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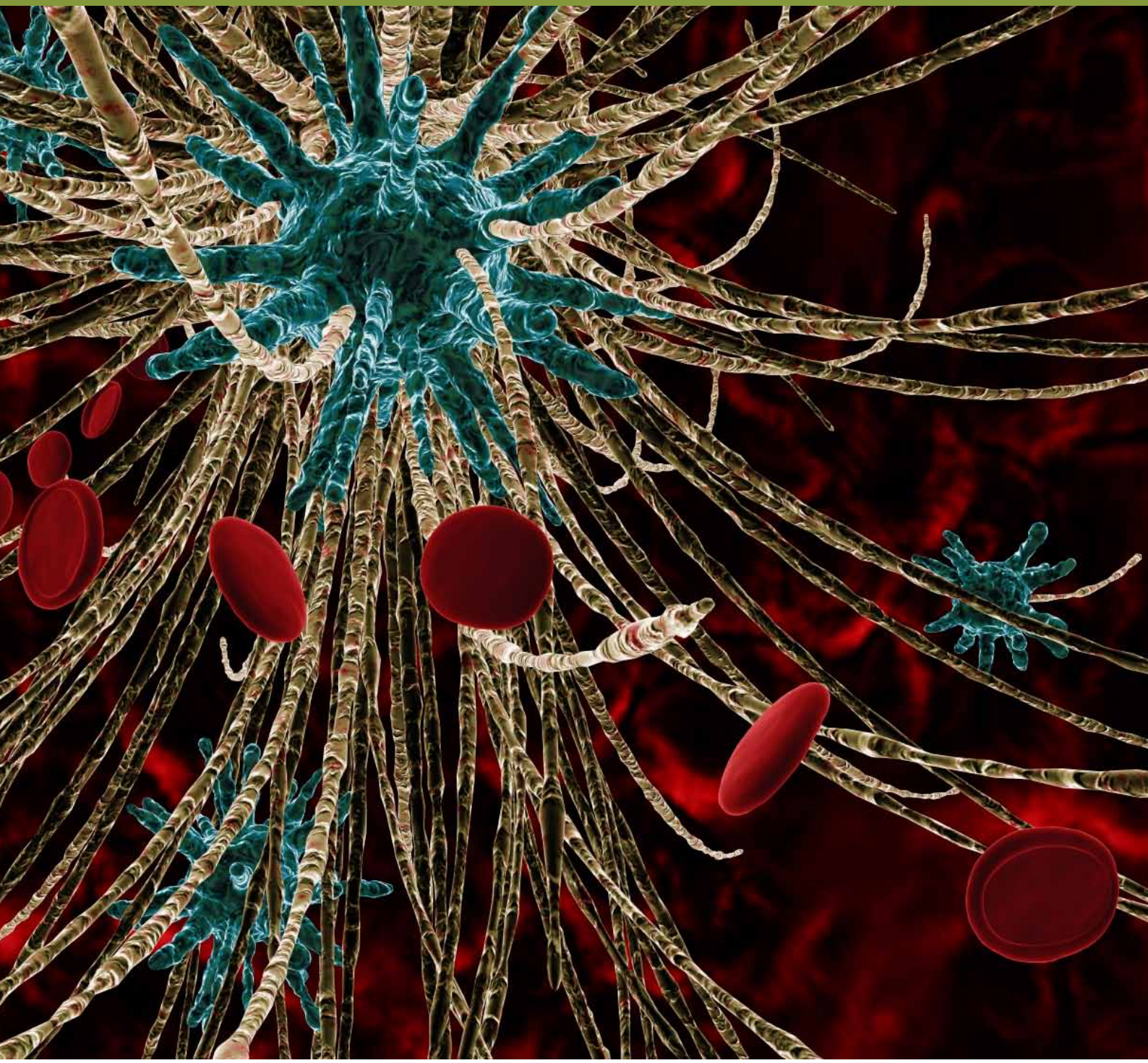
Volume 5, Issue 7: **Haematology Infectious Diseases**



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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

Emmanuelle Roumy
Managing Editor
123Doc Education
72 Harley Street
London
W1G 7HG
Tel: +44 (0)207 253 4363
Email: emmanuelle@123doc.com

