with "established inflammatory articular disease with at least 3 points from the following features: current psoriasis (assigned a score of 2; all other features were assigned a score of 1); a history of psoriasis (unless current psoriasis was present); a family history of psoriasis (unless current psoriasis was present or there was a history of psoriasis); dactylitis; juxtaarticular new bone formation, rheumatoid factor negativity; nail dystrophy".1

There are a number of patients whose dactylitis precedes the skin disease by months or years, particularly children and young adults. Dactylitis also occurs with the other manifestations of the HLA-B27-associated disease process: peripheral enthesitis, peripheral arthritis, inflammatory spinal pain, buttock pain, chest wall pain and acute anterior uveitis. Dactylitis may sometimes occur for a long time in isolation as the only clinically apparent manifestation of the HLA-B27-associated disease process.

Physical examination of the dactylitic finger or toe shows diffuse, painful swelling of a digit. It is caused by a combination of flexor tenosynovitis, soft tissue oedema, synovitis, enthesitis (inflammation of the ligament or tendon insertions into bone), and bone oedema. The fingers or toes are usually asymmetrically involved. Clinical examination is often sufficient for diagnosis, but in severe cases the dactylitis may look like cellulitis or osteomyelitis.

As dactylitis is most commonly associated with psoriatic arthritis, it is also important to look carefully for psoriasis on examination. 'Hidden' areas of psoriasis include the scalp, behind the ears, umbilicus, natal cleft, perineum and nails.

Most cases of dactylitis associated with seronegative inflammatory arthritis are self-limiting and settle with time and simple analgesia. However local corticosteroid injection to finger flexor tendon sheath or interphalangeal joint may speed recovery and prevent bony fusion of the interphalangeal joint which can occur in psoriatic arthritis. Disease-modifying antirheumatic drugs are reserved used for persistent cases or those with associated arthritis.

DACTYLITIS

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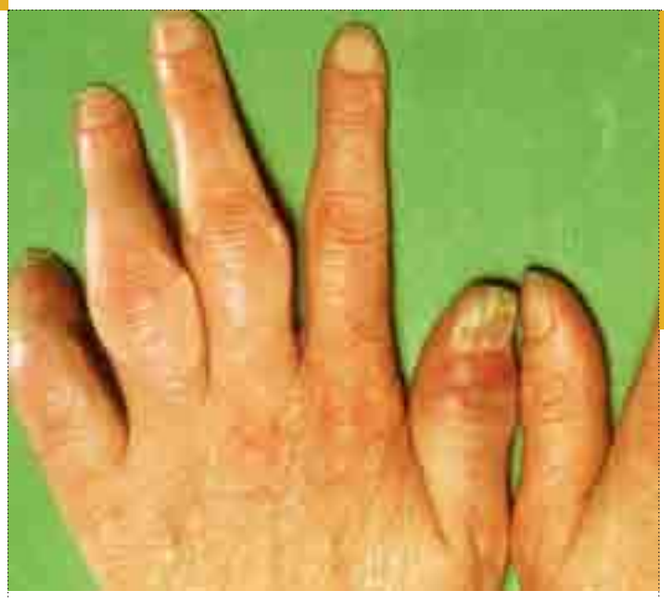

Dactylitis.
Good Clinical Care.

Other common causes of dactylitis:

Sarcoidosis

Sarcoid dactylitis is a rare manifestation of sarcoidosis, occurring in about 0.2% of patients. It is often associated with lupus pernio (chronic raised indurated skin lesions). Non-caseating granulomata invade the bones and adjacent soft tissue, leading to fusiform swellings which are usually bilateral, asymmetrical and painless.

Serum angiotensin converting enzyme level (ACE) may be raised and there may be associated hypercalcaemia and hilar lymphadenopathy. Diagnosis is confirmed by tissue biopsy from the digit or other skin lesions.

Sickle Cell Disease

Sickle cell disease dactylitis is caused by infarction of bone marrow during painful vaso-occlusive crises. Dactylitis affects 45% of the children homozygous for sickle cell disease by the age of 2 years, with most cases occurring before this age. It is sometimes the first manifestation of the disease. Episodes are significantly more common during colder months of the year, similar to the seasonal relationship in painful sickle cell crises. Clinically, it is characterized by a sudden onset of a warm, tender global swelling of the hands or feet, often with fever and a raised white cell count. X-ray appearance may resemble that of osteomyelitis, with a "moth-eaten" periostitis and focal osteosclerosis. Haemoglobin electrophoresis is used to test for sickle cell disease.

Tuberculosis

Tuberculous dactylitis is a rare extra-pulmonary manifestation of tuberculosis. It is caused by osteomyelitis extending into a digit's soft tissue. It usually presents as a painful soft tissue swelling around the diaphysis (shaft) of the involved bone. It occurs more commonly in children, but with changing patterns of tuberculosis worldwide, and increasing globalisation it is important to consider this diagnosis.

Clinically, signs and symptoms of tuberculosis and an abnormal chest radiograph point towards the diagnosis. Confirmation is currently by quantiferon or Elispot testing.

Other causes

Rarer causes of dactylitis include congenital syphilis, blistering distal dactylitis, and paraneoplastic syndromes.

The musculoskeletal system is frequently neglected during general inpatient or outpatient assessments and thus valuable clues to the diagnosis of underlying systemic diseases may be missed. Dactylitis in particular can be short-lived, and patients may only give a history of it if directly questioned. Dactylitis of the toes is not often looked for on examination, and therefore often missed.

Conclusion

Dactylitis can be the first sign of a systemic disease, and should lead to further investigations. The common and important conditions which are associated with dactylitis are inflammatory arthritis, sarcoidosis, sickle cell disease, and tuberculosis.

Further reading

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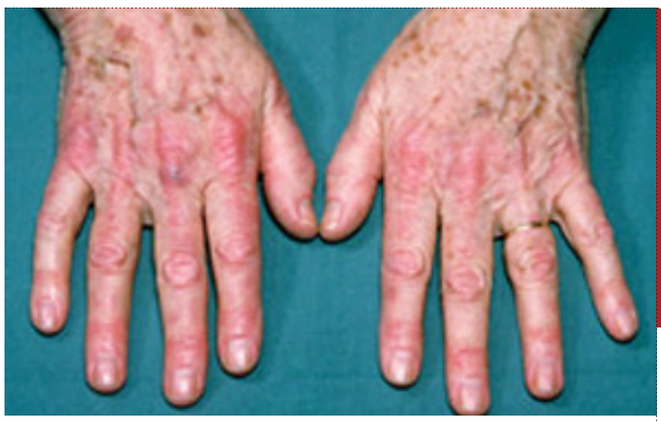
Authors

Dr Luke Daniel Williamson
F1 Doctor Royal Berkshire NHS Foundation Trust
London Road, Reading, RG1 5AN

Dr Lyn Williamson
Consultant Rheumatologist, Great Western
Hospital NHS Foundation Trust, Swindon SN3 6BB
Email: lyn.williamson@gwh.nhs.uk

CASE BASED DISCUSSION: DIAGNOSIS & MANAGEMENT OF A PATIENT WITH INFLAMMATORY MYOPATHY

M Popplewell



Abstract

We present a case of polymyositis associated with extra-muscular involvement of the lungs and oesophagus. This case discussion highlights the importance of diagnosis and treatment. Early diagnosis of the disease is important, as it is associated with high mortality and morbidity. The aetiology of inflammatory myopathy is poorly understood. However successful treatment with corticosteroids and disease modifying agents can greatly improve quality of life and reduce relapses of the disease.

Case History

A twenty-one year old female presented to the rheumatology clinic with a 6 month history of progressive proximal muscle weakness, bilaterally swollen lower limbs and lethargy. Her main symptoms were associated with arthralgia in the small joints of the hands and feet as well as progressive dysphagia from solids to liquids. The patient denied any respiratory symptoms or skin rashes. Her past medical history included epilepsy, a traumatic vertebral fracture and Hashimoto's thyroiditis.

On examination the patient looked unwell with clinical signs of active synovitis in the metacarpophalangeal and metatarsophalangeal joints. Decreased range of movement was found in the hips and shoulders with significantly reduced power (1/5) in all movements of upper and lower limbs.

The patient had been seen in a neurology clinic but was discharged when no immediate cause for her presentation was found. Symptoms were clearly affecting her life with absences from work and she was virtually wheelchair bound at presentation. After admission to the acute rheumatology ward, basic blood tests revealed normal parameters except a markedly raised creatine kinase (13,782 IU/L, range 15-165 IU/L) and lactate dehydrogenase (1062 IU/L, range 115-235 IU/L).

Further investigations were arranged. Musculoskeletal ultrasound revealed a moderate degree of active synovitis arising from all metacarpophalangeal joints with extensor tenosynovitis over the dorsum of both feet. Magnetic resonance imaging of both thighs showed a large degree of muscle inflammation and oedema. A provisional diagnosis of polymyositis was made and the patient remained in hospital to search for extra-muscular features of the disease.

Case based discussion: Diagnosis & management of a patient with inflammatory myopathy. Patient Management.

Treatment in the form of intravenous methylprednisolone, 1 gram per day for 3 days was commenced. This was followed by 30 milligrams (mg) of oral prednisolone once daily. The patient's physical functioning and lower limb swelling improved dramatically with this initial treatment. Daily physiotherapy and hydrotherapy allowed almost full mobility to be achieved at 3 weeks after admission to hospital.

Autoantibody screen was positive for anti-Jo1 but negative for anti-nuclear antibody, anti-neutrophil cytoplasmic antibody and rheumatoid factor. High resolution computed tomography of the lungs revealed areas of ground glass shadowing and mild bibasal pleural effusions (figure 1). An echocardiogram was normal. Oesophageal manometry confirmed the presence of lower oesophageal dysmotility. Electromyography and muscle biopsy from the right thigh suggested features consistent with inflammatory myopathy confirming the diagnosis.

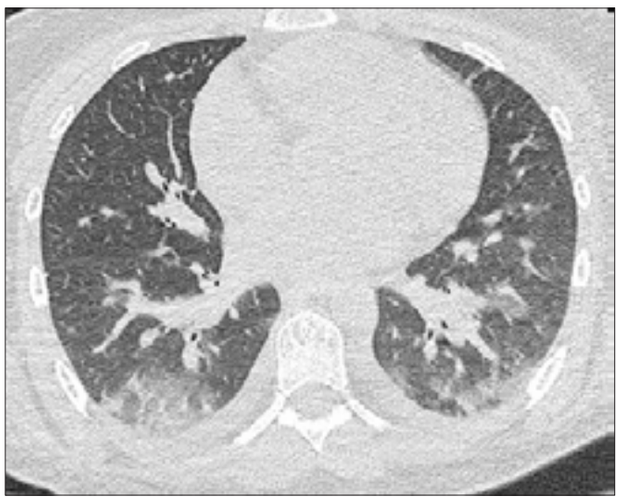
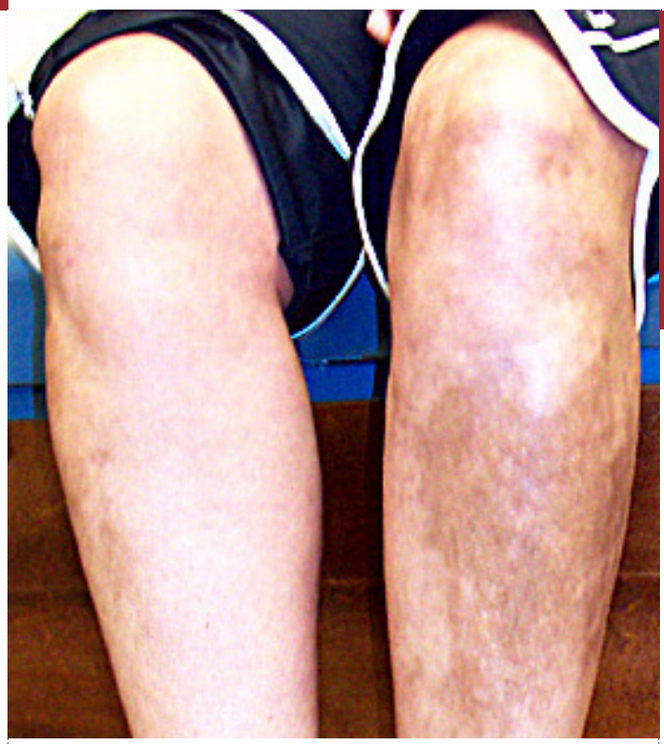


Figure 1

At discharge the patient was commenced on methotrexate 15mg once weekly, folic acid 5mg once daily with a continuing dose of 30mg of prednisolone. Routine follow up 2 months later found the patient to be coping better with daily living and significantly reduced CK levels (120 IU/L), although her long term prognosis still remains unclear due to the nature of the disease.

DIAGNOSIS & MANAGEMENT OF A PATIENT WITH INFLAMMATORY MYOPATHY

M Popplewell



Case based discussion: Diagnosis & management of a patient with inflammatory myopathy. Patient Management.

Discussion

Polymyositis (PM) is a subgroup of the idiopathic, immune mediated inflammatory myopathies. The disease is characterised by a sub-acute onset of progressive proximal muscle weakness with increased fatigability, affecting skeletal muscle and in some cases the myocardium. The inflammatory myopathies are rare with a prevalence of around 0.5 to 9.3 cases per million and are more common in females in the fifth and sixth decade of life. [1] Manifestations of the disease can include extra-muscular involvement of the skin, lungs, heart, GI tract and joints. The disease is considered to have considerable morbidity and mortality if not recognised early.[2] The pathophysiology of PM is poorly understood, however it is thought that the disease process is mediated by T-cell invasion of the muscle fibres with ongoing inflammatory change and microvessel damage.[3] Other subgroups of the immune mediated myopathies are dermatomyositis (DM) and inclusion body myositis. This case focuses on the diagnosis and management of PM.

How do we diagnose inflammatory myopathy?

Due to the insidious onset of the disease, presentation to medical services may be due to the disease process itself or through the development of extra-muscular features. Definitive diagnosis is made by the presence of symmetrical muscle weakness, raised skeletal muscle enzymes, an abnormal EMG and a positive core muscle biopsy with histology revealing a cellular infiltrate of macrophages and T-cells. Figure 2 shows diagnostic criteria as suggested by Bohan and Peter to aide health care professionals with the diagnosis of PM and DM.[4] Early diagnosis is important as some patients may become wheelchair bound or in rare cases require assisted ventilation due to muscle weakness of accessory respiratory muscles.

Adapted from "Diagnostic criteria for diagnosis of polymyositis and dermatomyositis" by Bohan and Peter [4]
1. Symmetric proximal muscle weakness
2. Elevation of serum levels of skeletal-muscle enzymes including CK, aldolase, AST, ALT and lactate dehydrogenase
3. Abnormal electromyogram with myopathic motor unit potentials, fibrillations, positive sharp waves, and increased insertional irritability
4. Muscle biopsy features of inflammatory infiltration and either degeneration/ regeneration or perifascicular atrophy
Definite polymyositis: criteria 1-4, *probable polymyositis* 3 of criteria 1-4, *possible polymyositis*: 2 of criteria 1-4.
The application of these criteria assumes that known infectious, toxic, metabolic, dystrophic, or endocrine myopathies have been excluded by appropriate evaluations. Symmetry is intended to denote bilateral but not necessary equal involvement
CK = creatine phosphokinase, AST = aspartate aminotransferase, ALT = alanine aminotransferase

Figure 2

Important differential diagnoses

Figure 3 shows important differential diagnoses that should be considered in this case.

Important differential diagnoses
1. Genetic muscle disorders (e.g. limb girdle, distal muscle dystrophy)
2. Neuropathies (e.g. amyotrophic lateral sclerosis, myasthenia gravis, Guillain-Barre)
3. Metabolic myopathies (e.g. glycogen storage disease, lipid storage disease)
4. Endocrine disorders (e.g. hyperthyroidism)
5. Infection (e.g. HIV)
6. Toxins and drugs (e.g. statins)
7. Others (e.g. granulomatous disease)

Figure 3

DIAGNOSIS & MANAGEMENT OF A PATIENT WITH INFLAMMATORY MYOPATHY

M Popplewell

What is the significance of the anti-Jo1 antibody?

The anti-jo1 antibody can signify the presence of the antisynthetase syndrome, which is present in around 20% of patients with inflammatory myopathy. It involves the formation of autoantibodies against synthetases such as anti-Jo1. The cellular target of the anti-Jo1 antibody is the enzyme aminoacyl-tRNA synthetase. The syndrome comprises:

1. A myositis

2. Interstitial lung disease

3. Raynaud's phenomenon

4. Non-erosive symmetric polyarthritis in small joints

5. Scaly skin changes of the hands known as mechanics hands

Features of the syndrome may not necessarily present at the same time. For example patients with interstitial lung disease may develop a myositis in the future or vice versa.

What are the extra-muscular features to look for in patients with PM?

Extra muscular features of PM are common in patients who have positive autoantibodies. The patient in the case displayed signs of possible lung involvement, although asymptomatic. Common manifestations include interstitial lung disease and restrictive defects due to muscle weakness. Lung involvement is associated with a poorer prognosis and is often the prime cause of mortality.[5]

Arthritis can play a role in the disease and may suggest an overlap syndrome with other rheumatological conditions such as rheumatoid arthritis or systemic lupus erythrematosus. Its clinical course is not usually significant. Patients may present with similar features of polyarthritis of the small joints of the hands and feet. Cardiac involvement is rare and is thought to be due to myocarditis, coronary artery disease and microvessel disease of the myocardium resulting in congestive cardiac failure and conduction abnormalities. Weakness of the pharyngeal muscles, tongue and lower oesophagus can precipitate dysphagia, with resulting nutritional loss and the potential for aspiration. The patient in this case had confirmed lower oesophageal dysmotility, although this quickly resolved after treatment.[3]

How do we treat inflammatory myopathy?

There are no internationally agreed guidelines for the treatment of inflammatory myopathy. Treatment is largely empirical and will depend on experience and expertise of local rheumatology centres.[1] The immediate treatment of the disease involves the use of glucocorticoids to suppress inflammation and mediate the immune response causing excessive muscle damage. Treatment with prednisolone is suggested for at least 3-6 months until inflammation, CK and levels of patient activity have all normalised. Significant improvement has been noted in up to 60-80% of patients.[6,7] Steroid sparing agents such as methotrexate, leflunomide, azothioprine, cyclophosphamide, ciclosporin and mycophenolate mofetil have been used to allow faster reduction of steroid dose and decrease relapse rates. Severe to life threatening cases associated with multiple, extra-muscular features can be treated with intravenous methylprednisolone, biologic agents or intravenous immunoglobulin.[2] Physiotherapy and occupational therapy is of use in improving patient mobility and quality of life once a patient is discharged home.

What is the prognosis of the disease?

Although relatively uncommon, untreated inflammatory myopathy can lead to high mortality and morbidity, usually due to respiratory and cardiac complications.[8] Early intervention and treatment is associated with improved remission rates and reduction in complications.[2] Although uncommon, the foundation doctor should have a basic awareness of the presentation of the disease and its treatment. Inflammatory myopathy should be considered as differential diagnosis in patients presenting with progressive weakness. Simple tests such as serum CK and LDH can raise suspicion and this should be followed by prompt referral to a specialist for further investigation, treatment and screening for extra-muscular features.

DIAGNOSIS & MANAGEMENT OF A PATIENT WITH INFLAMMATORY MYOPATHY

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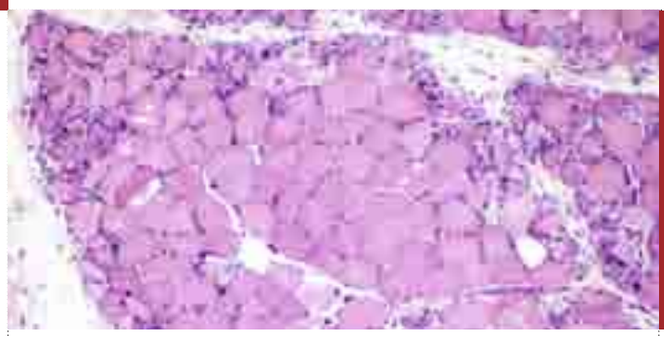

Case based discussion: Diagnosis & management of a patient with inflammatory myopathy.
Patient Management.