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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, 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. The answers will be published in the next issue, but 123Doc will advance answers to clinical tutor subscribers so they can engage their students in the learning process. 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 Neurology Issue Of Foundation Years Journal 2011

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

THE PREVALENCE OF OCCULT HEPATITIS B

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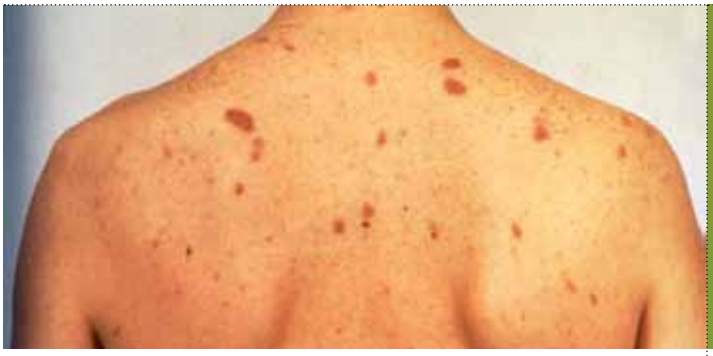

The prevalence of occult hepatitis B infection among hepatitis C virus genotype 4 chronically infected Egyptian patients and its effect on response to combined therapy (pegylated interferon alpha 2 a and ribavirin) for HCV chronic infection. Good Medical Practice.

Abstract

The aim of the present study was to detect the prevalence of occult hepatitis B among 2 groups of HCV chronically infected Egyptian patients who received combined treatment using pegylated interferon _2a and ribavirin for 48 weeks.

Group1 included 15 patients who were responders to combined treatment at 48 week and group 2 included 15 patients who were non responders to combined treatment at 48 week.

All patients were negative for HBV surface antigen but positive for HCV antibodies in serum.

All patients received pegylated interferon _2a (180µg/week) and ribavirin (dose adjusted according to the body weight) for 48 weeks, and were followed up clinically, biochemically and haematologically during the treatment period and 6 months thereafter. HBV DNA qualitative assay was tested in the serum of every patient at 48 week of therapy. Occult HBV was not frequent among HCV chronically infected patients and there was no significant difference (p>0.05) between both groups as regards the presence of HBV DNA. These results show that occult HBV infection was not frequent among HCV chronically infected Egyptian patients and its presence did not affect response to combined treatment using pegylated interferon _2a and ribavirin.

Introduction

Hepatitis B &C are the most common causes of chronic liver diseases world wide. Acute infection with hepatitis B virus or hepatitis C virus may result in chronic infection. **(Crockett and Keeffe, 2005).**

Hepatitis B virus infection in patient who lack detectable hepatitis B surface antigen with or without serologic markers of previous infection (HBs antibodies or hepatitis B core antibodies) are called occult infection. **(Cacciola et al.,1999).**

In patients chronically infected with HCV, combination therapy with ribavirin plus alpha 2 interferon has greatly improved the rate of sustained biochemical and virological response compared to those achieved with interferon monotherapy. **(Larrat et al., 2003).**

The clinical significance of occult hepatitis B alone or in combination with HCV infection remains unsettled. **(Kao et al., 2002).**

The present study aimed to determine the prevalence of occult HBV among chronic HCV genotype 4 infected Egyptian patients and also to determine the relationship between occult HBV infection and response to combined therapy (pegylated interferon _2a 180µg/week and ribavirin) for 48 weeks in HCV genotype 4 infected Egyptian patients.

Materials and methods

Thirty HCV infected Egyptian patients (29males and 1 female) aged 37-62 years who received pegylated interferon _2a 180µg/week and ribavirin (does adjusted according to body weight) for chronic HCV genotype 4 infection were entered into the study. All patients were positive for HCV antibody that was detected in the serum using a third generation enzyme linked immuonosorbent assay (ELISA) but negative for hepatitis B surface antigen. Patients were divided into 2 groups , group 1 included 15 patients who responded to combined treatment for HCV as confirmed by undetectable HCV RNA in the serum using polymerase chain reaction (PCR) at 48 week of therapy (end of treatment response).

Group 2 included 15 patients who did not respond to combined treatment for HCV as confirmed by detectable HCV RNA in the serum using polymerase chain reaction (PCR) at 48 week of therapy (end of treatment response).

HBV DNA level was measured in both groups using PCR (quantitative and qualitative assay) after end of combined treatment (48 weeks).

Results were collected, revised then analyzed statistically using SPSS statistical package version 13. The following tests were applied: mean value, standard deviation, t – student test for independent sample means, Chi-square test, and significance value was assumed when p value < 0.05.

THE PREVALENCE OF OCCULT HEPATITIS B

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Results

	Responders	Non responders	P value
number	15	15	
Mean age ± SD (years)	46.26± 6.3	48.53± 7	>0.05 (non significant)
Mean weight± SD (kg)	71.6± 10.8	86.6± 8.7	<0.01(highly significant)
Male /female ratio	15/0	14/1	>0.05 (non significant)

Table 1: pretreatment characteristics of the patients

Table 1 shows the pretreatment characteristics of the patients. There was no significant difference in the age and sex values between the 2 groups but there was a highly significant difference in body weight distribution between the 2 groups.

	Frequency	Percent
Positive	2	6.7
Negative	28	93.3
Total	30	100

Table 2: descriptive statistics showing the frequency of HBV DNA at 48 week of therapy

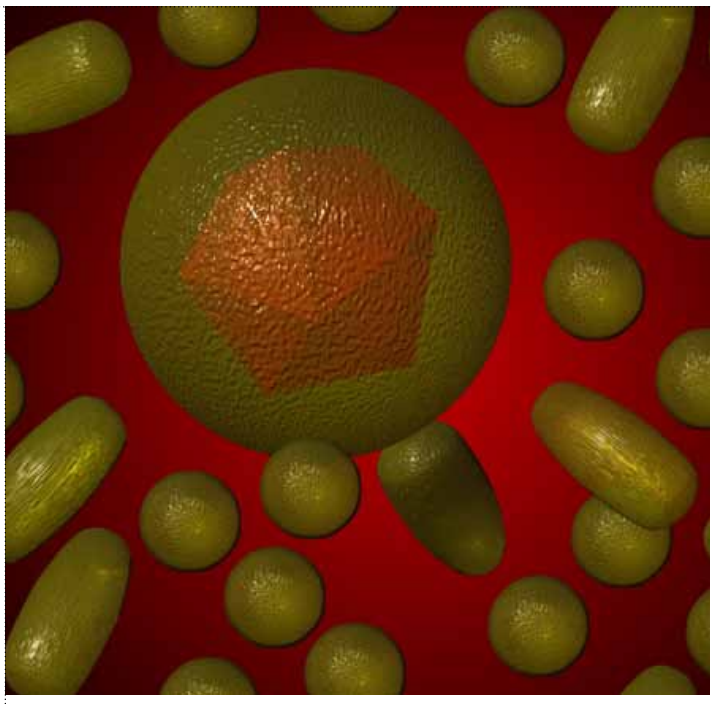
	responders		Non responders	
	Number	percent	Number	percent
Positive	---------	----------	2	13.3
Negative	15	100.0	13	86.7
Chi-Square : p value > 0.05 (non significant)				

Table 3: comparison between responders and non responders as regards the presence of HBV DNA

From tables 2 and 3 it can be seen that HBV DNA qualitative assay when tested in the serum at 48 weeks of combined treatment (end of treatment) for chronic HCV infection, there were 2 patients (6.7%) positive and 28 patients (93.3%) negative for HBV DNA.

In group 1 (responders) all patients were negative for HBV DNA, while in group 2 (non responders) 2 patients (13.3%) were positive and 13 patients (86.7%) were negative for HBV DNA and the difference between both groups regarding the presence of HBV DNA was not significant (p >0.05).

In the 2 patients who tested positive for HBV DNA, level of HBV DNA using quantitative PCR was done and measured 6000 and 2200 copies /ml.