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Test yourself

1. A diagnosis of polymyositis is best made by:

A) An elevated creatine kinase level
B) Positive muscle biopsy
C) Myopathic features at electomyography
D) Symmetrical muscle weakness
E) All of the above

2. A 45-year-old woman presents with proximal weakness and fatigability associated with dysphagia. Her symptoms appear to be worse by the end of the day and her family have commented that her eyelids "droop" from time to time. Neurological examination reveals weakness of the proximal muscles and normal reflexes. What is the most likely diagnosis?

A) Polymyositis
B) Dermatomyositis
C) Myaesthenia Gravis
D) Lambert-Eaton syndrome
E) Inclusion body myositis

Answers

1. Correct answer E.
Creatine kinase is a general marker of muscle damage and is not specific to polymyositis. Although markedly raised levels with a good history can be highly suggestive. All four features listed above should be present to make a firm diagnosis.

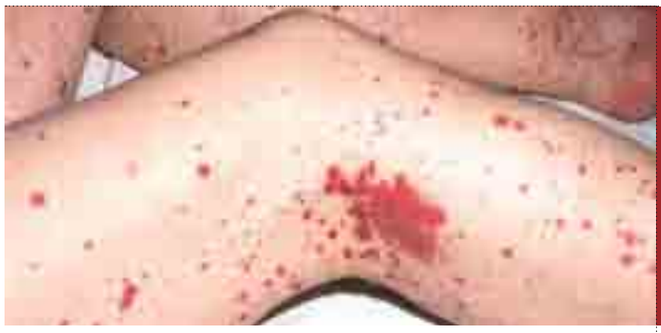
2. Correct answer C.
Proximal muscle weakness and dysphagia are present in polymyositis and dermatomyositis, however fatigability and extraocular involvement are more suggestive of myasthenia gravis. Lambert-Eaton syndrome may also present in a similar way, however autonomic involvement and hyporeflexia with a history of small cell lung cancer would be more suggestive.

Author

Dr Matt Popplewell

AN UNUSUAL RASH IN A YOUNG WOMAN - DIFFERENTIAL DIAGNOSIS & MANAGEMENT OF A VASCULITIC RASH WITH SYSTEMIC FEATURES

C Kelly



An unusual rash in a young woman - differential diagnosis and management of a vasculitic rash with systemic features. Patient Management.

Abstract

We present the case of a young lady aged 28 who developed an extensive skin rash over her lower limbs following a viral infection. The features were those of a palpable purpura and were associated with abdominal pain, diarrhoea which became bloody, arthralgia and asymptomatic haematuria. She had a low grade fever and elevated acute inflammatory markers. A clinical diagnosis of Henoch-Schönlein purpura was made and prednisone commenced at the dose of 20mg daily. A rapid symptomatic improvement followed, with resolution of the abdominal pain and diarrhoea, followed by a more gradual reduction in the rash over several weeks.

Henoch-Schönlein purpura is well recognised in children but also occurs in adults, and may be associated with the features of intestinal intussusception. It is important to consider this diagnosis in anyone with palpable pupura and abdominal pain, and to avoid unnecessary surgical intervention. This lady's presentation highlights the differential diagnosis associated with a vasculitic rash and systemic features and discusses the differential diagnosis and management issues which arose.

Case Study

A 28 year old woman with no previous past medical history of note attended her GP with a sore throat and was prescribed paracetamol 1 gram 6 hourly. Twenty four hours later she developed a rash over her legs which rapidly spread to her lower abdomen. This was purple and elevated to the touch but neither painful nor itchy. She noticed that her stools were looser and more frequent, and that her joints were aching, mainly at the ankles and knees, although no swelling was noticed.

Within forty eight hours she had deteriorated with a low grade fever and abdominal pain, focussed in the right iliac fossa and associated with blood in the stools. She felt nauseated and was unable to eat, although managed clear fluid. She attended the Casualty department of her local hospital, concerned that she may have meningitis or appendicitis.

On arrival, she had a mild sinus tachycardia of 80 with a low grade pyrexia of 37.8°C. She was normotensive with normal oxygen saturations. Examination demonstrated palpable purpura over the extensor surfaces of both legs and the trunk (Fig 1). Abdominal examination revealed tenderness and a palpable mass in the right iliac fossa but no rebound tenderness or guarding. Rectal examination revealed loose blood stained stool only. Lower limb joints were tender and walking was painful due to ankle discomfort. Routine urinalysis showed haematuria (2+) but was otherwise normal. There was no neck stiffness nor photophobia and Kernigs test was negative.

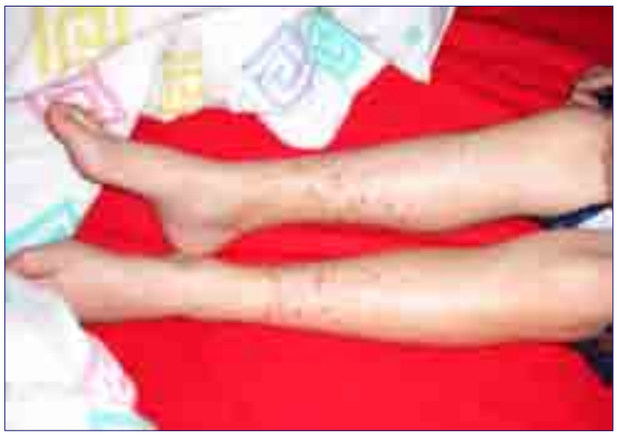


Figure 1
Skin manifestations of Henoch-Schonlein Purpura

Investigations revealed a mild neutrophil leucocytosis, with a haemoglobin of 11.0 gm/dL and a C reactive protein of 43 mg/L. Platelets were normal as were clotting, liver function and urea and electrolytes. A chest radiograph was normal, as were radiographs of her ankles and abdomen. Cultures of stool, blood and urine were obtained, and subsequently yielded no growth. No lumbar puncture was performed. Anti nuclear antibodies and ANCA were tested and found to be negative.

We suspected Henoch-Schönlein purpura (HSP) on clinical grounds, and performed a skin biopsy to confirm this and help exclude other causes of vasculitis. We were concerned about the possibility of intussusception and arranged an urgent ultra sound scan of the bowel and kidneys. This revealed thickening of the distal ileum with features of a probable resolving intussusception. The kidneys were felt to be normal.

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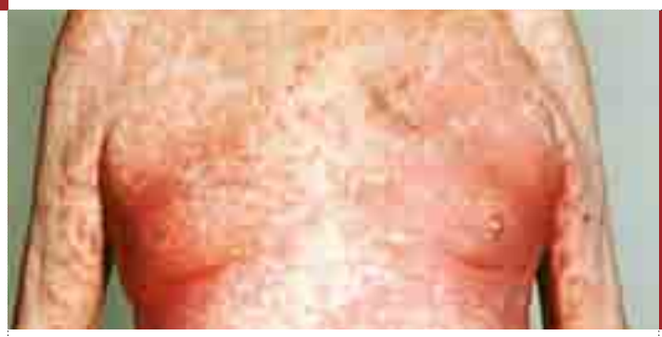

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We commenced steroid therapy at the same time as performing the skin biopsy. We administered intravenous hydrocortisone 100mg and then 20mg daily of oral prednisone. The intravenous hydrocortisone was given 24 hours prior to the ultrasound being performed. Her rash began to improve with no new lesions subsequently noted, and the joint pain receded. Most importantly, her abdominal pain improved dramatically and within two days her stools were normal and abdominal pain had resolved. Within a week the skin rash had faded and there was no blood on urine testing. A recurrence of abdominal pain led to a brief readmission requiring further intravenous hydrocortisone two weeks later. Following this, the patient was able to reduce her daily steroid dose at the rate of 5mg each fortnight until therapy was stopped after 8 weeks with no further signs or symptoms. The skin biopsy confirmed leukocytoclastic vasculitis (Fig 2) consistent with a diagnosis of Henoch-Schönlein purpura.

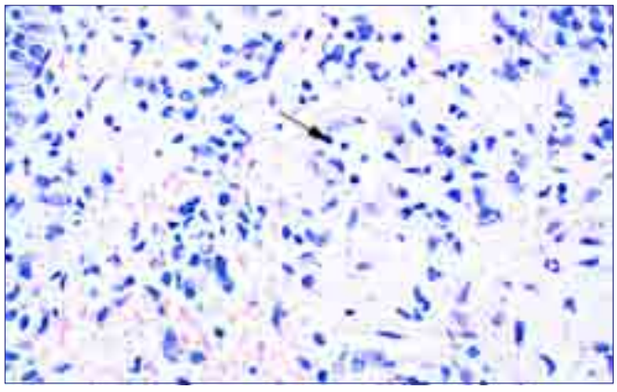

Figure 2
Leukocytoclastic Vasculitis

Discussion

Rashes associated with viral infection are very common. They usually take the form of an evanescent macular rash which is pink and fades with pressure (glass slide test). Patients with a purpuric rash which does not blanch must be carefully assessed for the possibility of meningococcal meningitis - for which there was no clinical evidence in our case. The distal distribution of the purpura over the buttocks and extensor surfaces of the lower limbs, with elevated purple patches (palpable purpura) are classic findings in HSP. Skin biopsy is not mandatory to make the diagnosis but if performed it invariably demonstrates histological features of leucocytoclastic vasculitis. This condition can accompany a variety of disorders and is not specific for HSP.

Other conditions associated with cutaneous vasculitis include Churg-Strauss syndrome (CSG), Wegeners Granulomatosis (WG) and rarely Polyarteritis Nodosa (PAN).[1] These vasulitides are usually associated with eosinophilia and markedly elevated inflammatory markers. Fever is common in WG and PAN. These disorders are all associated with a worse prognosis than HSP, and carry a different set of clinical features. CSG usually occurs on a background of resistant asthma and is often associated with mononeuropathy (mononeuritis multiplex), most commonly presenting with footdrop. High dose steroids are required, often with steroid sparing agents such as Azathioprine.

WG invariably involves the upper or lower airways and is often preceded by sinusitis or chronic ear problems. Renal involvement is usual and without treatment, the condition will often progress to renal or respiratory failure.

Treatment is usually with immunosuppressive agents such as methotrexate in milder cases and cyclophosphamide in more severely affected patients. PAN carries the worst prognosis, being invariably fatal until the introduction of cyclophosphamide. Internal organ infarction, affecting the gut, kidney, nervous system and kidneys led to a rapid decline, but the use of potent immunosuppression has revolutionised outcome. Patients resistant to the above agents have also been reported as responding to treatment with monoclonal antibodies to TNF (Infliximab) or B cells (Rituximab).

American College of Rheumatology (ACR) criteria for vasculitides including HSP are established [2,3]. ACR criteria for HSP are:

- Palpable purpura
- Age at onset ≤20 years
- Acute abdominal pain
- Granulocytes in the walls of small arterioles and/or venules on biopsy

Two or more of the criteria have 90% sensitivity and specificity in separating adult patients with HSP from those with other causes of vasculitis. There are no specific tests for HSP and diagnosis in our case was made on clinical grounds. The presence of palpable purpura and abdominal pain were the strongest clinical pointers to the diagnosis. Haematuria is also common in HSP and may be associated with IgA nepropathy and significant renal damage which can occur in up to 30% of adult patients.[4,5] There is otherwise little evidence of major clinical differences in patients presenting before and after the age of 20 years.[6] The exception to this general rule is the development of intussusception. This was heralded in our patient by the onset of abdominal pain and bloody diarrhoea, and confirmed by ultrasound.

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This is rarer in adults than children where up to 4% of cases may develop this complication. The role of steroids in treating this disorder is disputed, but on balance the evidence favours the use of such treatment.[7-9] Appendicitis may be suspected in cases of RIF pain but the absence of rebound tenderness or peritonism on examination was reassuring. However, the ultrasound examination provided more objective evidence for the true diagnosis and is useful in excluding an appendix mass.

Questions - True or false?

1. The following conditions may be included in differential diagnosis of HSP:

a) Appendicits
b) Subarachnoid haemorrhage
c) Polyarteritis nodosa
d) Diverticulitis
e) Ringworm

2. The diagnostic criteria for HSP include:

a) Acute chest pain
b) Palpable purpura
c) Acute abdominal pain
d) Age over 20 years
e) Small blood vessel inflammation histologically

3. The following treatments are often used in HSP:

a) Oral steroids
b) Surgery
c) NSAIDS
d) Immunosuppressives
e) Simple analgesia

4. The following are recognised complications of HSP:

a) Haematuria
b) Intussusception
c) Arthralgia
d) Meningitis
e) Renal failure

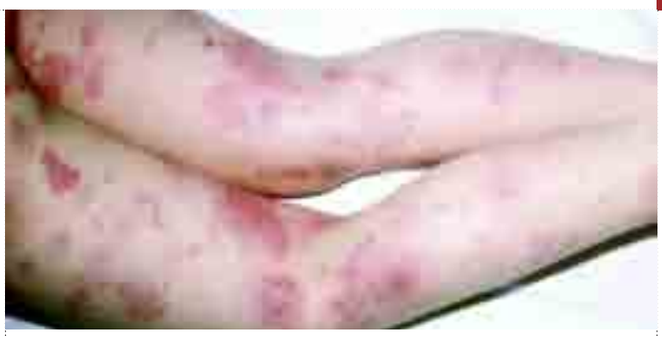
Answers

1. The correct answers are a and c.

Abdominal pain may be misdiagnosed as appendicitis, and in severe cases the cutaneous and visceral features may resemble those of polyarteritis nodosa. Meningitis may occasionally mimic HSP but subarachnoid haemorrhage does not. Diverticular disease does not occur in this age group and the rash is clearly different to that seen in fungal infection.

2. The correct answers are b, c and e.

Palpable purpura is the classic hallmark of the condition, and acute abdominal pain is common. Histological evidence of small vessel inflammation is seen on skin biopsy. Patients are usually under 20 and chest pain is not a feature.



3. The correct answers are a and e.

Steroids are often used and usually help, although simple analgesia may suffice for mild cases. Surgery is best avoided except in rare cases of complex intussusception. NSAIDS are best avoided because of the risk of perforation and immunosuppressive therapy is virtually never required.

4. The correct answers are a, b, c and e.

Haematuria is a common feature of HSP, and occasionally leads to renal failure. Intusscusception is rare but well recognised. Arthralgia ia almost invariable. Meningitis may occasionally be confused with HSP but is not a complication.

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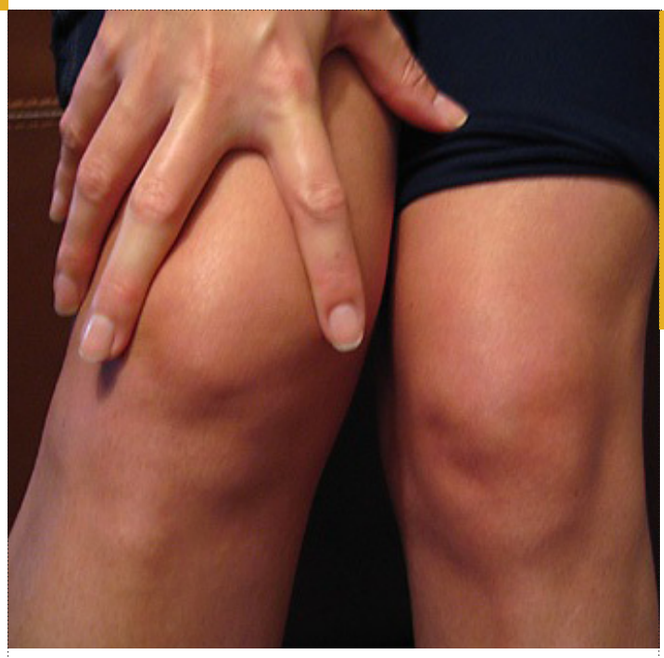
Author

Clive Kelly, MBBS, MD, FRCP
Consultant Physician and Rheumatologist, Gateshead
Departments of Medicine and Rheumatology,
Queen Elizabeth Hospital, Sheriff Hill, Gateshead NE9 6SX
Email: clive.kelly@ghnt.nhs.uk

AN APPROACH TO MANAGING A HOT, SWOLLEN JOINT: A CASE-BASED DISCUSSION

F Rees and C Deighton



An approach to managing a hot, swollen joint: a case-based discussion Good Clinical Care.

Introduction

The most important cause of a hot swollen joint to consider is a septic arthritis. Untreated this can cause joint destruction and ultimately lead to mortality similar to that of meningitis. It can sometimes be difficult to distinguish a septic joint from other causes of monoarthritis (see box 1) so thorough history, examination and investigation is important.

Differential diagnosis of a hot, swollen joint (Box 1)

Differential	Characteristic findings
Crystal arthritis (Gout/pseudogout)	Sudden onset of symptoms. Worst pain experienced Past history of gout or pseudogout Family history of gout History of excess alcohol consumption Diuretic use or dehydration Can be polyarticular in chronic disease
Reactive arthritis	Recent history of infection e.g. diarrhoea, urethritis, sore throat, or conjunctivitis, preceding onset of joint symptoms.
Seronegative inflammatory arthritis	May have psoriasis or symptoms of inflammatory back pain.
Bursitis (Prepatellar)	Warmth and swelling anterior to the patella, rather than a knee effusion which would surround the patella and extend along the knee joint line.

Case history

A 51-year-old man presents to the A&E department with a hot, swollen, painful knee (Figure 1). He says it started yesterday and is gradually getting worse. He is now finding it difficult to walk. He is usually fit and well, and was able to play football last weekend with his son. He has taken paracetamol with little effect.

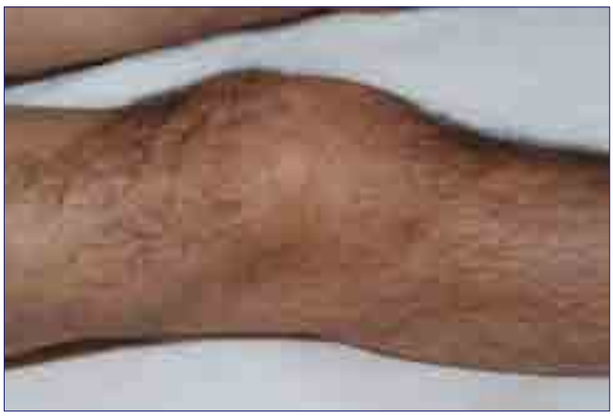


Figure 1: A hot, swollen knee.

On examination his right knee is warm to touch. There is a moderate effusion. His knee flexion is restricted to 70 degrees and he is unable to fully extend his knee. The rest of the musculoskeletal examination is normal.

Approach to the patient

1. Important points to consider in the history

- A history of warmth, pain, swelling and stiffness of the joint.
- Did this come on suddenly or gradually? Sudden onset could be more suggestive of crystal arthritis.
- Duration of symptoms
- Is this patient able to weight-bear? This may have implications for admission to hospital and gives an impression of pain severity.
- How does the patient feel in themselves? Are there any symptoms to suggest sepsis such as fevers, rigors or sweats?
- Do they have any underlying joint pathology e.g. osteoarthritis or rheumatoid arthritis? This may make sepsis or crystal more likely in that these are more likely to occur in damaged joints.
- Has the patient had a recent illness that might suggest a reactive arthritis, usually in the 2 to 6 weeks prior to the onset of joint inflammation?
- Do they have diabetes? This increases risk of infection.
- Does the patient have a history of chronic skin disease, particularly psoriasis?'

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- Are they on any diuretics, particularly thiazides, which can precipitate gout attacks?
- Is the patient an intravenous drug-user? These patients are likely to require a different choice of intravenous antibiotic as opportunistic infections are more likely.
- Have they travelled abroad or migrated from a country where tuberculosis (TB) is endemic?

2. Important features to look for on examination

- ABC – Does the patient need resuscitating if septicaemic?
- Observations: Temperature, pulse, blood pressure, respiratory rate, oxygen saturations, mental state (confusion). Is there any evidence of sepsis?
- Painful joint:
  - Look: for erythema, swelling and deformity.
  - Feel: for warmth and an effusion.
  - Move: Check the range of movement of the joint.
- Other joints: Are there any deformities of other joints which may suggest underlying osteoarthritis or an inflammatory arthritis.
- General examination: Are there any gouty tophi elsewhere? Is the patient dehydrated?
- Systems examination: Look for potential sources of infection, including skin infection (e.g. athletes' foot and psoriatic plaques). Importantly auscultate the heart for murmurs, which may suggest an infective endocarditis underlying a septic joint.