Discussion

Hepatitis B virus and hepatitis C virus infections account for a substantial proportion of cases of chronic liver diseases including chronic hepatitis, cirrhosis, and liver cancer. HBV and HCV are transmitted parentrally and share common routes of infection; thus, infection with both viruses may occur, particularly in areas where the two viruses are endemic **(Pontisso et al., 1993).**

Occult HBV represents a special form of HBV infection with clinical relevance. Perhaps, the most convincing clinical impact of occult HBV infection is the risk of HBV transmission through transfusion, organ transplantation, and perinatal route **(Hui, 2002).**

Occult HBV infection has greatly been identified in patients with chronic HCV infection **(Fukuda et al., 1999).**

The significance of occult HBV infection in chronic HCV patients including its incidence and the potential effect on treatment of hepatitis C is a matter of interest. Many researchers have centered on this occurrence and have come up with conflicting results **(Anwar et al., 2006).**

In the present study we found that 2/30 (6.7%) of chronic HCV patients harbor occult HBV infection.

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These results are comparable to those found by **Anwar et al., 2006** (3.33%), **Hasegwa et al., 2005** (7.9%) **and Giannini et al., 2003** (6.7%) but are less than those found by **Besisek et al., 2003** (36.4%) (12/33) and **Cacciola et al., 1999** (33%) (66/200), This discrepancy may be explained by the difference in the population groups studied; all patients of the current study had no obvious risk factors for HBV infection (patients were not IV drug users, did not receive any form of antischistosomal therapy and did not receive any form of renal replacement therapy), this differs from B**esisek et al., 2003** who studied 33 HCV RNA positive, HBV surface antigen negative, haemodialysis patients. This discrepancy also raises the question of the effect of different HCV genotypes on the prevalence of occult HBV among HCV chronically infected patients, to answer this question further study on a larger scale of patients with different HCV genotypes infection should be carried out.

In our study 0/15 (0%) of group 1 (responders) had occult HBV infection and 2/15 (13.3%) of group 2 (non responders) had occult HBV infection and there was no significant difference between both groups (P> 0.05) as regards the presence of occult HBV infection.

Our finding goes in agreement with **Anwar et al., 2006, Hui et al., 2005, Georgiadou et al., 2004,** and **Ferraro et al., 2003** who concluded that the presence of occult HBV did not alter the outcome of treatment of chronic HCV infection.

But this result disagrees with those founded by **Khattab et al., 2005** and **Cacciola et al., 1999** who suggested that occult HBV infection may correlate with a lack of response to interferon therapy in patients with chronic HCV infection.

In conclusion occult HBV infection does not seem to affect the response rate to combined therapy for HCV chronic infection, but the questions of whether treatment of occult HBV infection before combined therapy for chronic HCV infection or whether higher doses or longer duration of combined therapy are of benefit in increasing the response rate or reducing the relapse rate in patients with chronic HCV infection associated with occult HBV infection, can only be answered by future studies on a larger scale of patients.

Summary

The clinical significance of occult hepatitis B alone or in combination with HCV infection remains unsettled.

The present study aimed to determine the prevalence of occult HBV among chronic HCV genotype 4 infected Egyptian patients and also to determine the relationship between occult HBV infection and response to combined therapy (pegylated interferon _2a and ribavirin) for 48 weeks in HCV genotype 4 infected Egyptian patients.

Thirty Egyptian patients who received pegylated interferon _2a and ribavirin for chronic HCV genotype 4 infection were entered into the study. Patients were divided into 2 groups, group 1 included 15 patients who responded to combined treatment, and group 2 included 15 patients who did not respond to combined treatment.

HBV DNA level was measured in both groups using PCR (quantitative and qualitative assay) after end of combined treatment.

In group 1(responders) all patients were negative for HBV DNA , while in group 2(non responders) 2 patients (13.3%) were positive and 13 patients (86.7%) were negative for HBV DNA and the difference between both groups regarding the presence of HBV DNA was not significant (p >0.05).

Key words

Occult, HCV, HBV, Genotype 4 ,pegylated ,interferon, ribavirin

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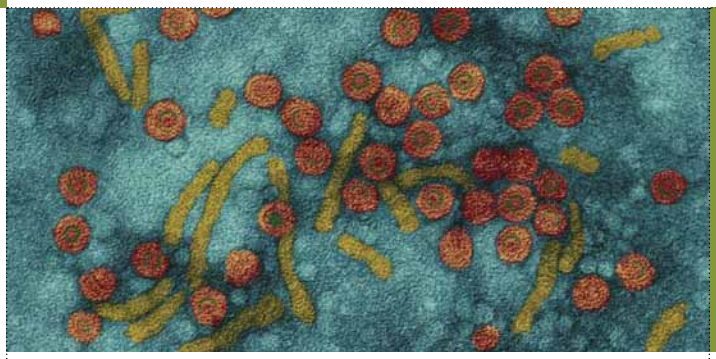

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Authors

Yehia El-Shazly, MD
Professor Of Internal Medicine
Ain Shams University, Cairo, Egypt

Khaled El-Kamoty, MD
Assistant Professor Of Internal Medicine
Ain Shams University, Cairo, Egypt

Ahmed Morris, MD
Assistant Professor Of Internal Medicine
Ain Shams University, Cairo, Egypt

Reham Al Swaff, MD, MRCP (UK)
Lecturer Of Internal Medicine
Ain Shams University, Cairo, Egypt

Correspondence

30 Manshiet Al Bakry, Heliopolis, Cairo, Egypt
Email drrehamalswaff@yahoo.com

ANTIBIOTIC PRESCRIBING AUDIT – THE EFFECT OF JUNIOR DOCTOR EDUCATION

EA Hudson, P Stanley

Antibiotic Prescribing Audit - the effect of junior doctor education. Good Medical Practice.

Abstract

Background

Antibiotics play a key role in treatment of infection and appropriate prescribing of antibiotics relies on using agents which are effective whilst limiting the risk of promoting resistance and adverse effects. We conducted an audit to establish whether doctors were documenting indication and duration of antibiotics, allergy status and whether the regimen prescribed was in accordance with Trust antibiotic guidelines. The effect of junior doctor education about the importance of correct documentation and choice was examined.

Methods

Audit criteria were developed based on the Trust's antibiotic guidelines, including prescription documentation. The active drug charts of patients on the two main medical wards were reviewed against the audit criteria. The majority of prescriptions were done by junior doctors and a teaching session was conducted for Foundation Year (FY) 1 doctors. The audit was repeated five weeks later.

Results

The audit included 42 patients on antibiotic regimens, and the reaudit included 52 patients. Documentation of antibiotic indication improved from 20% initially to 62% following teaching. Documentation of antibiotic duration also improved from 26% to 52%. The choice of antibiotics was in accordance with Trust guidelines or microbiology advice in the majority of prescriptions; the exceptions were related to poor documentation in medical notes. Ninety eight percent of allergy statuses were correctly recorded in the first audit and 100% following the educational session.

Conclusions and recommendations

Antibiotic prescriptions, predominantly written by junior doctors, mostly complied with Trust antibiotic guidelines and recording of antibiotic allergy was good. However the prescriptions often lacked documentation of duration and indication. The educational session conducted for FY1 doctors raised awareness and improved practice across the whole team. As junior doctors rotate frequently this teaching should be included at all induction sessions and performance checked by ward pharmacists.

Background

Appropriate antibiotic prescribing practices are important to reduce the incidence of resistance and treat infections appropriately to reduce morbidity and mortality. The Department of Health defines prudent antimicrobial prescribing as;

The use of antimicrobials in the most appropriate way for the treatment or prevention of human infectious diseases, having regard to the diagnosis (or presumed diagnosis), evidence of clinical effectiveness, likely benefits, safety, cost (in comparison with alternative choices), and propensity for the emergence of resistance. The most appropriate way implies that the choice, route, dose, frequency and duration of administration have been rigorously determined.' [1]

Adhering to Trust guidelines has been shown to be an effective method of achieving these aims[2]. A qualitative study showed that junior doctors were not aware of how to access guidelines and their prescribing practices were often influenced by the instructions from seniors, which may or may not comply with hospital guidelines[3].

A popular method of ensuring antibiotic prescriptions are appropriate is to document indication and duration of the drug on the patient's drug chart. This can be reviewed by the pharmacist who can prompt reviews as appropriate.

Objectives

The aim of the audit was to assess the standard of antibiotic prescribing in comparison to hospital policy and guidelines. The objectives of the audit included;

Review existing literature on antimicrobial prescribing by hospital doctors

Establish a set of criteria that each doctor should adhere to

Analyse the data collected against the criteria set

From the results obtained develop recommendations to improve practice

Re-audit to assess the changes made in practice

ANTIBIOTIC PRESCRIBING AUDIT – THE EFFECT OF JUNIOR DOCTOR EDUCATION

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Methods

On the basis of the literature review and hospital prescribing policies, the audit criteria were developed (Table 1). A pilot proforma was designed to assess whether these criteria were being met. This was conducted on 10 drug charts on a medical ward in the hospital. Based on the ease of data interpretation and ability to form conclusions a final proforma was created. The final proforma used contained a field to input the working diagnosis treated with antibiotics and also whether the appropriate antibiotics prescribed conformed to the guidelines or were discussed with a Microbiologist.