3. What investigations should be ordered?

The most important investigation for any patient with a hot, swollen joint is a joint aspirate. This may confirm the diagnosis and allows you to distinguish a septic joint from a crystal arthropathy. It also helps to guide further treatment. If you are not yet competent at knee joint aspirates then ask a senior colleague for assistance. The joint aspirate should be sent to the microbiology laboratory in a sterile universal container for microscopy, culture and sensitivity (M, C & S) and for examination under polarised light for crystals. There may be organisms visible on the gram stain, or positively or negatively birefringent crystals on polarised light microscopy. Depending on local microbiological recommendations, if enough synovial fluid is aspirated from the joint, blood culture bottles can be inoculated and sent to the laboratory. If there is any suspicion of TB then examination for Acid-Fast bacilli (AFB) should be requested. The most common bacteria causing septic arthritis in adults are listed in box 2.

The second most important test is to take a set of blood cultures. This looks for systemic evidence of sepsis and may be important even if the joint aspirate is falsely negative. A Full Blood Count (FBC) may show raised white cells and a C Reactive Protein (CRP) may be elevated, but these are not specific and may occur with the other differential diagnoses.

A plain radiograph (Figure 2) of the swollen joint is required to look for underlying joint pathology such as joint space narrowing, chondrocalcinosis (calcium deposition in cartilage seen in pseudogout) and bone destruction (osteomyelitis).

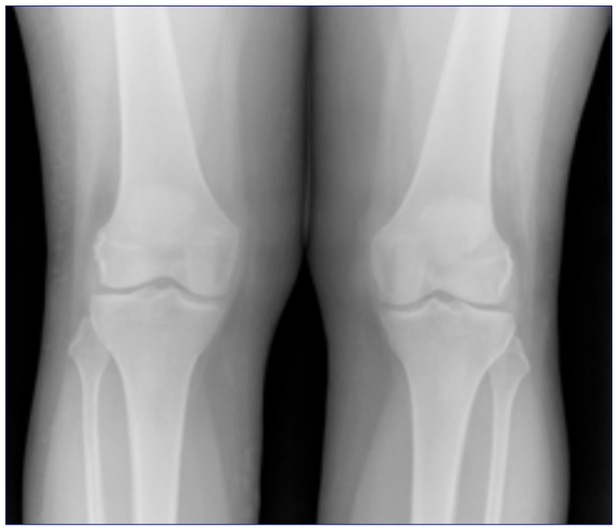

Figure 2: Plain radiograph of normal knees.

Checking the urate may be useful in patients with suspected gout, but it can be lowered as part of the acute-phase response. Urea &Electrolytes (U&E) are useful to check as they will give you evidence of dehydration and may be necessary for drug dosing. Calcium, Magnesium, Ferritin and Phosphate can be useful to check if the patient has pseudogout, looking for metabolic conditions predisposing to the disease.

If there are systemic signs of sepsis then appropriate investigations should be ordered, for example, an echocardiogram for infective endocarditis.

Bacterium	Frequency (%)
Staphylococcus aureus	54
Streptococcus spp	18
Coliform bacilli	7.5
Haemophilus influenza type b	7.5
Neisseria spp	4.5
Enterococci	1.5
Other	6.5

Box 2: The most common bacteria causing septic arthritis in adults3.

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What treatment is required?

If there is any suspicion of a septic joint the most usual antibiotic to prescribe empirically is an intravenous infusion of flucloxacillin 1-2g four times a day. This is because the most common organism found in septic arthritis is staphylococcus aureus (Figure 3). If the patient is allergic to penicillins, then second-line therapy can be clindamycin, a cephalosporin or vancomycin, but this can be confirmed by checking local hospital protocols or discussion with the on-call microbiologist. This treatment will be continued until the results of the 48 hour culture and sensitivity is known. At this point antibiotics may be changed if the organism is resistant or stopped if a septic joint is not confirmed. For a confirmed septic joint, antibiotic treatment is usually continued for a minimum of 2 weeks intravenously and 4 weeks orally.

Figure 3: Staphylococcus aureus

(With thanks to Matthew Fairbrother, Biomedical Scientist at Royal Derby Hospital, who provided the images for Figure 3)

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It is important to control the patient's pain with appropriate analgesia, using the WHO analgesic ladder e.g. paracetamol, NSAIDs, codeine. If there is a crystal arthropathy, then oral colchicine 0.5mg two times a day can be prescribed for approximately 5 days, if NSAIDS are contra-indicated.

The patient should receive physiotherapy on the ward and may require an opinion from an orthopaedic surgeon for consideration of a joint lavage. An orthopaedic referral is always needed if the affected joint is an arthroplasty. Once initial treatment is instituted then the patient should be referred to either an orthopaedic surgeon or a rheumatologist for ongoing treatment depending on your local hospitals policy. If septic arthritis is not improving then orthopaedics should be involved sooner rather than later to consider joint lavage.

Outcome

In this case the patient had confirmed septic arthritis and required 2 weeks of intravenous flucloxacillin, followed by 4 weeks of oral flucloxacillin. He required a joint lavage in theatre and physiotherapy to improve his range of movement. No underlying cause was found. He made a full recovery.

Questions

1. In a patient presenting with a hot swollen knee the most important investigation is:

a) Blood cultures

b) CRP

c) Knee joint aspirate

d) Plain radiograph of the knee

e) Urate

2. In a case of suspected septic arthritis the most appropriate empirical antibiotic choice is:

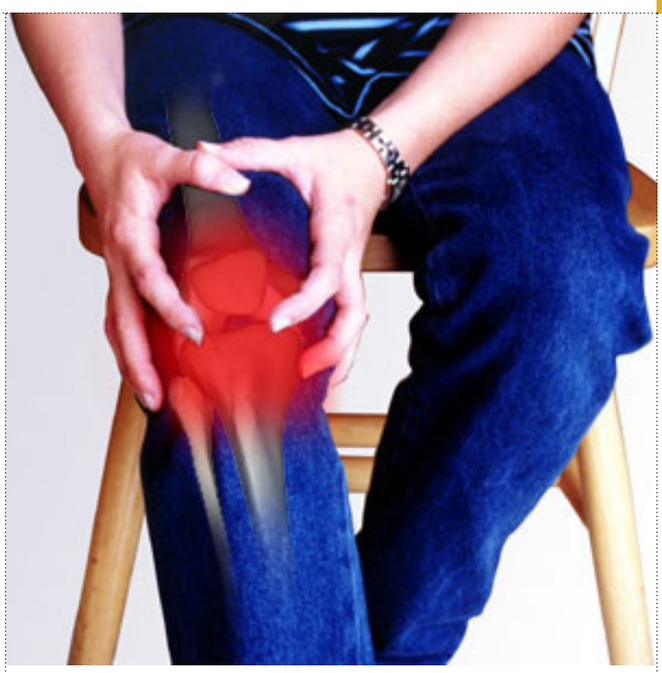
a) Intravenous co-amoxiclav 1.2g tds

b) Intravenous benzylpenicllin 1g tds

c) Intravenous vancomycin 1g bd

d) Intravenous flucloxacillin 2g qds

e) Oral flucloxacillin qds 1g qds



Answers

1. Answer c:
A Knee joint aspirate is the most important investigation to confirm a diagnosis of septic arthritis. It may guide antibiotic treatment and also reveal a differential diagnosis of gout.

2. Answer d:
Intravenous flucloxacillin 2g qds is the most appropriate empirical antibiotic as in septic arthritis the most common organism is staphylococcus aureus.

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Authors

Frances Rees
Chris Deighton

INFLAMMATORY BACK PAIN

SG Sheth, R Adshead & H Tahir

Inflammatory Back Pain.
Patient Management.

Abstract

This is a case summary based on a 28 year old man with a two year history of lower back pain and stiffness. The article highlights his clinical history, examination, investigations and multidisciplinary management.

Case study

You are asked to review a 28 year old student who presents in an outpatient clinic with a two year history of lower back pain intermittently radiating into his buttocks. He rates his pain as 8/10 at worst. His symptoms worsen with sitting for more than 20 minutes and he has to get up and walk around to ease his pain. He describes feeling stiff in the mornings lasting at least an hour which eases off when he plays football. He feels he is very active and exercises 4 times a week playing football and going to the gym.

What else do you want to know?

History taking is the most important skill required in rheumatology. When a young patient presents with lower back pain it is essential to know how to differentiate between mechanical and inflammatory pain. It is also important to explore the Red Flags of back pain which are suggestive of serious causes of spinal pathology (table 1).

Features	Signs	Symptoms
Age <16yr or >50yr with new onset pain. Acute onset in the elderly	Saddle anaesthesia	Fevers / rigors/ night sweats
History of malignancy	Reduced anal sphincter tone	Malaise
Unexplained weight loss	Urinary retention	Thoracic pain
Prolonged steroid treatment	Generalised neurological deficit (alternating or bilateral)	Non-mechanical pain (worse at rest)
Recent serious illness	Spinal and structural deformity	Nocturnal pain
Recent significant infection	Hip or knee weakness	Loss of bladder / bowel control

Table 1: Red Flags – Back Pain

Closer questioning reveals:

- His pain wakes him up frequently between the hours of 3-5am. His back feels uncomfortable lying in bed in the mornings.
- His left Achilles tendon has been sore for the past 4 months which does not appear to be improving with physiotherapy
- He has no other past medical history or history of sexually acquired diseases.
- His brother has Crohns disease. He does not have any symptoms of inflammatory bowel disease.
- He takes ibuprofen intermittently which helps to ease his symptoms

On the basis of the above information, the patient has inflammatory back pain (IBP) (table 2). The main causes of IBP are the Spondyloarthropathies which include Ankylosing Spondylitis, Reactive Arthritis, Psoriatic Arthritis and inflammatory arthritis related Inflammatory Bowel Disease and sexually acquired infections.

	Mechanical	Inflammatory
Past History	+/-	++
Family History	-	+
Onset	Acute	Insidious
Age (years)	15-90	<40
Sleep disturbance	+/-	++
Morning stiffness	+	+++
Involvement of other systems	-	+
Effect of exercise	Worse	Better
Effect of rest	Better	Worse
Radiation of pain	Anatomic (L5, S1)	Diffuse (thoracic, buttock)
Sensory symptoms	+	-
Motor symptoms	+	-

Table 2: Features of Mechanical and Inflammatory Back Pain

INFLAMMATORY BACK PAIN

SG Sheth, R Adshead & H Tahir

What does an examination reveal?

Examination reveals a reduced lumbar spine lordosis and restricted movement into lumbar flexion and side flexion. Lumbar flexion is measured by performing the modified Schober's test (figure 1) revealing an excursion of 4cm demonstrating a mild restriction of movement. His tragus to wall distance was 14cm. His chest expansion measures 4cm.

His left Achilles tendon is sore at the insertion of the calcaneus. There is no evidence of psoriasis or swelling within the small joints of the wrist or hand, knees or elbows. Cardiovascular and respiratory examinations are normal.

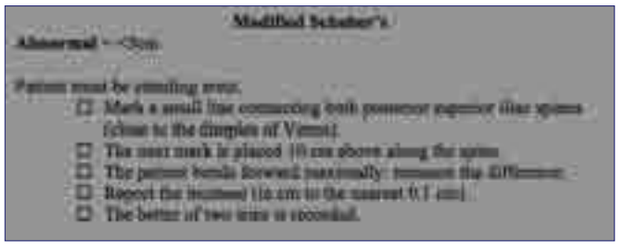

Figure 1: Modified Schobers

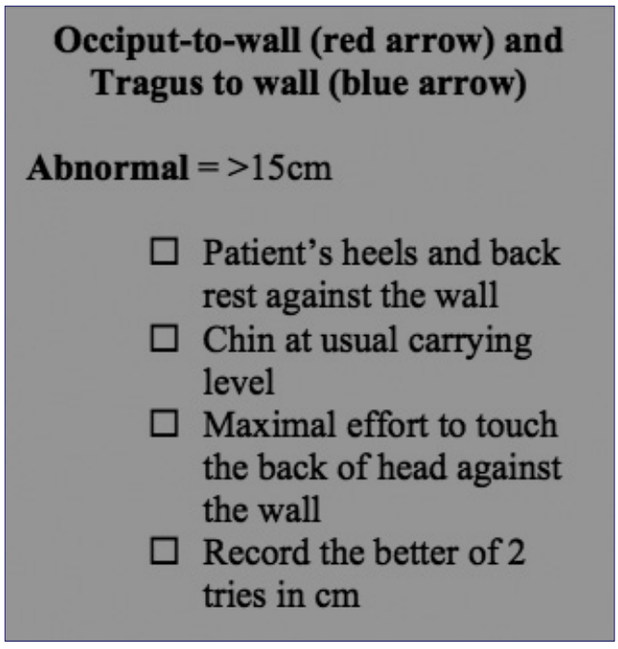

Figure 2: Tragus-to-wall/ Occiput-to-wall

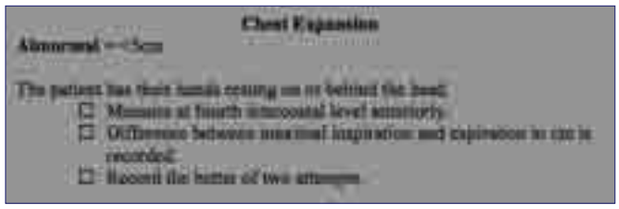

Figure 3: Chest Expansion

What would you do next?

Baseline blood tests:

- Full blood count, Renal and Liver function
- ESR/CRP

His investigations reveal an elevated CRP of 21mg/L, ESR 15mm/H. His renal and liver function blood results are within normal range.

Imaging:

His sacroiliac joint X-ray reveals some sclerosis and erosion of the articular margins of the sacroiliac joints, suggesting a Grade 2 sacroiliitis.

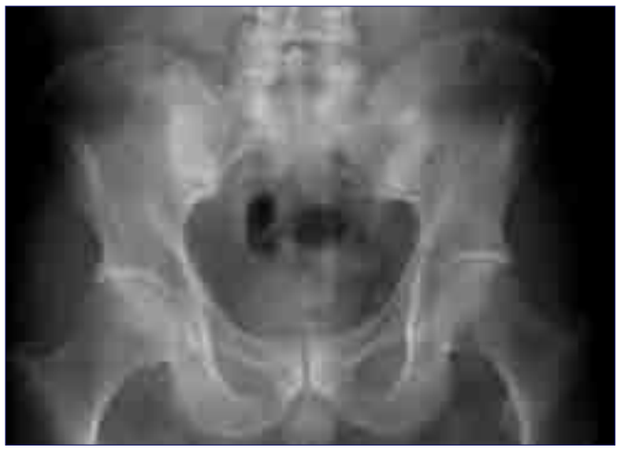

Figure 4: Pelvic Xray – arrows show sacroiliitis; bony sclerosis and joint space narrowing

MRI of the sacroiliac joints is considered if the X-ray is normal and the patient's symptoms of IBP persist.

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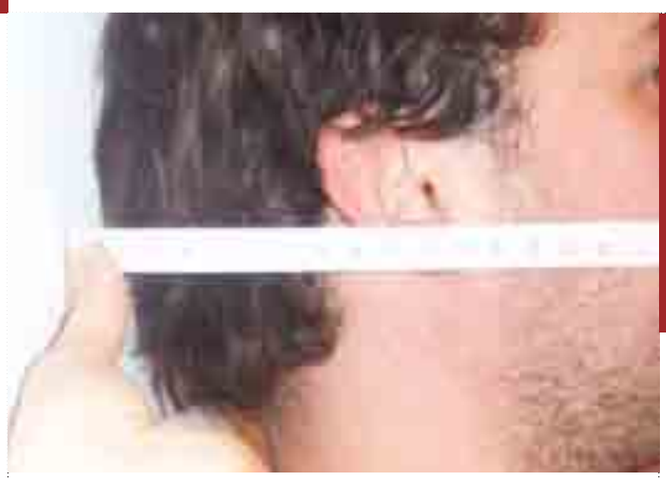

Inflammatory Back Pain.
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What is his diagnosis?

The patient has inflammatory back pain with radiographic evidence of grade 2 sacroiliitis and limited lumbar spine motion, therefore using the Modified New York Criteria a diagnosis of Ankylosing Spondylitis is made (table 3).

Clinical Criteria	Radiographic Criteria
1. Limitation of Motion of the Lumbar Spine	+ Grade 2 bilateral sacroiliitis (normal sclerosis with some erosion) or Grade 3 unilateral sacroiliitis (severe erosions with widening of joint space +/- some ankylosis) Grade 4 unilateral sacroiliitis (complete ankylosis)
2. Low back pain and stiffness for more than 3 months that improves with exercise but is not relieved by rest	
3. Limitation of Chest Expansion	
Definite AS if the radiological criterion is associated with at least one clinical criterion	

Table 3: Modified New York Clinical Criteria for diagnosis of Ankylosing Spondylitis[1]

AS is a condition which causes chronic inflammation of the axial skeleton and sacroiliac joint (sacroiliitis). The process of chronic inflammation (spondylitis), in time, may lead to fusion of the vertebrae (ankylosis), decreased thoracic excursion, kyphosis, neck hyperextension and spinal-cranial ankylosis. Ankylosing Spondylitis is a multi-system disease and can involve the heart (carditis, valvular incompetence), eyes (anterior uveitis and iritis), lungs (apical fibrosis), and kidneys (amyloidosis).

Costocondritis, achilles tendonitits, plantar fasciitis and periostitis of the calcaneum or ischial tuberosities may develop. AS is associated with the gene HLA-B27. Approximately 90% of the patients with AS carry this gene, however it is not used as a definitive test to diagnose or rule out AS.

How would you manage him?

Patient Education and Exercise

The patient should receive a clear explanation of their condition once you have provided a diagnosis. A management strategy should be discussed and agreed. Patient education is essential for long-term conditions such as Ankylosing Spondylitis and support from the rheumatology team and National Ankylosing Spondylitis Society (NASS) should be available to them.

Physiotherapy is important to maintain correct posture and provide a self management exercise programme and hydrotherapy. Your patient should be advised to exercise on a daily basis to help prevent restrictions and spinal deformities.

Medication Management

Non-steroidal anti-Inflammatories

Your first line of management would be with non-steroidal anti-inflammatory drugs (NSAIDs) (table 4). He responds well initially to slow release diclofenac 75mg daily, however after 3 months his symptoms are increasing again. You decide to change his NSAIDs to Etoricoxib 90mg daily which reduces his stiffness in the mornings to 30 minutes and pain intensity to 6/10. There is no strong evidence for the use of Disease Modifying anti-rheumatic drugs such as methotrexate and sulfasalazine in patients with axial symptoms, however, benefit is seen in patients with peripheral disease.

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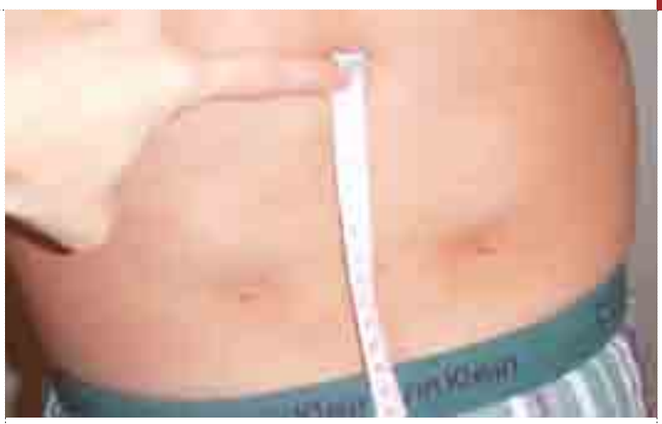
NSAID	ADULT DOSE	Notes
Ibuprofen	300-400mg 3-4 times daily, increased to max 2.4g daily. Maintenance 0.6-1.2g daily may be adequate	
Naproxen	0.5-1g daily in 1-2 divided doses	Good efficacy, low side effects, however, more than Ibuprofen
Diclofenac	75-150mg daily in 2-3 divided doses. Or 75mg modified release (MR) 1-2 times per day	Similar action and side-effects as Naproxen
Indomethacin	50-200mg daily in divided doses. Or 75mg MR 1-2 times per day	Equal superior action to Naproxen. Higher incidence of headache, dizziness, gastrointestinal disturbance
Etoricoxib	90mg daily	Peripheral oedema, fatigue, influenza-type symptoms, exothymosis

Table 4: NSAIDS in Ankylosing Spondylitis[2]

Tumour Necrosis Factor (TNF) Blocker therapy

If your patient fails to respond to two different NSAIDS, maximally tolerated doses for a minimal duration of four weeks each then Tumour Necrosis Factor (TNF) blockers are considered. More recently Tumour Necrosis Factor (TNF) blockers have been employed to alleviate AS uncontrolled by NSAIDs and steroids. TNF is a protein which is a signalling molecule in the inflammatory process; current anti-TNF's include Etanercept, Adalimumab, Infliximab and Golimumab. The National Institute for Clinical Excellence and Health (NICE) currently recommend the use of Etanercept and Adalimumab only after confirmed diagnosis by a specialist, assessment of pain and active disease on two separate occasions three months apart.3 The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is used for this assessment. Studies assessing the use of Etanercept demonstrate a rapid reduction in disease activity and improvement in work stability.4 Patients using Infliximab for 5 years demonstrated benefits in 61.8% patients with a minimum of 40% improvement in symptoms and 27.6% achieving ASAS partial remission.5 The use of regular anti-TNF treatment on a continuous basis has shown significant improvement in symptoms over on-demand treatment.6 It is important that once initiated, anti-TNF treatment is continued as patients are likely to relapse after withdrawal of treatment.



Current treatment options, although non-curative, can successfully reduce inflammation and suppress the immune process. Complemented by physiotherapy, treatment can lead to significant improvement in movement, posture and other symptoms such as tendinopathies and reduced lung capacity.7

Would you discharge him from your clinic?

AS is a chronic disease and progression of symptoms is variable amongst patients. Prognosis is generally regarded as good for patients, with a 70-90% chance of remaining fully independent with minimal long-term disability.8 You would not want to discharge this patient from your clinic due to his raised disease activity despite the use of NSAIDS and therefore the potential for TNF blocker therapy. He should be followed-up by the multidisciplinary team to monitor his disease activity, spinal movements, and peripheral joint involvement. Extra-articular symptoms will require appropriate referral. Absence of peripheral arthritis, HLA-B27 positivity and uveitis are associated with early extensive radiographic change in patients with ankylosing spondylitis.9

Questions

True or false?

1) Which of the following are Red Flag Symptoms of back pain?

a) Night sweats
b) Thoracic pain
c) Urinary incontinence
d) Increased anal sphincter tone
e) Nocturnal pain
f) Headache

2) Which of the following are common features of Ankylosing Spondylitis?

a) Conjunctivitis
b) Achilles tendinopathy
c) Aortic stenosis
d) Bronciectasis
e) Atlanto-axial subluxation

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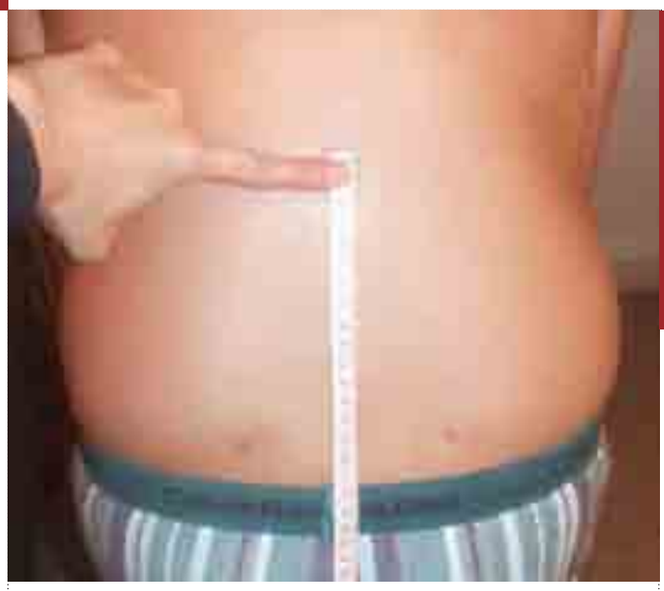

Inflammatory Back Pain.
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Answers

1. Answers: a, b, c, e

When a young patient presents with lower back or sacral pain it is essential to be know how to differentiate between mechanical and inflammatory pain. It is essential that serious causes of spinal pathology are excluded by thorough questioning relating to Red Flags of back pain.

Saddle anaesthesia, urinary dysfunction (retention - the bladder distends because sensation of fullness is lost; incontinence - bladder control is lost because there is no sensation when passing urine), faecal incontinence, and progressive neurological deficit in the legs are all red flags and important features of cauda equina syndrome. Age, a history of malignancy and constitutional features such as fever, weight loss, malaise are suggestive of infection or cancer. Thoracic pain, structural spinal deformity, night pain and pain that persists when lying down are also suggestive of cancer.

2. Answers: a, b, d, e

Ankylosing spondylitis is associated with both conjunctivitis and acute anterior uveitis (AAU). It is thought that 20% of HLA-B27 individuals will suffer from AAU. Symptoms often begin in one eye, usually progressing to bilaterally asymmetrical and can be more severe than in idiopathic anterior uveitis. Enthesitis refers to inflammation of a joint capsule and ligament or tendons and is a feature of AS. In the foot two areas are affected; the Achilles tendon and the heel plantar fascia.

AS can lead to inflammation in the heart, particularly around the aorta and aortic valve and there is an association with mitral and aortic regurgitation, not stenosis. Bronchiectasis is a rare finding in AS, more commonly ankylosis of the costovertebral junction is seen leading to reduced chest expansion. Atlanto-axial subluxation is a complication of AS and can occur in early disease.

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Authors

Rebecca Adshead
Specialist Ankylosing Spondylitis Physiotherapist
Whipps Cross University Hospital Trust, London
Email: Rebecca.Adshead@whippsx.nhs.uk

Dr Swati G Sheth
FY2 Doctor
Whipps Cross University Hospital Trust, London

Dr Hasan Tahir
Consultant Rheumatologist
Whipps Cross University Hospital Trust, London
Email: Hasan.Tahir@Whippsx.nhs.uk

IDIOPATHIC INFLAMMATORY MYOPATHIES

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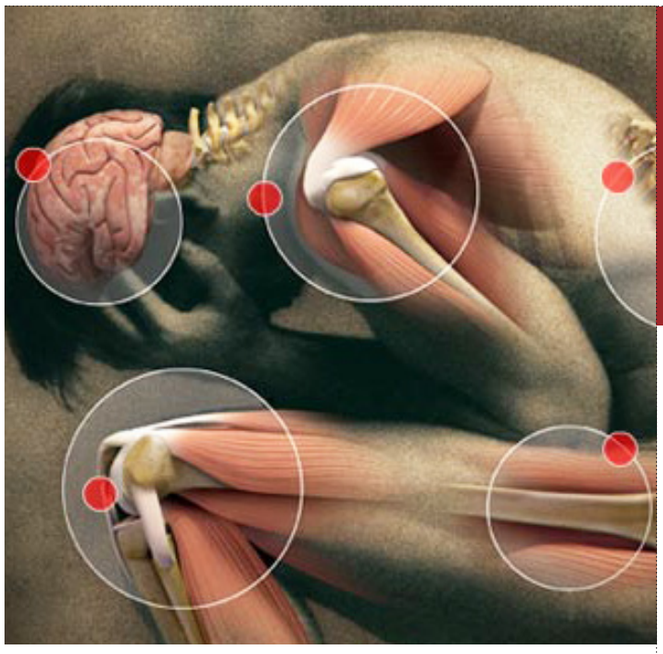

Idiopathic Inflammatory Myopathies.
Patient Management.

Abstract

This report describes the presentation of a gentleman with dematomyositis (DM) complicated by severe interstitial lung disease (ILD). The case is used to illustrate clinical features of DM, the differential diagnosis, investigations required and treatment options.

Case History

A 49 year old decorator presented with a 3 month history of polyarthralgia and skin lesions over his knuckles and elbows. He had been prescribed prednisolone 40mgs od elsewhere for presumed inflammatory arthritis. Whilst this had had an initially positive effect on his symptoms, these had recurred on reducing the dose of steroid and he had also developed mild upper limb weakness, Raynaud's phenomenon and increasing breathlessness. There was a family history of rheumatoid arthritis. He smoked 10 cigarettes/day.

Examination showed coarse, fissured hands. He had prominent nail fold capillaries and digital infarcts. There was a psoriaform rash overlying his knuckles. Auscultation of the chest revealed left basal crepitations. Neurological examination showed 4/5 proximal upper limb weakness. Subtle lower limb and truncal weakness were excluded by tests described in Table 2.

What is the differential diagnosis?

The differential diagnosis for muscle pain or weakness is wide (Table 1). In this patient the development of arthralgias, rash, Raynaud's phenomenon and respiratory symptoms in association with muscle weakness is strongly suggestive of an idiopathic inflammatory myopathy (IIM) or a myositis associated with another connective tissue disease.

Type	Cause
Idiopathic	Dermatomyositis Polymyositis Inclusion body myositis
Associated with other connective tissue diseases	Systemic lupus erythematosus
Infective	Viral Bacterial Fungal Protozoal
Metabolic	Muscle glycogenoses Lipid storage disorders Mitochondrial myopathies
Neurological	Myasthenia gravis Genetic muscular dystrophies
Endocrine	Hypo/hyperthyroidism Osteomalacia Hypoparathyroidism Cushing's disease Acromegaly
Drug toxicity	Alcohol Statins Anti-malarials Colchicine Penicillamine Corticosteroids Cocaine Zidovudine

Table 1. Differential Diagnosis of Idiopathic Inflammatory Myopathy.

What would you look for on clinical examination?

A thorough examination needs to be undertaken, focusing particularly on the skin and musculoskeletal system. In this case the 'mechanic's hands' and the psoriaform rash over the hand joints pointed towards a diagnosis of DM (Table 2).

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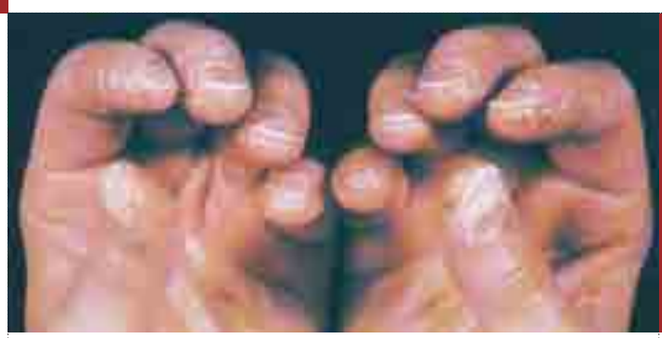

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System	Features
General	Low grade fever Lymphadenopathy
Hands	Raynaud's phenomenon Mechanic's hands (rough, cracked, dirty skin) Dilated nail fold capillaries Cuticle hypertrophy Nail fold infarcts
Other cutaneous features	Gottron's patches (over hand and elbow joints +/- thick psoriaform scale) Periorbital heliotropic rash with oedema Shawl and V signs (photosensitive erythema in sun exposed areas of back and chest respectively) Malar erythema
Musculoskeletal	Proximal muscle weakness (patients may have difficulty raising their arms above their heads or rising from a squatting position or chair without using their arms) Truncal weakness (inability to perform a sit up) Joint tenderness and swelling
Other systems	Late inspiratory crepitations within the lower lung fields suggestive of interstitial lung disease Breast lumps, abdominal or rectal masses or ascites suggestive of malignancy

Table 2. Examination Findings in Dermatomyositis.

How would you investigate this patient?

Blood Tests

Full blood count, renal function, liver function, thyroid function, inflammatory markers, creatine kinase (CK), bone profile, vitamin D level and clotting profile should be requested to help confirm the diagnosis and exclude other differential diagnoses. On rare occasions the CK may be normal or only mildly elevated despite active myositis, especially in patients with chronic disease or when it is associated with an underlying connective tissue disorder. Extreme elevations of the CK (> 100 fold) are unusual.

The anti-nuclear antibody (ANA) test involves serum staining of Hep-2 cells and will be positive in some patients with DM or polymyositis (PM). The staining of Hep-2 cells may be nuclear or cytoplasmic and the pattern of staining and antibody specificity may help in diagnosis (Table 3).

Autoantibody	Staining pattern of Hep-2 cells	Antigen	Clinical association
Anti-Mi-2	Nuclear	218/240kDa helicase family proteins	DM > PM
Anti-SRP	Cytoplasm and nuclear	7SL-RNA complex	PM Severe disease
Anti-Jo-1	Cytoplasm	Histidyl-tRNA synthetase	PM > DM Interstitial lung disease
Anti-PL-7	Cytoplasm	Threonyl-tRNA synthetase	PM or DM Interstitial lung disease
Anti-PL12	Cytoplasm	Alanyl-tRNA synthetase	PM or DM Interstitial lung disease
Anti-EJ	Cytoplasm	Glycyl-tRNA synthetase	PM or DM Interstitial lung disease
Anti-Ku	Nuclear	70/80kDa DNA-PK regulatory subunit	Myositis/scleroderma overlap
Anti-PM-SCL	Nuclear	Exosome complex	Myositis/scleroderma overlap
Anti-U1 RNP	Nuclear	U1 small ribonuclear protein	Myositis/connective tissue disease overlap

Table 3. Common Autoantibodies in Dermatomyositis and Polymyositis[1].

Electromyography (EMG)

Myopathic features characterized by spontaneous activity may be seen.2

Magnetic resonance imaging (MRI)

MRI scan is useful to identify the location and extent of inflammation and helps in selecting a suitable site for biopsy.

Muscle Biopsy

Every patient with suspected inflammatory myositis should have a muscle biopsy. There is a 10-25% false negative rate due to uneven muscle involvement.3 Specimens, ideally taken surgically, should be sent immediately for immunohistochemical staining (fresh sample) as well as for standard histochemical staining (formalin sample) to a histopathologist with myositis expertise.

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Other tests

All patients should have a urine dipstick, electrocardiogram and be screened for presence of ILD with a chest X-ray (CXR) and pulmonary function tests (PFTs) with a view to high resolution computed tomography (HRCT) of the chest if there is reduction in gas transfer or lung volumes. Oesophageal motility studies may be needed to detect pharyngeal or upper oesophageal involvement in patients with dysphagia. Investigation of a possible underlying malignancy should be guided by symptoms, risk factors and age.

Investigation of this patient showed a normochromic normocytic anaemia. Renal and liver function tests were normal and the CK was also normal at 72U/l. The initial erythrocyte sedimentation rate was 37mm/hr but subsequently rose to 95mm/hr. The C-reactive protein was high at 61g/l. Autoantibody screen showed a weakly positive ANA with specificity for 52kDa Ro. Notably the patient had no clinical features of Sjögren's syndrome.

Despite a normal CK, EMG showed myopathic changes in the proximal limbs. In contrast to the clinical picture, the EMG findings were more marked in the lower rather than upper limbs and so MRI was performed of the thigh. This showed patchy high signal within the semimembranosus muscles consistent with myositis (Figure 1).

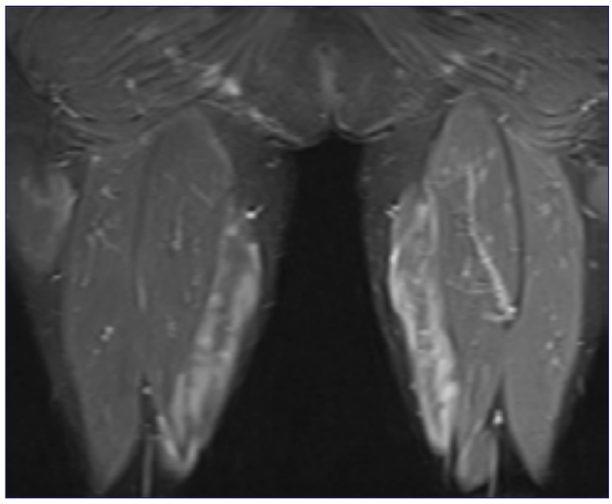

Figure 1. MRI STIR sequences revealing patchy high signal within the semimembranosus muscles indicating inflammation.

Muscle biopsy confirmed DM with hallmark features including perifascicular atrophy, infiltration of CD4+ T cells and C5-9 complement deposition.

An initial CXR revealed minor left basal reticulation (Figure 2a) but this progressed to bibasal reticulonodular shadowing. PFTs showed restriction with a reduced carbon monoxide diffusing capacity (DLCO 53% predicted). HRCT confirmed ILD with areas of ground glass shadowing (Figure 2b).

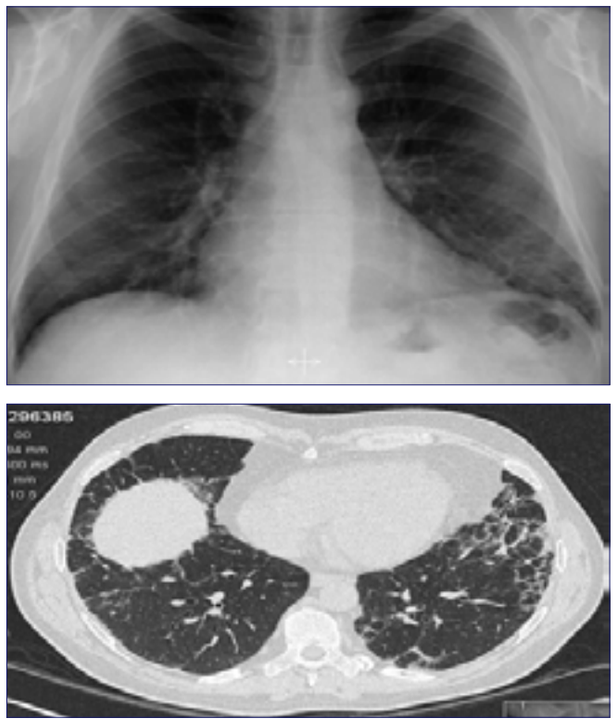

Figure 2. Imaging of lungs at presentation. a) CXR showing left basal reticulation. b) CT scan showing interstitial lung disease with areas of ground glass change.

How would you treat this patient?

Immunosuppressive Therapy

Patients with cutaneous features of DM without muscle involvement may respond to topical corticosteroids and hydroxychloroquine. Patients with muscle involvement from DM or PM require systemic immunosuppression with prednisolone 0.5-1mg/kg/day as first line therapy. Individuals with severe disease may also benefit from an initial course of intravenous (IV) methylprednisolone 500-1000mgs for 3 days. A second agent such as methotrexate, azathioprine, mycophenolate mofetil or cicloporin is best introduced within the first month of treatment and prior to reducing the oral prednisolone. Cyclophosphamide may be preferred as a second agent where a patient has severe myositis, bulbar or respiratory involvement.2,4,5 Intravenous immunoglobulin (IVIG) has proven efficacy although its role in ILD associated with IIM has not been evaluated.2,6 Rituximab may be considered in resistant cases.2,5 There is also anecdotal experience suggesting efficacy of anti- tumour necrosis factor agents.5

Physiotherapy

A physiotherapist guided exercise programme is advised to prevent joint contractures, disuse atrophy and long-term disability. Passive stretching and splinting are important in early stages of disease. More active strength building exercises can begin once inflammation is controlled.

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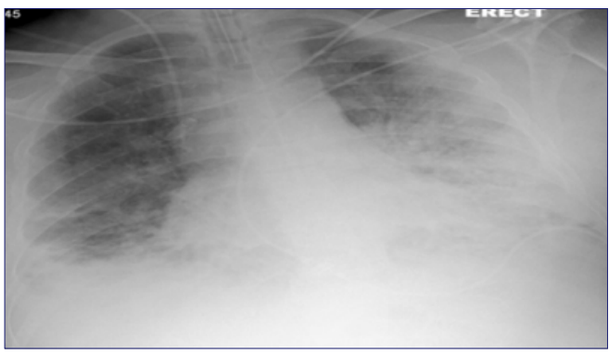
Other

The need for bone protection with a bisphosphonate, gastrointestinal protection with a proton pump inhibitor and DVT prophylaxis should be considered.

Our patient was taking prednisolone when he presented to the department and was given hydroxychloroquine for cutaneous disease and iloprost infusions and nifedipine as management for severe Raynaud's phenomenon with fingertip ulceration. He developed septicaemia secondary to staphylococcal infection of a cutaneous lesion and required intravenous antibiotics. Following confirmation of the diagnosis of DM, the ongoing staphylococcal septicaemia favoured IVIG over an anti-proliferative or cytotoxic drug to be given in addition to corticosteroids in the first instance. However his breathing deteriorated with desaturation to 70% on minimal exertion, requiring intubation and transfer to intensive care. CXR (Figure 3a) and HRCT (Figure 3b) appearances deteriorated significantly.



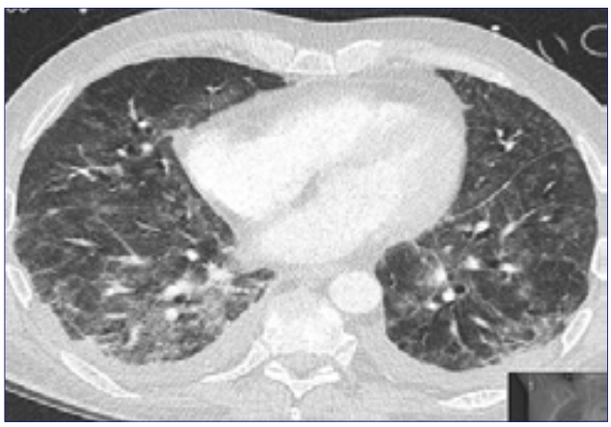


Figure 3. Imaging of lungs following deterioration in respiratory symptoms. a) CXR showing increasing shadowing at both lung bases. b) CT scan showing severe interstitial lung disease.

Idiopathic Inflammatory Myopathies. Patient Management.

Bronchoalveolar lavage excluded pulmonary infection enabling a 3 day course of pulsed IV methylprednisolone and institution of monthly pulsed IV cyclophosphamide to treat life-threatening ILD. His condition improved slowly and he was extubated after 3 months. He needed intensive physiotherapy to treat generalised weakness and was discharged after 2 months of rehabilitation. Pulsed IV cyclophosphamide was continued to 6 months and followed by maintenance therapy with azathioprine. The dose of prednisolone was gradually tapered. At 10 months he is in remission and has returned to work.

Idiopathic Inflammatory Myopathies

The IIMs are a group of rare multisystem disorders characterized by skeletal muscle inflammation and weakness. They include DM, PM and inclusion body myositis (IBM). In DM and PM the myositis is usually proximal and symmetrical whereas inclusion body myositis (IBM) characteristically involves quadriceps and muscle groups within the forearm.3,7 DM and PM should be separated from IBM as they are treatable, have associations with malignancy and frequently have multisystem involvement.8

DM is commoner than PM with an annual incidence of 2.18- 8.8 cases per million.9 It can present in childhood (<15yrs) or adulthood (45- 54 years) with a female predominance (F:M 1.5:1).9 It is thought to be triggered by unknown environmental factors in genetically predisposed individuals.4 Myositis usually occurs with or follows within 1-2 years of typical cutaneous features but the latter may predominate with only minor or absent muscle involvement (amyopathic DM).

Risk of malignancy, most commonly ovarian, lung, breast and non-Hodgkin's lymphomas, is greatest in the five-year period prior to and subsequent to diagnosis.4,10 It is more commonly associated with DM than PM, and may be present in up to 15% of DM patients overall although the risk is higher in the elderly.2

Pulmonary complications include ILD, diaphragmatic weakness leading to ventilatory failure and pneumonia secondary to aspiration, opportunistic infection or drugs.4 Pharyngeal and upper oesophageal striated muscle involvement may lead to dysphagia and aspiration. Cardiac involvement may rarely cause arrythmias (50%).4

Prognosis in DM and PM varies but is negatively affected by age, myositis severity, associated dysphagia, cardiopulmonary disease and malignancy.4

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Myositis and ILD

ILD affects 23-65% of patients with DM or PM and the 5 year survival of individuals with this complication is 60-86%.6,11 Lung disease may precede, occur concomitantly with or post-date the onset of muscle and skin manifestations. Patients may be asymptomatic or may present with acute or insidious onset of symptoms which usually include a cough and/or breathlessness. Examination typically shows bibasal crepitations.11 Presentation with acute onset, rapidly progressing, life-threatening disease as occurred in this patient is rare.

The strongest predictor of ILD is the presence of antibodies specific for aminoacyl-t-RNA synthetases (anti-synthetase antibodies). Of these, anti-Jo 1 antibody is the most common, occurring in ~20% of all patients with PM or DM but ~70% of patients with associated ILD. Patients with anti-synthetase antibodies characteristically have Raynaud's phenomenon, arthritis and 'mechanic's hands' in addition to the myositis and ILD. This clinical syndrome is referred to as the anti-synthetase syndrome.11

Summary

This case highlights some of the difficulties in diagnosing and managing patients with DM. Our patient had relatively mild weakness, a normal CK level, an atypical antibody profile and rapidly developed life-threatening ILD as the main feature of his disease.

Multiple Choice Questions

True or false?

1. Patients with DM develop:

a) Sudden onset muscle weakness
b) Raynaud's phenomenon
c) Severe muscle pain
d) Erosive arthritis
e) Abnormal nail folds

2. Pulmonary complications of DM include:

a) Type 1 respiratory failure
b) Type 2 respiratory failure
c) Lung carcinoma
d) Interstitial lung disease
e) Pulmonary hypertension

3. In DM, CK levels:

a) Are always elevated
b) Are often >100 fold the upper limit of normal
c) When elevated are diagnostic of myositis
d) Should fall with treatment
e) Can be used to monitor disease activity

Answers

1. b and e are true; a, c and d are false

Patients with DM characteristically develop gradual onset muscle weakness over weeks to months. Patients experience muscle stiffness but pain and tenderness are uncommon. The arthritis of connective tissue disease may resemble that of rheumatoid arthritis clinically, but plain radiographs typically reveal a non-erosive picture. Vascular changes within the nail bed area and Raynaud's phenomenon are very common and should be actively looked for on history and examination.

2. a, b, d and e are true; c is false

Patients may develop both type 1 and 2 respiratory failure secondary to ILD or diaphragmatic muscle involvement respectively. Pulmonary hypertension may occur secondary to ILD. Lung carcinoma is not a direct complication of DM; it should however be considered in newly diagnosed patients with DM in view of the association between DM and malignancy.

3. d and e are true; a, b, and c are false

The CK level can be normal or only mildly elevated in some patients despite presence of active inflammation on muscle biopsy. Very high elevations of the CK are rare and point to an alternative diagnosis. The differential diagnosis of an elevated CK levels is wide and the only definitive diagnostic test in DM is a muscle biopsy. Treatment aims to normalise the CK level which can be followed serially to monitor disease activity.

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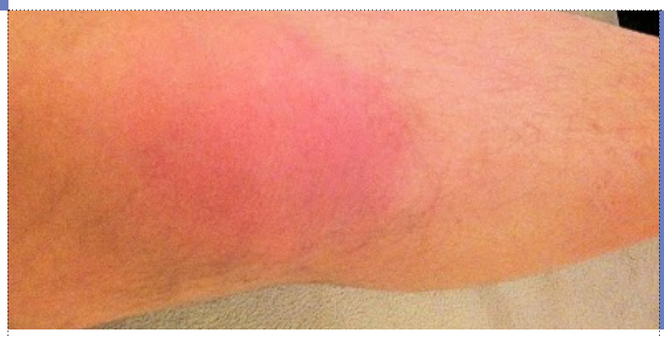
Authors

Leena Patel
Alexander Brand
Margaret Callan

JOINT ASPIRATION CASE

S Goudie



Joint aspiration case.
Practical Procedures.

Abstract

Knee joint aspiration is a commonly used practical procedure in the investigation of a swollen, painful knee joint. A step by step guide to safely carrying out knee joint aspiration is described in the context of a pyrexial 58 year old male presenting with a red, hot, swollen knee. The relevant anatomy contraindications, side effects and interpretation of results are discussed.

History

A 58-year-old male presents to Accident and Emergency with a 24-hour history of a painful, red and swollen right knee. There is no history of trauma. He is now feeling feverish, sweaty and having difficulty weight bearing.

Examination

Pulse 106, BP 134/85, temperature 38.1 degrees C.

His right knee is swollen, feels hot to touch and the overlying skin is erythematous. He is generally tender on palpation of the knee. Exquisite pain limits knee flexion to 20 degrees and extension to 5 degrees.

Initial Management

Question

What is your differential diagnosis and how would you investigate further?

Answer

Differential diagnosis: Septic arthritis, gout, pseudogout, cellulitis or arthritis. Investigation: Full blood count, urea and electrolytes, C-reactive protein, blood urate level, blood culture - microscopy, culture and sensitivities. AP and lateral view x-rays of the knee.

When septic arthritis is suspected clinically, the gold standard investigation is aspiration of the joint.

Analysis of joint aspirate can confirm the diagnosis and guide antibiotic therapy. It should be carried out prior to starting antibiotic treatment, but should not delay administration of suitable analgesia, antipyretic and intravenous fluid.

Contraindications to joint aspiration in the Emergency Department

Relative

- Joint prosthesis (Contact Orthopaedics prior to aspiration as they may decide to aspirate in theatre.)
- Overt infection in skin overlying the joint
- Refusal by patient
- Very distorted anatomy
- Coagulopathy
- Osteomyelitis in adjacent bone

Complications

- Haemorrhage causing haemarthrosis or soft tissue haematoma
- Introduction of infection
- Failure to aspirate fluid
- Nerve damage

Preparation and Equipment

Obtain informed consent discussing above complications and possible alternatives.

- Sterile gloves
- Apron
- Sterile pack including – swabs, drape, pot
- Chlorhexidine
- Adhesive dressing
- 1% lignocaine
- Green (21G) needle and blue (23G) needle
- A 10 mL and a 20 mL syringe
- Sterile specimen pots

JOINT ASPIRATION CASE

S Goudie

Positioning

Lay the patient in a comfortable supine position on a bed at a suitable height for working. Position the knee slightly flexed, resting on a pillow. For aspiration, a lateral approach to the knee is used.

Identify site

Using a lateral approach to the knee, the superolateral pole of the patella is palpated. A point one finger's breadth superior and one finger's breadth lateral to this point is then identified and marked with a pen.

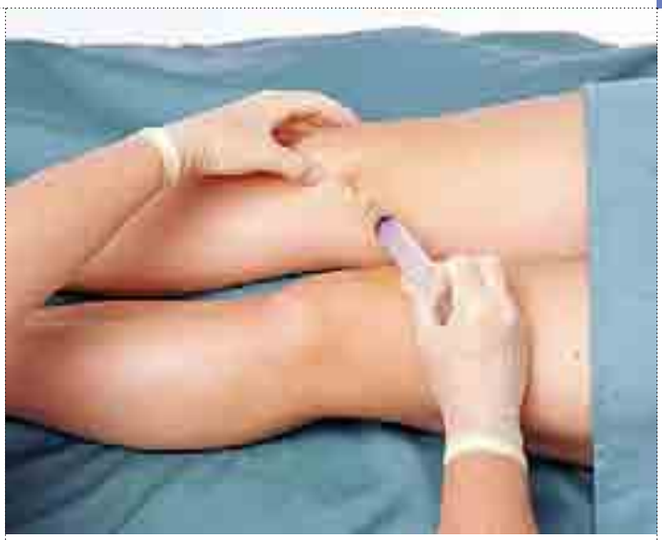
Figure 1

Preparation of site

Using strict aseptic technique, don apron and sterile gloves. Using a trolley at the patient's bedside, open all equipment. An assistant is very useful at this stage to avoid contamination. Using chlorhexidine soaked sterile swabs, clean the area around the aspiration site in a circular motion moving out from the planned entry site. Place a drape beside the leg on bed to increase the size of sterile field.

Local Anaesthetic

Confirm the patient's drug allergies. Using a green 21G needle, draw 10 mL 1% lignocaine into 10mL syringe. The maximum dose of lignocaine is 5mg/kg, but in reality a much smaller dose is needed. Attach a syringe to a blue 23G needle. Insert the needle into subcutaneous tissue at the proposed entry site. Draw back to confirm the needle has not entered a vessel and inject a small bleb of local anaesthetic. Advance the needle deeper drawing back and injecting local anaesthetic down to the level of bone.



Aspiration

Attach a 21G green needle to a 10mL syringe. Enter the skin at the marked entry site and advance the needle pointing 45 degrees distally and 45 degrees inferiorly, tilted under the patella. At a depth of 3-5cm, the needle should be in the synovium and fluid can be aspirated. Leave the needle in situ and remove the syringe. Dispense the synovial fluid into a sterile specimen pot to be sent to Microbiology. The syringe can then be reattached to the needle and the knee aspirated until dry. This can provide some symptomatic relief in the case of a tense effusion. Remove the needle and cover the wound entry site with an adhesive dressing. Apply pressure to reduce bleeding from the aspiration site.

Investigation of Aspirate

Inspect the aspirate and match the typical aspirate appearance with the diagnosis:

a) Bloody – traumatic / fracture / ligament rupture.
b) Straw coloured and transparent – normal.
c) Cloudy / pus – infection.

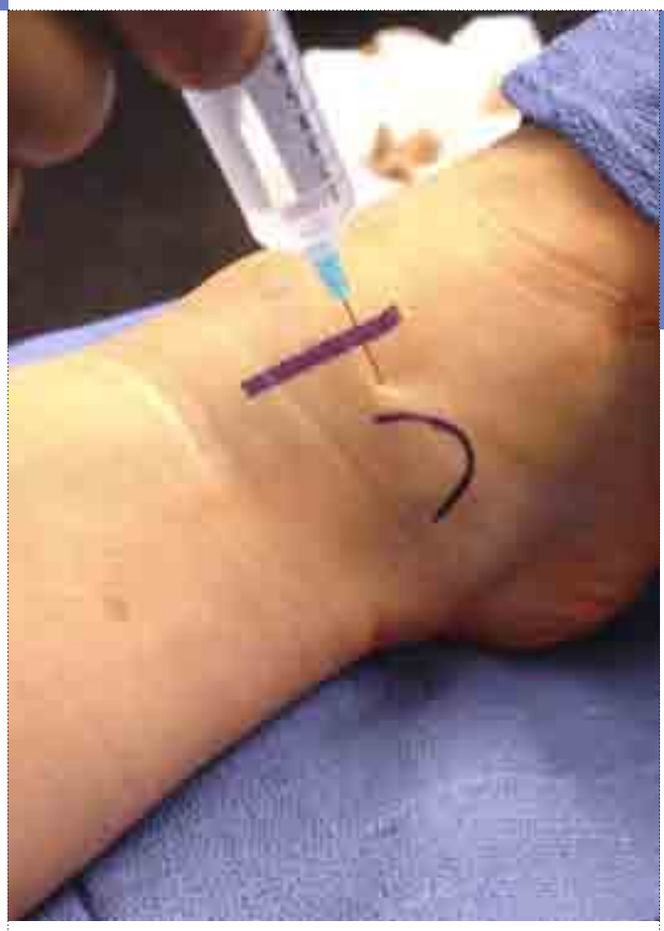
The sample should be sent to Microbiology for urgent Gram stain. This provides information as to the presence of infection in the knee. Microscopy, culture and sensitivity can identify microorganisms and guide antibiotic therapy. Polarized light microscopy should be requested to look for crystals seen in gout and pseudogout.

Documentation

- The date, time and name of the staff involved in the procedure
- The consent obtained from the patient
- A brief description of the technique and any complications encountered
- The drugs used and their doses
- A note of the volume and appearance of the aspirate
- Print and sign the name, state training grade

JOINT ASPIRATION CASE

S Goudie



Joint aspiration case.
Practical Procedures.

Further treatment
Start broad-spectrum antibiotic therapy according to local policy and change as appropriate in accordance with the Microbiology results.

Questions

1. Which is the most common pathogen found in septic arthritis?

a) Staphylococcus aureus
b) Neisseria gonorrhoeae
c) Pseudomonas aeruginosa
d) Streptococcus pneumoniae
e) Campylobacter

2. Which of the following is not a relative contraindication to joint aspiration in the Emergency Department?

a) Osteomyelitis in adjacent bone
b) Previously diagnosed gout in the same joint
c) Cellulitis of the skin overlying the joint
d) A young patient with haemophillia
e) A prosthetic joint

Answers

Answer: a
Staph aureus is the most common pathogen found in septic arthritis in adults. Streptococcus pneumoniae, a beta-haemolytic strep, is the second most common. Infection is most often a result of seeding caused by a transient or persistent bacteraemia secondary to infection elsewhere. Gram-negative bacilli and Haemophilus influenzae are the most common organisms in neonates and children under the age of five. Gram-negative bacilli must also be considered in immunocompromised patients, intravenous drug users and the elderly.

Answer: b
Osteomyelitis of adjacent bone and cellulitis over the joint increase the risk of infection into a joint, which may be aseptic at the time of aspiration. A patient with coagulopathy is at increased risk for haemorhage causing haemarthrosis or soft tissue haematoma following aspiration. This should be discussed with a haematologist prior to aspiration. A patient with a prosthetic joint should be discussed with Orthopaedics and may be aspirated in theatre. Gout may mimic septic arthritis and can be diagnosed following polarized light microscopy of the aspirate.

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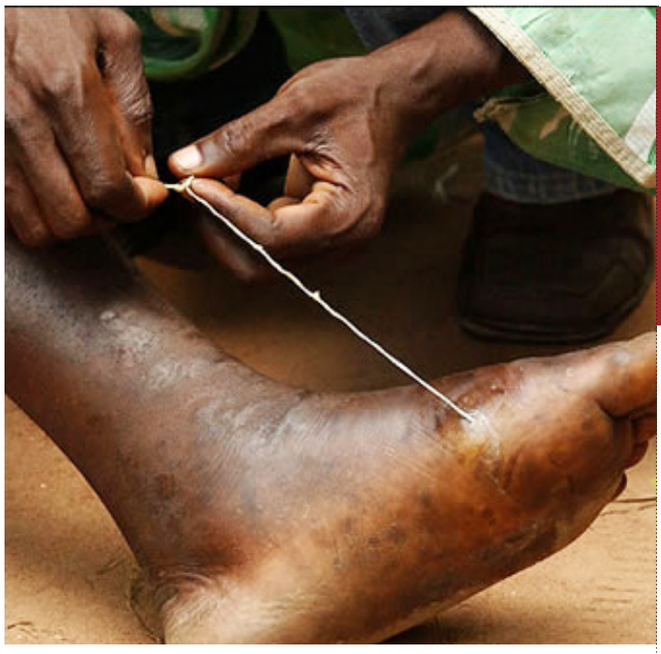
LOA LOA REACTIVE ARTHRITIS

R Rajak



Abstract

We describe a unique case of reactive arthritis secondary to Loa Loa filariasis after treatment with anti-helminthic therapy. The case highlights that in patients with unclassifiable oligoarthritis, who have travelled abroad, reactive arthritis due to parasitic infections should be considered in the scope of differential diagnoses. Furthermore, one must distinguish between musculoskeletal involvement during parasitaemia and reactive inflammatory disease to either the infection itself or, as in our patient, the helminthic carcasses.

Reactive arthritis should be monitored for after anti-helminthic treatment for filariasis, so that early appropriate treatment and rehabilitation can be instituted to prevent long-term sequelae.

Case History

We present a unique case of reactive arthritis to nematode corpses developing in a patient after anti-helminthic treatment for Loa Loa filariasis.

A 37-year-old man, who was previously fit and healthy, was diagnosed with loa loa infection in early 2008. He had been undertaking voluntary work in Cameroon in 2007, working mainly with chimpanzees in a primate orphanage. He recalled having numerous insect bites. In June 2007, he developed erythematous and pruritic swellings in the lower limbs with associated lethargy and intermittent fevers. In December 2007, he developed a right knee effusion and subsequently underwent arthroscopy. A blood film at the time showed a marked eosinophilia. Arthroscopic histology revealed loa loa microfilariae. He was diagnosed with Loaiasis, referred to the London School of Tropical Medicine and treated with diethyl carbamazine (DEC). Judging retrospectively, the initial reported lesions were likely Calabar swellings.

Loa Loa Reactive Arthritis. Patient Management.

A few weeks after his second and final course of anti-helminthic treatment, the patient developed pain and stiffness in multiple joints particularly affecting his ankles, heels and toes, worse on the left than right. The symptoms in the left ankle became so severe that he became wheelchair bound. He did not describe swelling in the affected joints. There were no spinal or sacroiliac symptoms. He required plaster cast immobilization of the left leg which led to marked muscle wasting and contractures and eventually an inversion deformity of the ankle joint.

Over the following 2 years, he continued to experience intermittent bouts of pain and stiffness in the affected areas and was dependent on crutches for mobility.

In January 2010, the patient was seen by the regional orthopaedic team with a painful, swollen right wrist at the site of a previous swelling which had settled after treatment with DEC. An arthrotomy revealed a sterile abscess in the extensor tendons sheath. The abscess was drained. Following recurrence of his wrist symptoms, he had a second operation with a synovial biopsy of the wrist and extensor tendon. This showed chronic active inflammation consistent with an immuno-inflammatory response secondary to the loa loa corpses causing arthritis; no eosinophilic infilitrate observed.

We saw him in April 2010. His mobility was still impaired due to his persistent left ankle symptoms but he was improving with physiotherapy. Examination revealed limited left ankle movements with an inversion deformity that was passively correctible and he had no achilles tendon or plantar fascia abnormalities. Aside from the incision scar over his right wrist, all other joints were unremarkable.

Autoimmune serology was negative. He was HLA B27 positive. There was no family history of seronegative spondyloarthropathies or any other autoimmune connective tissue disease.

LOA LOA REACTIVE ARTHRITIS

R Rajak

Loa Loa Reactive Arthritis.
Patient Management.

Ultrasound imaging of left foot revealed tenosynovitis in several tendon compartments associated with enthesopathy of the Achilles tendon. There was no synovitis or effusions in the joints of the hind and midfoot. The right foot was normal.

Treatment consisted of anti-inflammatories and physiotherapy, both of which have controlled his symptoms thus far. We planned to manage any relapses or progression of his symptoms with disease modifying drugs (DMARDs) namely sulfasalazine or methotrexate.

Discussion

Reactive arthritis (ReA) is an autoimmune disorder characterized by an inflammatory response to musculoskeletal structures, such as joints, tendons and entheses. It is thought to occur as a result of a cross-reaction in the immune response mounted against infectious organisms, where the individual's body structures are also attacked. This is due to molecular similarities between the antigenic target in the microbe and cellular structures in the body. It has been reported with many infectious agents in the UK, mostly following Chlamydia urethritis, dysentery (enteric bacteria) and streptococcal throat infection1, however, any infection can potentially trigger ReA (see table 1 below). It is classed as a seronegative spondyloarthropathy with up to 75% of cases being HLA-B27 antigen positive.

Most cases are self-limiting though 15 - 20% can develop a chronic, disabling course5; HLA-B27 positive patients are more likely to have persistent disease. The triad of oligoarthritis (usually large lower limb joints), sterile conjunctivitis and urethritis, is also known as Reiter's Syndrome though the presence of all the features together is uncommon. Other associated clinical problems include circinate balanitis, mouth ulcers and keratoderma blenorrhagica.

Gastrointestinal	Viral
Salmonella enterica	Parvovirus
Shigella flexneri	Hepatitis
Yersinia enterocolitica	
Campylobacter jejuni	Others
	Beta-haemolytic streptococci
Sexually transmitted	Borrelia burgdorferi
Chlamydia trachomatis	Mycobacterium tuberculosis

Table 1: Common microbial agents implicated in ReA3.

The Loa Loa parasite, colloquially known as the African eyeworm, is a nematode worm that can infect humans and animals. The typical vectors for interspecies transmission are the Mango fly (Chrysops silicea) or Deer fly (Chrysops dimidiata), commonly found in the West African ecosystem. The symptoms of Loa Loa filariasis are usually confined to subcutaneous structures4. Cutaneous lesions are characterized by erythematous, tender, pruritic urticarial swellings (calabar swellings) and occasionally adult worms are seen migrating through the subconjunctiva and other soft tissues. Filarial antigen detection by immunoassaying is not in clinic practice as yet5 and current diagnostic practice remains in identifying via microscopy, Loa Loa microfilariae from tissue samples. Treatment is with diethylcarbamazine, an anti-helminthic drug used in many of the filarial infections. Surgical excision of adult worms especially from the conjunctiva is occasionally required6.

LOA LOA REACTIVE ARTHRITIS

R Rajak

Seldom are cases of ReA associated with parasitic infections reported but a history of foreign travel, especially to West Africa where loaiasis is endemic, should alert suspicion. Filariasis is the commonest reported cause of ReA secondary to parasitic infection7. Many filarialial infections present asymptomatically with no systemic features, making the connection between the arthritis and infection difficult. Interestingly, articular symptoms may be present in 10% of patients with filariasis, most of whom develop oligoarthritis affecting the large joints in the lower limbs7. Most patients develop a self-limiting sub-acute synovitis but some progress to a chronic disease. A clue to diagnosis is eosinophilia and raised IgE levels, however, this is found in only 20% of patients8.

When dealing with musculoskeletal involvement in filariasis, the two aspects that have to be distinguished are the symptoms that arise from the inflammatory response to the nematode parasitaemia and the reactive immuno-inflammatory response induced by either the nematodes while they are alive or, as in our patient, the dead nematodes. In the first instance treatment should be focussed on symptom control with NSAIDs, analgesia and physiotherapy, and in the second instance, on reduction of ongoing inflammation and damage limitation which may involve treatment with DMARDs such as sulfasalazine or methotrexate.

Our patient most likely developed ReA to the dead nematodes. Once the worms die, they calcify and remain in subcutaneous tissues and lymphatics. Their carcasses can obstruct lymphatic drainage but also induce an immunological response resulting in a reactive inflammatory disease; ReA being the common sequelae. Circulating immune complexes and synovial infiltration by eosinophils mediated by TH2 T-cells have been suggested to be causative in this 8,9.

There is a growing body of evidence that ReA may be due to the immune response to antigens not only from infective organisms found generally in the body but actually from the dead or 'inactivated' organisms in the synovium of patients with ReA10. The carcasses of parasitic organisms, once killed with anti-helminthic therapy, can remain in the system for up to 18 months; this is generally a much longer time for clearance of the antigenic components of viral or bacterial pathogens.

Therefore, monitoring for reactive musculo-skeletal disease, after the completion of anti-helminthic treatment is crucial to avoid delayed diagnosis and subsequent long-term disability.

Key Message

Loa loa filariasis can cause direct involvement of the musculoskeletal system or a reactive inflammatory disease to either the nematodes or their carcasses after anti-helminthic treatment.

Questions

Choose the best of 5.

1. A 40-year-old gentleman of Swedish origin presents to his GP feeling generally unwell, fatigued and complaining of joint pains. He had just returned one week ago from a business trip to Spain. During his trip he had one episode of abdominal pain followed by non-bloody diarrhoea. He is otherwise medically fit. Examination reveals tenderness in his knees, ankles and left wrist. These joints are stiff with slightly decreased range of movement. There are bilateral knee effusions. His vital observations are within normal limits. No other abnormalities are detected. Which is the most distinguishing test in achieving the diagnosis?

a) X-ray of affected joints

b) Joint aspirate culturing

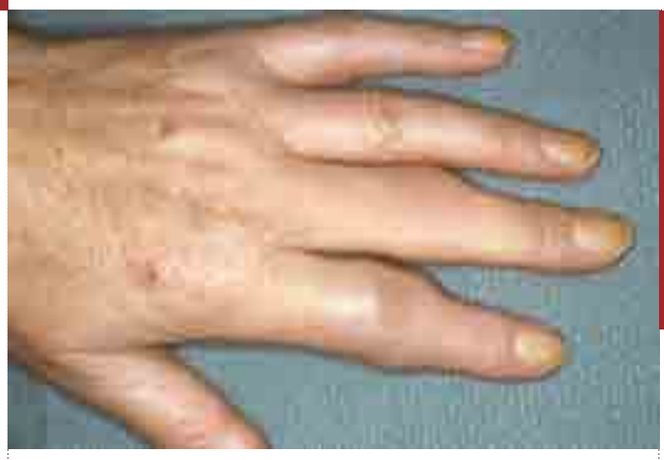
c) Inflammation markers

d) Stool culturing

e) Abdominal ultrasound scan

LOA LOA REACTIVE ARTHRITIS

R Rajak



2. A 39-year-old is seen in the Rheumatology clinic. She describes a 6 week history of tenderness in her fingers associated with morning stiffness and swelling. She was previously well with no significant medical illnesses. She also reports that her three young children had been unwell with a flu-like illness consisting of fever, rhinorrhoea and a macular, erythematous rash. Examination displayed synovitis in several proximal interphalangeal and metacarpophalangeal joints of both hands. Her inflammation markers were slightly raised and complement counts (C3/C4) were reduced. What is the likeliest diagnosis?

a) Rheumatoid arthritis

b) Parvovirus B19 infection

c) Lyme disease

d) Streptococcal reactive arthritis

e) Systemic Lupus Erythematosis

Answers

1. Answer: d

The commonest gastroenteritic pathogens implicated in reactive arthritis are salmonella, shigella, campylobacter, e.coli and yersinia. HLA-B27 antigen positivity is highest among Caucasians, and is found to be positive in up to 25% of the Scandanavian population. The lower limb, large joints are the commonest joints to be affected but potentially any joint can involved. Only stool cultures in the above tests would find the causative agent. X-rays are likely to be normal. Joint aspiration would help rule out septic and crystal arthritis but would not distinguish the diagnosis of post-gastroenteritic reactive arthritis.

Loa Loa Reactive Arthritis.
Patient Management.

2. Answer: b

Parvovirus B19 is a single-stranded DNA virus which is spread by respiratory secretions. Symptoms include upper respiratory tract symptoms, fever, myalgia and skin lesions. Erythema Infectiosum ('slapped cheek') occurs in children and is not seen in adults. Post-infectious arthritis is a complication mainly in adults which can persist for weeks to months. It presents typically with a symmetrical small joint polyarthropathy with pain and swelling of the fingers, wrists and feet. Large joints are infrequently involved. Hypocomplementaemia and transient aplastic anaemia are associated. IgM parvovirus positive titres are suggestive of acute infection. Unlike rheumatoid arthritis, reactive arthritis associated with parvovirus B19 does not cause a destructive and deforming joint disease.

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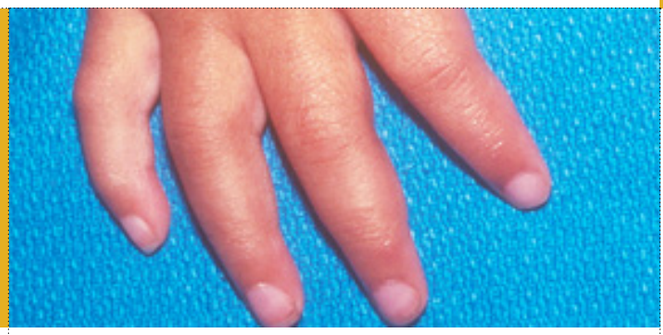
Authors

R Rajak

SARCOID ARTHROPATHY

J V McGowan



Sarcoid Arthropathy.
Good Clinical Care.

A 42 year old Afro-Caribbean male attended the rheumatology clinic with a 4 year history of swelling of the joints in his hands. He denied early morning stiffness, joint involvement elsewhere, dry eyes or mouth, Raynaud's phenomenon or weight loss. He was diagnosed with sarcoidosis 5 years previously following a biopsy of a 1cm lump in the posterior triangle of his neck, which showed- non-caseating granulomas, and a chest radiograph showed bilateral hilar lymphadenopathy.

Whilst under the care of the respiratory physicians he received multiple courses of prednisolone up to 40mg to control his massive mediastinal lymphadenopathy and swollen, painful joints. He received calcium and vitamin D supplements to prevent osteoporosis. He had poor compliance with treatment and often missed appointments. He had no other significant past medical history or family history. He was a non-smoker and worked as a chef. He was born in Ghana and lived in the UK for 6 years.

On examination he had gross soft tissue swelling of both hands, dactylitis (sausage fingers), swelling of the proximal interphalyngeal joints (PIPJ) and metacarpal phalyngeal joints (MCPJ), shortening of the digits, particularly ring fingers, and dystrophic nails (Figure 1). He retained good hand function. He had the violaceous rash of lupus pernio on the tip of his nose.

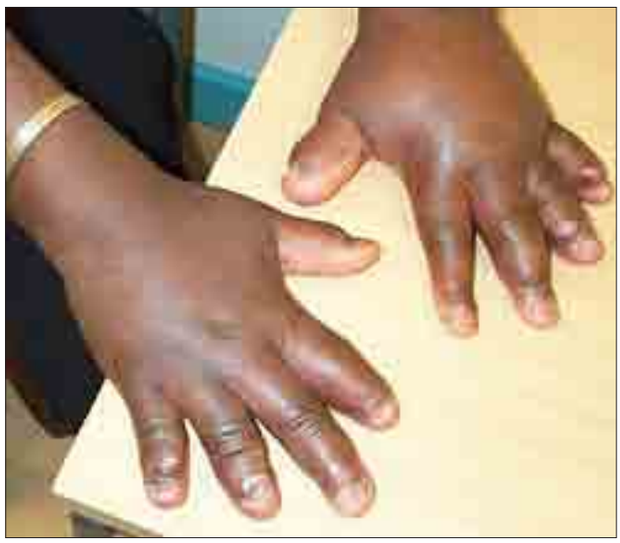


Figure 1: Swollen hands with dactylitis, digital shortening and nail dystrophy.

Plain film radiographs of his hands (Figure 2) showed a diffuse lace-like pattern of the proximal and middle phalanges, multiple articular surface erosions, acroosteolysis and general soft tissue swelling. Blood tests (full blood count, renal function, liver function tests) were normal. He had a mild hypercalcaemia. Serum ACE was 122 (Baseline 85 at the time of diagnosis of sarcoidosis).

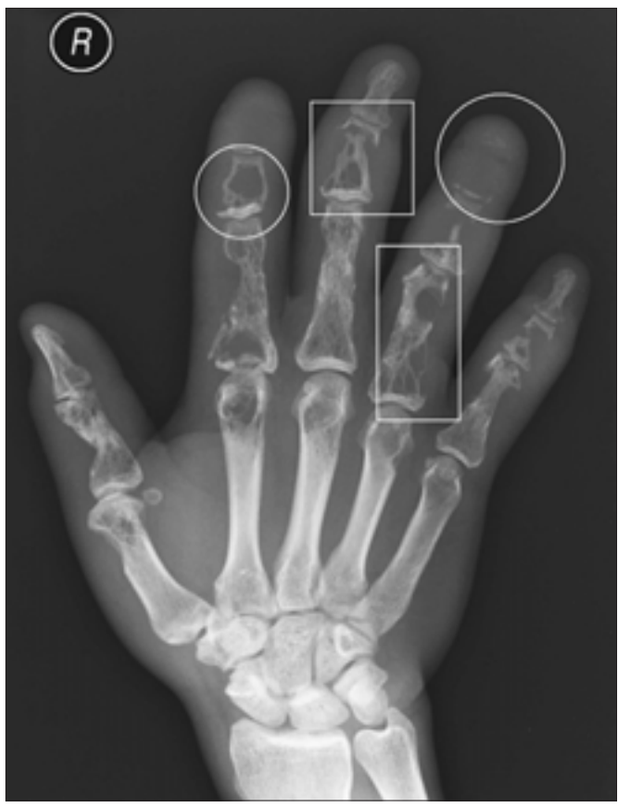


Figure 2: Radiographical features of sarcoid arthropathy. Bone cyst (small circle), phalynx shortening (square), lace-like reticular pattern and punched out granuloma of proximal phalynx (rectangle), acroosteolysis (large circle).

SARCOID ARTHROPATHY

J V McGowan

He was commenced on hydroxychloroquine 200mg daily. Three months later the lupus pernio had resolved. The hands remained swollen but less painful and felt stronger. He remained able to work as a chef.

Due to the ongoing deformity of the hands, we considered treating him with infliximab, an anti-tumour necrosis factor (anti-TNF) agent. However, due to the preserved function, poor compliance with treatment and little evidence of the success of infliximab for sarcoid arthropathy we decided to continue active surveillance.

Introduction to sarcoidosis

Sarcoidosis is a multisystem granulomatous disease that predominantly affects adults younger than 40 years. It most commonly affects the lungs but the extrapulmonary manifestations are vast. Most cases of sarcoidosis are acute and self-limiting. In the minority, sarcoidosis can cause severe organ dysfunction, including pulmonary fibrosis, cirrhosis and cardiac failure.

There is a marked geographical variation in the incidence of sarcoidosis. It is most common in the temperate climate of northern Europe, where the incidence is up to 40 cases per 100,000 people. It is much less common in South America and the Indian subcontinent. It is three times more common in Americans of African descent than Caucasians (35.5 cases compared with 10.9 cases per 100,000), where it is associated with a later onset (4th decade compared to 3rd decade) and more severe, disseminated disease.Due to the varied incidence around the world, genetic, environmental and infective factors have been proposed as causative agents in developing sarcoidosis.

There is an association with HLA class II antigens, particularly HLA-DRB1 and HLA-DQB1. TNF-alpha plays a key role in granuloma formation and is the interest of recent therapeutic strategies. Associations with exposure to air-borne environmental antigens have been investigated for many years given sarcoidosis most commonly affects the lungs, eyes and skin. Many antigens that agricultural workers are exposed to have been associated with developing sarcoidosis, including mould, mildew and pesticides.1 Infections, such as Mycobateria, Propionibacterium acnes and Borrelia burgdorferi, have been associated with sarcoidosis in small studies.1

The pathological hallmark of sarcoidosis is the non-caseating granuloma. Granulomas form to isolate pathogens, reduce inflammation and prevent neighbouring tissue damage. They are a cluster of macrophages around a pathogens encased by a layer of lymphocytes.

Some of the macrophages develop into epitheliod cells, gainging secretory function and losing phagocytic function, which fuse to form multinucleated giant cells. These giant cells secrete large volumes of TNF, interleukin-12, -15, -18, macrophage inflammatory protein 1 (MIP-1), monocytic chemotactic protein 1 (MCP-1) and granulocyte macrophage colony-stimulating factor (GM-CSF). CD4+ T cells interact with the macrophage complex and differentiate into type 1 helper T cells, which secrete interleukin-2, interferon-gamma and augment macrophage TNF secretion.

Sarcoid Arthropathy.
Good Clinical Care.

Caseous (meaning cheese-like appearance) necrosis is necrosis the centre of granulomas, which leaves an acellular pink area on haematoxylin and eosin (H&E) stain. Caseating granulomas are associated with tuberculosis, where confluent caseating granulomas in the lungs form cavitations. Sarcoid granulomas are non-caseating because they do not develop central necrosis. Most granulomas do not cause tissue damage and resolve spontaneously. However, if a granuloma becomes established, fibrinogen and collagen add to the granuloma causing sclerosis and adjacent organ damage.1

Whilst granulomas can form in any organ, intrathoracic involvement is most common (Box 1).

Organ	Incidence	Feature
Lungs	90%	Asymptomatic, incidental hilar lymphadenopathy, pulmonary infiltrates, 25% pulmonary fibrosis
Skin	30%	Sarcoid papules, nodules, plaques. Associated with lupus pernio and erythema nodosum
Eyes	25-60%	60% anterior uveitis, chronic form leading to glaucoma. 30%posterior uveitis associated with neurosarcoidosis
Musculoskeletal	25%	25% sarcoid arthropathy, 75% asymptomatic myopathy, 2% symptomatic myopathy
Cardiac	Clinically <5%, 25% at autopsy	Scars in the left ventricle (LV) free wall leading to LV failure, scars in the LV septum leading to conduction delay
Liver	10% elevated LFTs, clinically silent. Cirrhosis <1%	Cholestatic symptoms (pruritis & jaundice), hepatic failure and portal hypertension
Neurological	Clinically 10%, 25% at autopsy	Cranial nerve palsies, ataxia

Box 1: Clinical Features of Sarcoidosis

SARCOID ARTHROPATHY

J V McGowan

Sarcoid arthropathy

Sarcoid arthropathy affects a quarter of patients with sarcoidosis. It may present as an acute (95%) or chronic arthritis (5%). Typically, the acute presentation is with an oligoarthritis (fewer than 4 joints). The ankles are most commonly affected (up to 90%), followed by the knees, wrists and MCPJs.1

Lofgren's syndrome is characterised by the triad of hilar lymphadenopathy, acute arthritis and erythema nodosum. Fever is also common. It is usually self-limiting and results in minimal joint destruction. The erythema nodosum resolves within two to three months. The hilar lymphadenopathy resolves in 90% of cases. Non-steroidal anti-inflammatory drugs (NSAIDs) are the first-line treatment and for most the acute arthritis resolves within two to six months of commencing NSAIDs.

Chronic arthritis is much less common, accounting for only 5% of cases. It is clinically significant as it can be very destructive and disabling. It tends to affect older people and is associated with parenchymal pulmonary disease and elevated serum ACE. It affects the ankles, knees and wrists in a symmetrical pattern. It also affects the small joints of the hands, predominantly the PIPJs. There is often gross swelling of the dorsum of the hands, wrist and dactylitis (sausage fingers).

Myopathy is estimated to be present in up to 75% of patients with sarcoidosis but is symptomatic in only 2%. Three patterns of myopathy are recognised. The most common presentation is an insidious onset of proximal myopathy, similar to corticosteroid-induced proximal myopathy. Nodular myopathy presents with multiple palpable nodules, which may resemble tumours. Acute myositis is rare and tends to occur in young adults early in the course of their disease. A muscle biopsy may be needed to distinguish acute myositis from polymyositis as both cause an elevation in muscle enzymes and abnormal electromyogram. Methotrexate has been used effectively in treating acute myositis.1,2

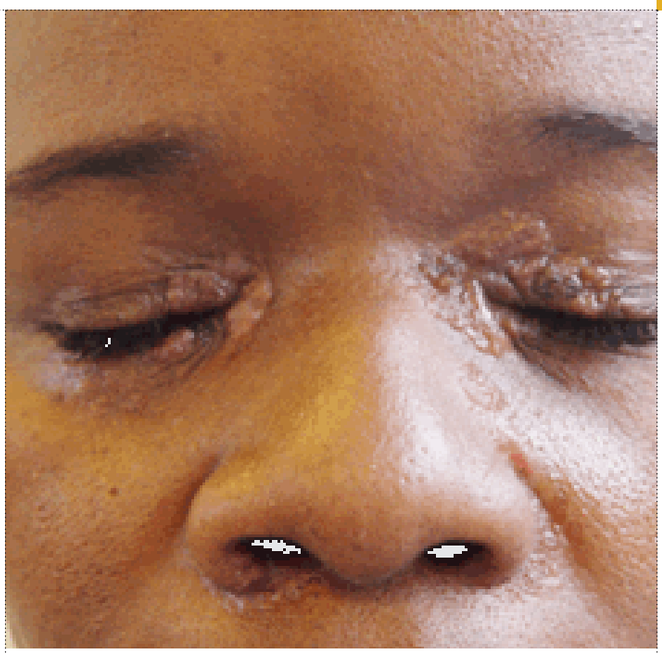
Radiographical appearances can be striking and correlate poorly with the often mild functional disability. Radiographical features are:

1) Lace-like reticular pattern of the bone because of multiple granulomas/ bone cysts

2) Bone cysts

3) Punched-out granulomas in the heads of the middle and proximal phalanges and less frequently the metacarpal head

4) Acroosteolysis (loss of the distal phalynx) in advanced cases



The diagnosis of sarcoid arthropathy may be made clinically if the patient presents with Lofgren's syndrome. Many cases, however, may prove difficult to diagnose. This is largely because sarcoid arthropathy may mimic other arthropathies. If the presentation is with the common oligoarthritis it may be mistaken for psoriatic arthritis, reactive arthritis, infective arthritis or gout. A symmetrical polyarticular presentation especially in the chronic form may mimic rheumatoid arthritis. A monoarticular presentation is rare and can therefore be mistaken for gout, pseudogout and infection.1 It is important to exclude a septic joint in such circumstances.

It is not uncommon for a patient whose first symptoms of sarcoidosis are joint symptoms to be misdiagnosed, often receiving the correct diagnosis later once more common signs develop, such as hilar lymphadenopathy on a chest radiograph.

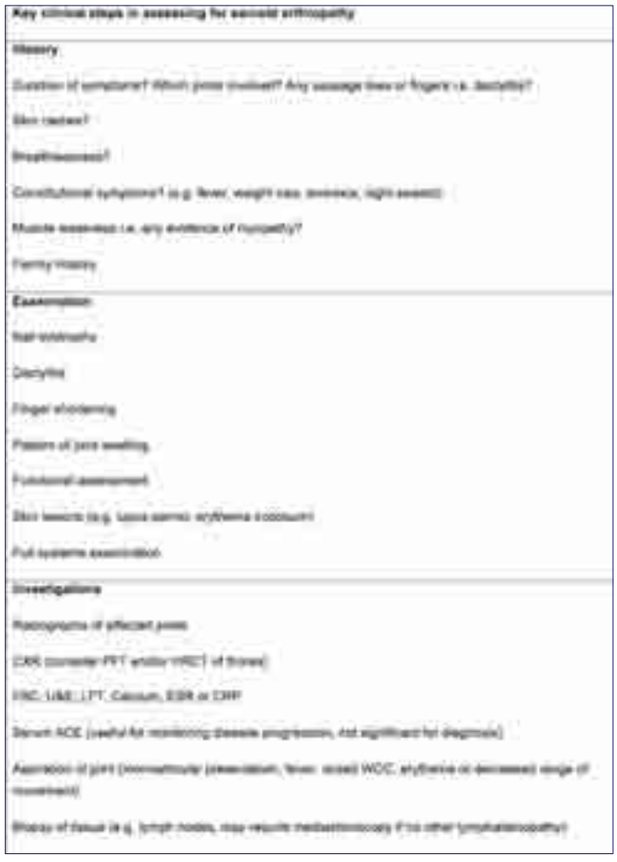
Most cases of acute arthritis are self-limiting. NSAIDs are used as the first-line treatment. If symptoms persist despite NSAIDs, many physicians use corticosteroids, though colchicine and hydroxychloroquine have been used. As most patients are relatively young, if corticosteroids are used they should be used in the smallest possible effective dose, typically prednisolone 10-15mg daily. Methotrexate has been used as a steroid-sparing agent but again is not without side effects. Liver function, renal function, full blood count and hepatitis B & C status should be evaluated before initiating Methotrexate. Full blood count, renal function and liver function should be tested regularly to monitor for bone marrow or liver toxicity.

SARCOID ARTHROPATHY

J V McGowan

As the release of TNF by macrophages is important in granuloma formation there has been much interest in the effect of anti-TNF (e.g. infliximab, adalumimab, etanercept) as a therapeutic strategy. Whilst there is evidence from small studies supporting the use of infliximab in refractive pulmonary sarcoidosis, there is a paucity of evidence in sarcoid arthropathy, with few case studies only reporting its use.1,2 Anti-TNF drugs are not without their risks.

Care should be taken to exclude latent tuberculosis as they can cause reactivation of tuberculosis, especially infliximab.1 All anti-TNF drugs can worsen cardiac failure.4 There are case reports of a paradoxical development of sarcoid-like granulomatosis in patients receiving anti-TNF therapy for rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis, which resolved on withdrawal of the drug.2 This phenomenon is not well-understood and highlights the difficult immune processes underlying sarcoidosis.



Box 2. Key clinical steps in assessing for sarcoid arthropathy. ACE, angiotensin converting enzyme; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FBC, full blood count; HRCT, high resolution computed tomography; LFT, liver function test; PFT, pulmonary function test; U&E, urea and electrolytes; WCC, white cell count.

Sarcoid Arthropathy. Good Clinical Care.

Questions

1. Lofgren's syndrome consists of the triad:

a) Arthritis, Lupus Pernio and Hilar Lymphadenopathy
b) Arthritis, Erythema Nodosum and Hilar Lymphadenopathy
c) Arthritis, Erythema Nodosum and Fever
d) Arthritis, Lupus Pernio and Fever
e) Arthritis, Erythema Nodosum and Lupus Pernio

2. Radiographical features of Sarcoid Arthropathy include:

a) Bone cysts and subchondral sclerosis
b) Acroosteolysis and subchondral sclerosis
c) Lace-like reticular pattern and osteophytes
d) Acroosteolysis and asymmetric joint space narrowing
e) Punched-out lesions and lace-like reticular pattern

3. Which drug is not a treatment for sarcoid arthropathy?

a) Methotrexate
b) Colchicine
c) Rituximab
d) Infliximab
e) Hydroxychloroquine

4. What percentage of Sarcoid Arthropathy presents as a chronic disease?

a) 1%
b) 5%
c) 10%
d) 20%
e) 50%

SARCOID ARTHROPATHY

J V McGowan

5. Which of the following is most closely associated with neurosarcoidosis?

a) Cardiac conduction delay
b) Pulmonary fibrosis
c) Lupus Pernio
d) Anterior uveitis
e) Posterior uveitis

Answers

1. b) Fever is common in LDfgren's syndrome but is not one of the triad.

2. e) Subchondral cysts and sclerosis are seen in osteoarthritis.

3. c) Rituximab is a monoclonal antibody against CD20 on B-cells. It is not to be confused with infliximab, which is a monoclonal antibody against TNF-alpha.

4. b) Chronic arthropathy is associated with active systemic disease, reflected by a raised ACE count .

5. e) Posterior uveitis is less common than anterior uveitis but is more closely associated with neurosarcoidosis.

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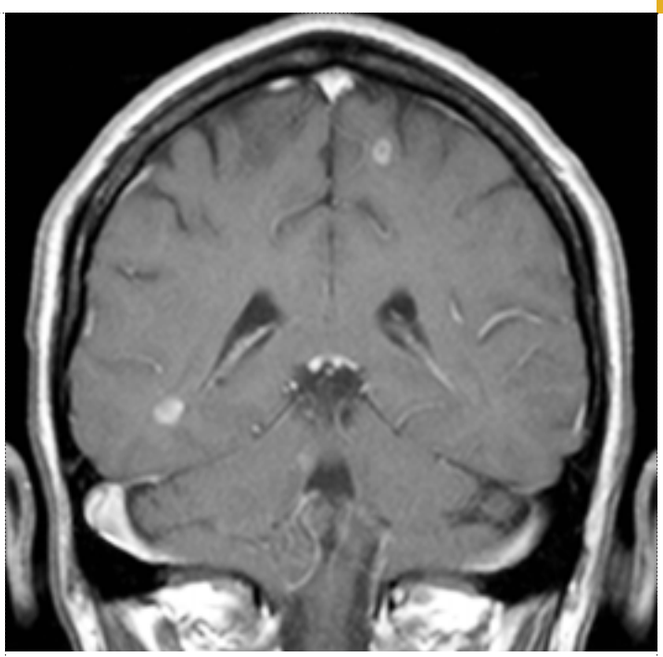

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Author

J V McGowan

TEMPORAL ARTERITIS

K Nadesalingam

Temporal arteritis.
Good Clinical Care.

Abstract

Temporal arteritis (or giant cell arteritis) is a chronic vasculitis affecting large and medium vessels. We present a case based discussion encompassing the presentation, investigations, management and complications of temporal arteritis.

Case Study

A 74 year old Caucasian lady presented to her GP with a 6 month history of back, neck, shoulder and hip pain. Her GP had noted her ESR was raised at 90mm/hr and referred her to rheumatology with a working diagnosis of polymyalgia rheumatica. When asked about her past medical history she mentioned a recent onset of headaches investigated by a CT scan by her GP. The scan was normal.

What else do you need to know?

A detailed history of the headache and any other symptoms is important.

The patient had pain and stiffness affecting mainly the proximal muscles in a bilateral and symmetrical distribution. Symptoms were worse in the morning and she had difficulty getting out of bed. She had also given up her hobby of running due to pain in her legs. Physiotherapy had not helped. Ibuprofen, fentanyl patches and co-codamol gave her partial relief.

On further questioning, the patient was noted to have had a 3 month history of severe headaches partially relieved by co-codamol. She had noted tenderness of the scalp particularly when combing her hair and the left side felt worse than the right. She described jaw aching when chewing food. Over the last two days her left eyelid had started to close but there was no visual loss. Her GP had done a CT head scan which was normal.

Examination findings

There was a left ptosis with a small left pupil which was reacting. Eye movements were normal. She was tender over the scalp and she had large tortuous temporal arteries which were non tender. The right side was pulsatile but the left was not. General examination was unremarkable.

What is your differential diagnosis?

The site and severity of the headache along with polymyalgic symptoms and raised ESR in an elderly Caucasian lady leads to a strong suspicion of temporal arteritis. About 20% of polymyalgia rheumatica patients also develop temporal arteritis, while 40–60% of patients with temporal arteritis have symptoms of polymyalgia rheumatica.

Temporal arteritis is a vasculitis of unknown aetiology affecting large and medium vessels. It has a reported incidence of 2.2/10,000 patient years in the UK1 and 29/100,000 in Europe in a population group of age above 50 years. It is commoner in northern latitudes and more frequent in women than men (variable reported ratio of 2:1 - 5:1).

Classical symptoms include:

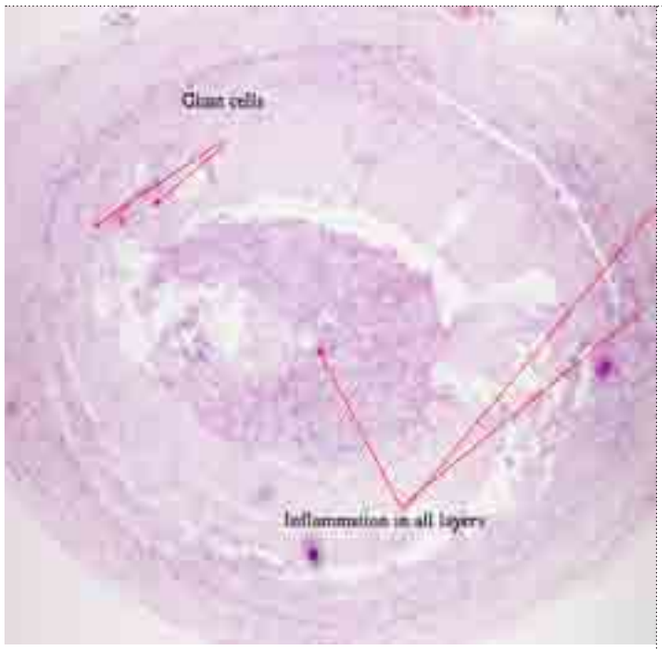
- Abrupt onset headache (usually unilateral in the temporal area and occasionally diffuse or bilateral)
- Scalp pain (diffuse or localized), difficulty in combing hair.
- Jaw and tongue claudication
- Visual symptoms (amaurosis fugax, blurring and diplopia)
- Systemic symptoms e.g. fever, weight loss, loss of appetite, depression, fatigue
- Polymyalgic symptoms
- Limb claudication

Examination may reveal

- Abnormal superficial temporal artery (tender, thickened or beaded with reduced or absent pulsation)
- Scalp tenderness.
- Transient or permanent reduction in visual acuity (partial / complete).
- Visual field defect.
- Relative afferent papillary defect on the swinging flashlight test.
- Pale, swollen optic disc with haemorrhages on fundoscopy (anterior ischaemic optic neuritis).
- Unilateral or bilateral central retinal artery occlusion.
- Upper cranial nerve palsies.
- Features of large-vessel giant cell arteritis (GCA): asymmetry of pulses and blood pressure and bruits (usually of the upper limb).

TEMPORAL ARTERITIS

K Nadesalingam



Other differentials to consider would be

- Serious intracranial pathology, such as infiltrative retro-orbital or base of skull lesions
- Migraine
- Other causes of visual disturbance e.g. transient ischaemic attack
- Cluster headache
- Cervical spondylosis
- Sinus disease
- Temporo-mandibular joint pain

How would you confirm the diagnosis?

The following blood tests may be helpful

- FBC – may show anaemia or thrombocytosis
- Urea and electrolytes – to exclude any biochemical abnormality / renal impairment
- Liver function – may show raised alkaline phosphatase (ALP)
- ESR & CRP – typically raised

Other causes of raised ESR (for example, neoplasia, infection, myeloma) should be considered and other investigations e.g. CXR booked as appropriate.

A temporal artery biopsy should ideally be arranged to confirm histological evidence of granulomatous inflammation (usually with multinucleate giant cells) typical of giant cell arteritis. This can be done under local anaesthetic as a day case procedure but needs to be organised ideally within 1 week of commencing any steroid treatment 2,3 (although positive results may still be obtained up to 2-4 weeks after starting treatment)3,4. A negative biopsy does not rule out the diagnosis as it may be due to inadequate tissue sampling or "skip lesions".

A prompt response to steroids is also indicative of temporal arteritis but not diagnostic.

Diagnostic criteria for temporal arteritis

For purposes of classification, a patient shall be said to have temporal arteritis if at least three of these five criteria set by the American College of Rheumatology (ACR) are present.5

- Age at disease onset ≥50 years; development of symptoms or finding beginning at the age of ≥50 years.
- New onset of or new type of headache.
- Temporal artery abnormality unrelated to atherosclerosis of cervical arteries.
  - temporal artery tenderness to palpation
  - or decreased pulsation.
- Elevated ESR: ESR ≥50mm/hr by the Westergren method.
- Abnormal artery biopsy: biopsy specimen with artery showing vasculitis characterised by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells.

The presence of any three or more criteria yields a sensitivity of 93.5% and a specificity of 91.2%.

How would you manage this patient?

Initial treatment

High dose glucocorticosteroid treatment should be initiated as soon as the suspicion of temporal arteritis is made to prevent one of the main early complications of visual loss.2 An initial starting dose between 40-60mg of prednisolone is typical6,7 although higher doses may need to be considered if there is evidence of actual or impending visual loss.8-11

This lady was commenced on 60mg prednisolone and booked to have a temporal artery biopsy the following day. A follow up appointment was booked four days later to assess her response to steroid treatment

TEMPORAL ARTERITIS

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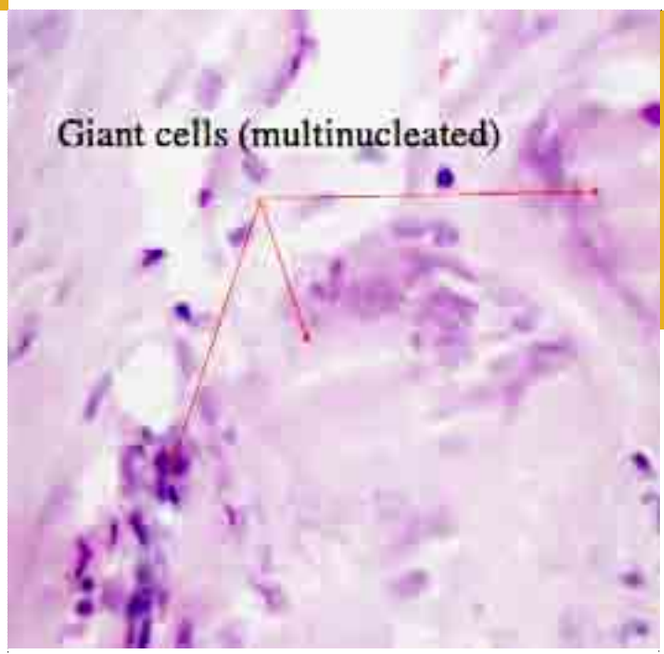

Temporal arteritis.
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Follow up

The patient noted a rapid improvement in her symptoms following initiation of steroid therapy with resolution of headaches within 48 hours. Her joint pains and myalgia had also settled enabling her to take up running again.

The patient's initial ESR when reviewed in the rheumatology clinic was 104mm/hr. A repeat sample was 12mm/hr two months later.

The temporal artery biopsy was positive for granulomatous inflammation. This patient will need to continue on steroid therapy for approximately 18 months to 2 years. It is important to gradually taper therapy over time to prevent inadequate resolution of inflammation.

Suggested tapering regimen 12,13

- 40-60mg prednisolone (not <0.75 mg/kg) continued for 4 weeks (until resolution of symptoms and laboratory abnormalities).
- Then dose is reduced by 10mg every 2-4 weeks to 20 mg.
- Then by 2.5mg every 2-4 weeks to 10 mg
- Then by 1mg every 1-2 months provided there is no relapse

(For patients preferring enteric coated prednisolone, the reduction <10mg should be as follows: 10/7.5mg alternating for 2 months, then 7.5mg daily for 1-2 months, then 7.5/5mg alternating for 1-2 months, then 5mg daily for 1-2 months, etc)

Adjuncts to therapy: As the patient is going to be on steroids for more than 3 months bone protection agents (calcium supplements and bisphosphonate) should be co-prescribed along with a proton pump inhibitor for gastric protection. Low dose aspirin is also recommended in addition to reduce the risk of visual and cerebrovascular complications (i.e. strokes).

Over the next couple of months the patient manages to reduce her prednisolone by 10mg per month without problems. Inflammatory markers also begin to improve.

When she gets to 10mg, however, she notices recurrence of her headache and proximal muscle pain.

What do you do next?

Symptoms may recur at any point during treatment. A detailed history and examination are important to evaluate if this is a flare of arteritis or not. Inflammatory markers should be checked to see if they are rising again. If a flare occurs, escalation of glucocorticosteroid dosage should lead to resolution of symptoms.

In resistant cases or frequent relapses steroid sparing agents such as methotrexate or azathioprine may be considered to reduce the cumulative steroid exposure. However, there is currently limited evidence to support their benefit.

This lady's repeat ESR was 38mm/hr. Her prednisolone was increased to 60mg again to which she responded. She is undergoing regular follow ups approximately monthly to monitor response to treatment and check for any complications.

TEMPORAL ARTERITIS

K Nadesalingam

What are possible complications?

Without early and effective treatment, mortality and morbidity can be high in temporal arteritis.14 The neurological complications are irreversible. This lady will continue to have ptosis as a consequence of her temporal arteritis. Blindness is the most serious and irreversible feature.

A late complication is aorto-arteritis complicated by aneurysms or dissection.15

Complications related to glucocorticosteroid therapy include:16

- Weight gain
- Bruising
- Osteoporosis and fractures
- Diabetes
- Cataracts
- Glaucoma
- Hypertension
- Accelerated atherosclerosis and hyperlipidaemia

Summary

This case highlights the importance of a detailed system review which led to the link being established between this patient's initial complaints of muscle pains (polymyalgia rheumatica) with the headaches and other symptoms. It is important to consider the diagnosis of temporal arteritis in patients presenting with poylmyalgia rheumatica as early recognition and treatment of temporal arteritis is the key to preventing complications such as blindness.

Questions:

Best of Five:

1. Temporal arteritis;

a) is a chronic vasculitis affecting small vessels
b) has a male predisposition
c) usually presents with an abrupt onset of headache
d) requires a positive temporal artery biopsy for diagnosis
e) can cause reversible blindness

2. Regarding management of temporal arteritis

a) Treatment should only be commenced after a temporal artery biopsy has been obtained
b) Involves a gradually increasing dose of glucorticosteroids
c) Bone protection should only be prescribed in patients with previous fractures
d) Proton pump inhibitors should only be considered in those with a history of gastric symptoms
e) A usual starting dose of glucorticosteroids in uncomplicated temporal arteritis is 40-60mg prednisolone.

Answers

1. c)

Temporal arteritis is a vasculitis affecting large and medium vessels. It is commoner in northern latititudes and has a female predisposition. Classical symptoms include abrupt onset unilateral, temporal headache, scalp pain, jaw and tongue claudication, visual symptoms, systemic symptoms of fever, weight loss and tiredness, polymyalgic symptoms and limb claudication.

The American College of Rheumatology (ACR) classification criteria for temporal arteritis requires three of the five criteria present to yield a sensitivity of 93.5%. Skip lesions occur and therefore biopsies may be negative. Features that increase the likelihood of a positive temporal artery biopsy include, jaw claudication and diplopia on history and temporal artery prominence and tenderness on examination.

The neurological complications of temporal arteritis are permanent and therefore immediate initiation of high dose glucorticosteroid treatment after clinical suspicion of temporal arteritis is recommended.

2) e)

Early treatment is imperative to prevent visual loss and should not be delayed. Patients should be commenced on high dose glucorticosteroid therapy after clinical suspicion of temporal arteritis is raised.

An initial starting dose of 40-60mg prednisolone is typical in uncomplicated cases. If there is a history of evolving visual loss or a history of amaurosis fugax higher doses of glucorticosteroids will be required. Doses are tapered down and only increased if the disease is not under control.

If not contraindicated, all patients over the age of 65 years or with prior fragility fracture commencing long term glucorticosteroid therapy should be co-prescribed a weekly bisphosphonate and calcium and vitamin D supplementation due to the risk of osteoporosis. Those not in this group should have bone mineral density assessment and action taken on the result as per steroid guidelines. Similarly, proton pump inhibitors should be used for all patients for gastric protection.

TEMPORAL ARTERITIS

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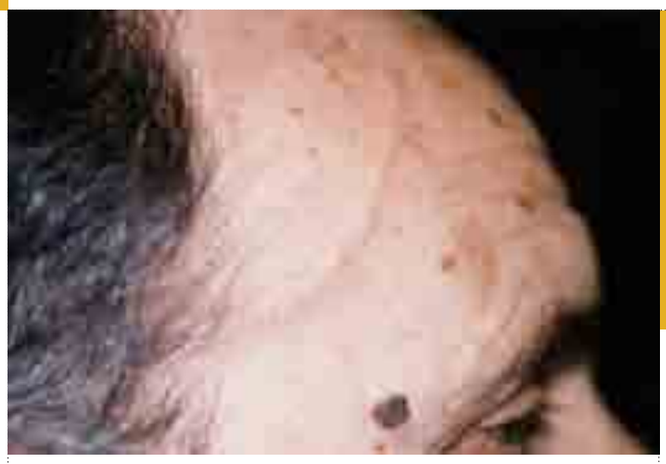

Temporal arteritis.
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Authors

Dr Kavitha Nadesalingam
ST3 in Rheumatology at Dewsbury District Hospital and

Dr Sharmin Nizam
SpR in Rheumatology at Dewsbury District Hospital

Supervisor and Contributor of Pictures from own collection:

Dr Lesley Hordon
Consultant in Rheumatology at Dewsbury District Hospital

CASE-BASED DISCUSSION - PSORIATIC ARTHROPATHY

C Holroyd and S Richards

Case-based discussion - Psoriatic Arthropathy. Patient Management.

Abstract

Inflammatory musculoskeletal symptoms in the setting of psoriasis are suggestive of psoriatic arthritis. This affects 6-30% of individuals with psoriasis. Joint manifestation typically follow skin disease but may precede it. Joint involvement can vary considerably from an isolated monoarthritis to an extensive destructive polyarthritis. The commonest presentation is either a monoarthritis or an asymmetrical arthritis only affecting a few joints. Other common features include dactylitis or 'Sausage digits', enthesitis: inflammation at the sites where tendons insert to bone, especially Achilles tendonitis and plantar fasciitis. Many patients may be well controlled on NSAIDs alone. Intra-articular steroid injections are commonly used to target one or two inflamed joints. Leflunomide and sulfasalazine are the main stay disease modifying drugs used for persistent disease and Anti TNF drugs are reserved for those with refractory disease.

Clinical Scenario

A 54 man presents presents to clinic with a history of joint pains going back 2-3 years. More recently he has developed a painful, swollen right knee and last summer had an episode where one of his toes became acutely swollen, lasting 3 weeks. He does not describe any obvious injury. For the last 2 years he has noticed a scaly rash on his knees and a flaky scalp on occasion. He has been using over the counter emollient cream for this. His mother suffers from psoriasis. He is currently on sick leave from his job as an army officer and is worried that he might not be able to return to work.

On examination there is a warm effusion of the right knee, and a psoriatic rash on the extensor surfaces of both knees and scalp.

A diagnosis of psoriatic arthritis is suspected.

What else do you want to know?

Take a full history and system review.

Important questions to ask include:

- Is he describing arthritis or arthralgia?
- What joints are affected and is it symmetrical?
- When are his joints at their worst and is there diurnal variation?
- Hong long does the stiffness last?
- Has he noticed any changes to his finger nails?
- Is there a family history of arthritis
- Has he had any recent illness or infection?
- What makes his back pain better or worse?

On examination:

- Ensure all joints are examined carefully – including feet
- Make sure the spine is also examined fully
- Look thoroughly for the presence of psoriasis.

Include "hidden areas" such as the scalp, perineum and periumbilical area

- Look for any tendon involvement/ inflammation
- Examine the patient's nails

Psoriatic arthritis is an inflammatory arthritis associated with psoriasis, and is estimated to affect between 6-30% of individuals with psoriasis. In contrast to Rheumatoid Arthritis which affects women predominantly, psoriatic arthritis affects men and women equally. Interestingly, not all patients with this form of arthritis will have psoriasis at the time of diagnosis; roughly 2/3rds of patients develop psoriasis before the onset of arthritis. However up to 15% will develop psoriasis after the onset of arthritis by more than 1 year. Psoriatic arthritis is more common in individuals with psoriasis who also have nail changes, such as pitting and onycholysis

Classification of Psoriatic arthritis

Psoriatic arthritis is classified within the group of seronegative spondyloarthopathies (Box 1), meaning that Rheumatoid Factor is usually negative. In 2006, new classification criteria (CASPAR (ClASsification criteria for Psoriatic Arthritis)) were developed to aid diagnosis of this form of arthritis. This is illustrated in Box 2.

Psoriatic arthritis

Ankylosing spondylitis

Enteropathic arthritis

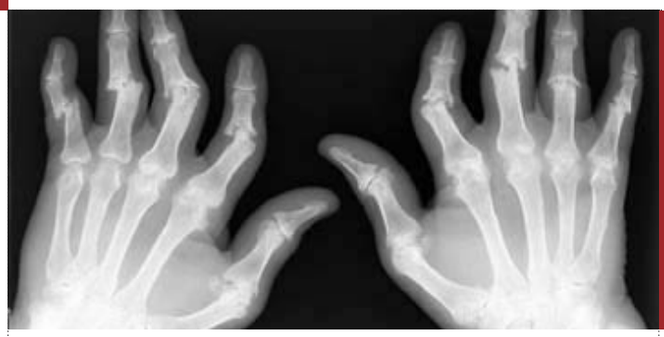
Reactive arthritis

Undifferentiated spondyloarthropathy

Box 1: Seronegative Spondyloarthropathies

CASE-BASED DISCUSSION - PSORIATIC ARTHROPATHY

C Holroyd and S Richards



Case-based discussion - Psoriatic Arthropathy. Patient Management.

1) Inflammatory articular disease (joint, spine or enthesis)

2) **AND at least 3 points from the following:**
- Current psoriasis (2 points), a personal history of psoriasis (1 Point), or a family history of psoriasis (1 point)
- Typical nail dystrophy (1 point)

Box 2: Classification Criteria for Psoriatic Arthritis (CASPAR) Criteria

Pattern of joint Involvement

Joint involvement in psoriatic arthritis can vary considerably from an isolated monoarthritis to an extensive destructive polyarthritis. The axial spine can be affected with varying frequencies. The pattern of joint involvement may help in differencing this condition from other types of inflammatory arthritis, however occasionally the pattern of joint involvement may mimic rheumatoid arthritis or anklyosing spondylitis.

Most commonly individuals with psoriatic arthritis present with either a monoarthritis or an asymmetrical arthritis only affecting a few joints (unlike the characteristic presentation of RA - symmetrical polyarthritis), however the number of joints affected may increase with time in a high proportion. Distal phalangeal involvement is considered a distinctive feature, and these joints are affected more frequently in psoriatic arthritis than the other types of inflammatory arthritis. This may only be present in between 1-16% of cases. Moll and Wright, in 1973, described 5 classical subtypes of psoriatic arthritis, which are:

- Distal interphalangeal joint predominance (1-16%)
- especially associated with nail changes
- Oligoarticular (14-63%)
- More common in men. The number of joints affected may increase over time.
- Polyarticular (25-63%)
- May be identical to RA. More common in women
- Spondyloarthropathy (2-10%)
- Clinically uncommon, however up to 40% of psoriatic arthritis patients may have involvement of the axial spine on MRI
- Arthritis Mutilans (0-16%)
- Rarest form but worse prognosis. Severe destructive arthritis associated with long-standing disease.

Other musculoskeletal features

Dactylitis: "Sausage digits" are a feature of all the sero-negative arthropathies and represents compete swelling of as single digit in the hand or foot, in around 30-40% of individuals. The feet tend to be more commonly affected than the hand

Enthesitis: Inflammation at the sites where tendons insert to bone are a characteristic feature of sero-negative spondyloarthropathies. They occur in 20-40% of patients. The Achilles tendon and plantar fascia insertion at the calcaneum are common sites.
Peripheral oedema: This is an increasingly recognised feature of psoriatic arthritis. It is usually asymmetrical and affects the lower limbs predominantly.

Differential Diagnosis
- Reactive arthritis
- Anklyosing spondylitis
- Rheumatoid arthritis
- Palindromic rheumatism
- Septic arthritis
- Gout
- Osteoarthritis

What investigations would be helpful?

There are no diagnostic laboratory tests for psoriatic arthritis, however certain tests may help add weight to the diagnosis and exclude other pathologies.

Serological Tests

- C-reactive Protein/ ESR are often elevated and show a good correlation with disease activity
- Full Blood Count - An anaemia of chronic disease may be present, white cell count is usually normal
- Rheumatoid Factor – usually negative
- Anti –cyclic citrullinated peptide (CCP) – usually negative
- Urate – usually normal. If elevated consider acute gout.
- Urea and electrolytes/ liver function tests – Although this will not help with diagnosis, baseline levels should be measured prior to starting medication

Examination of synovial fluid

CASE-BASED DISCUSSION - PSORIATIC ARTHROPATHY

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· If possible, an attempt at aspirating any obvious joint effusions should be made. Fluid should be sent for:
- Gram stain and microscopy (to exclude septic arthritis)
- Crystal analysis (to exclude gout or pseudogout crystal arthropathies).
· Joint aspiration is generally easier in large joints such as the knee. Ultrasound guidance may help target the fluid more easily if aspiration is proving difficult.

Imaging modalities

· Radiographs: It is often difficult to distinguish between the different types of inflammatory arthritis on x-ray, however a baseline x-ray of the affected joint is indicated to see whether bony damage has already occurred (which may indicate more severe disease activity). Important features to look for include:

- Erosions may be present at the affected joint, especially the distal interphalangeal joints. It has been estimated that erosions occur in between 22-70% of cases and are more common with disease duration. Nevertheless erosive changes are seen less commonly than in rheumatoid arthritis

- Osteolysis may result in "pencilling" of a phalanx. This can occur alone or with erosion at the base of the adjacent phalanx – "pencil in cup" deformity. More commonly seen in arthritis mutilans

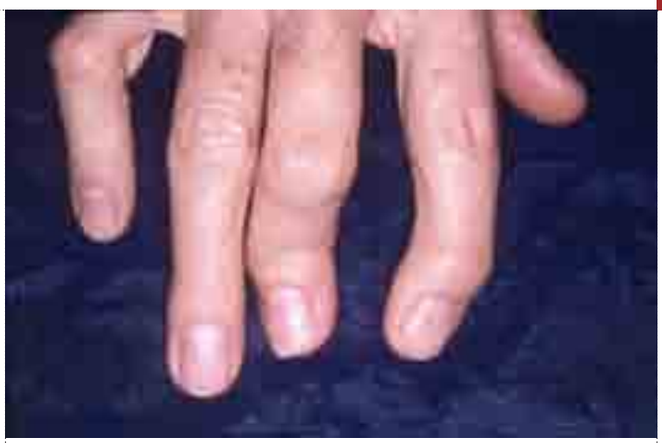
- Proliferative changes. New bone formation may occur along the shaft of the metacarpal and metatarsal bones, sometimes described as "whiskering"

- Soft tissue swelling may be seen at sites of active inflammation

- Spinal changes. Sacroileitis may be seen and is usually asymmetrical in psoriatic arthritis (whereas in ankylosing spondylitis the sacroileitis is characteristically symmetrical). The lumbar spine is less extensively affected, however the cervical spine is frequently affected. syndesmophyes may also be seen.

· *Musculoskeletal Ultrasound:* This is becoming increasingly used by rheumatologists in outpatients to identify synovitis and soft tissue changes, to aid in diagnosis and response to treatment. It can also be used to guide targeted joint injections.

· *MRI:* This is also becoming more widely used and gives more information than plain radiographs. MRI scanning is able to identify synovitis and can detect even subclinical musculoskeletal changes. Extra-articular changes in tendons, ligaments and soft tissues may also be seen



Management

This patient initially had his knee aspirated and injected with glucocorticoid with good success. However a few weeks later developed painful effusions in both knees, which again were aspirated and injected with glucocorticoid. At his next clinic review he has pain in both knees and ankles and was started on sulfasalazine. He developed a rash 2 weeks after starting this, so the drug was stopped. Methotrexate was tried for 6 months but made little improvement in his joint symptoms. Finally he was commenced on leflunomide which dramatically improved his arthritis. His psoriasis has also improved on leflunomide.

He is currently well controlled and is seen annually for review.

NSAIDs (Non-steroidal anti-inflammatories)

Generally psoriatic arthritis is less aggressive than rheumatoid arthritis and many patients may be well controlled on NSAIDs alone, especially if back pain is the salient feature.

Glucocorticoids

Intra-articular glucocorticoids are commonly used to target one or two synovitic joints. Oral steroids should be used with caution due to the risk of a flare of "post-steroid" psoriasis.

Disease Modifying Drugs

Methotrexate: Although methotrexate is one of the most commonly prescribed systemic medications for inflammatory arthritis, there is minimal evidence for its use in psoriatic arthritis from controlled trials. A 2-year retrospective study of psoriatic arthritis patients either on or off methotrexate showed no significant difference in radiologic progression between the groups. Despite this, it is still commonly used in psoriatic arthritis with good anecdotal effect, and as it also effective in treating psoriatic skin disease, is a good choice in patients in whom both skin and joint disease is a problem.

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Patients on methotrexate need regular blood monitoring (Full blood count, liver function tests and creatinine). Significant elevation in liver tests or a significant reduction in blood count should prompt a dose adjustment or cessation of therapy. It appears that patients with psoriasis have an increased risk of hepatotoxicity on methotrexate compared to individuals with other inflammatory arthropathies. It has been suggested that this is because of higher levels of obesity, alcohol use and fatty liver amongst patients with psoriasis.

Sulfasalazine: Of all the DMARDs available, the largest number of controlled trials in psoriatic arthritis has been with sulfasalasine. In the largest, 211 patients were given 2 grams daily of sulfasalazine, with a significant improvement in arthritis score in the treatment group. Possible side effects include rash and agranulocytosis and so regular blood count monitoring is also needed (FBC, LFT monthly for 3 months then 3 monthly until 1 year and every 6 months for the second year of treatment. After 2 years of therapy, blood monitoring can be discontinued as risk of agranulocytosis diminishes).

Leflunomide: This has also shown efficacy in psoriatic arthritis at a dose of 20mg/day and more effective than methotrexate.

Case-based discussion - Psoriatic Arthropathy. Patient Management.

Anti-TNF Inhibitors: The biological therapies currently approved by NICE (National Institute of Clinical Excellence) in the UK for psoriatic arthritis are infliximab, etanercept and adalimumab, all of which have proven efficacy in controlled trials. Due to the cost of these drugs, their use is limited by NICE guidelines. Currently to fulfil the criteria for an anti-TNF therapy, a patient with psoriatic arthritis must:

- have not responded or been intolerant to 2 traditional DMARD drugs (either sequentially or in combination)
- and has peripheral arthritis with 3 swollen and 3 tender joints

Non-pharmacological approach

All patients should receive a comprehensive multi-disciplinary approach, including education, physical therapy and occupational therapy. Surgery (often joint replacement) may be needed in some individuals, although this is becoming less common with advances in pharmacological therapy.

Prognosis

The general impression is that psoriatic arthritis is associated with less long-term disability than rheumatoid arthritis. Poor prognostic features include presence of HLA B27 and at least 5 effusions at the time of presentation.

Authors

Dr Christopher Holroyd BM MRCP
Dr Selwyn Richards
Poole Hospital NHS Foundation Trust

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