Criterion 1	Every antibiotic prescribed has the indication documented on the drug chart
Criterion 2	Every antibiotic prescribed has the duration documented
Criterion 3	All drug charts have the allergy status documented clearly
Criterion 4	The antibiotics prescribed are in accordance with the hospital guidelines or microbiology advice

Table 1. The audit criteria.

The audit was conducted on two acute medical wards on two days, four weeks apart. Patients who were included on the first audit round were excluded from the second. Of the drug charts reviewed 42 patients were prescribed antibiotics, 33 patients were not prescribed antibiotics and 5 drug charts were not available on the ward. Medical colleagues were not aware that the audit was being conducted in order to avoid altered prescribing behaviours that may have affected the reliability of the results.

Some patients had more than one antibiotic prescribed and these were treated as one result set. In order to fulfil the criteria all antibiotics prescribed within a regimen needed to have the indication and duration documented. The results were assessed according to the team and also the grade of doctor prescribing. Any prescribing doctor that did not document their name or bleep number on the drug chart or in the patient's notes was recorded as unknown for both their grade and team.

Limitations

The limitations of this audit include the small sample size. Ideally the audit would have been conducted using at least 50 drug charts though the number of patients prescribed antibiotics was less than this. This limitation could have been overcome by conducting a third round of audit in the future, though the timescale limited the feasibility within this audit.

Also the audit addresses two medical wards and therefore does not include other medical wards or any medical patients outlying to non-medical wards.

Data collection

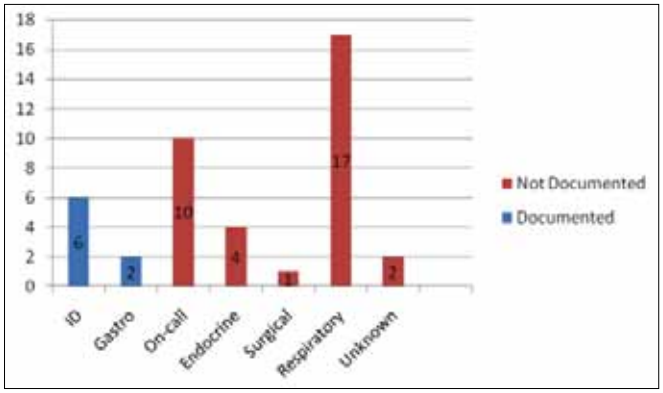

Figure 1 shows the number of drug charts with the indication documented (Criterion 1) according to the team of the prescribing doctor.

The indication was not documented in 34/42 (81%) cases. The Infectious Diseases (ID) and Gastroenterology (Gastro) teams documented the indication for all antibiotics prescribed but the other teams did not. Two doctors did not clearly document their name or bleep number and one patient's antibiotics were prescribed by a Surgeon following referral of a medical patient.

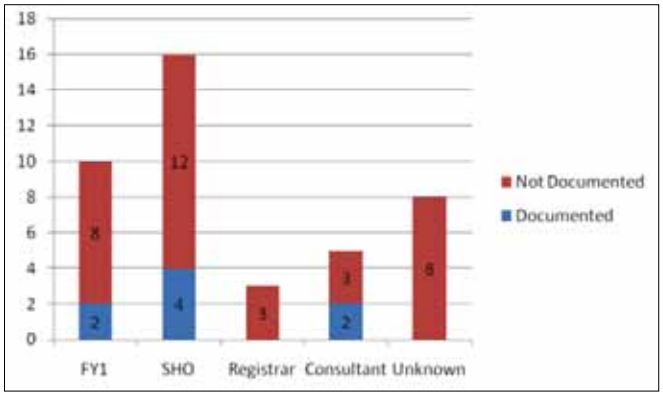

Figure 2 shows the doctor's grade to assess those who are responsible for the prescribing of antibiotics and hence those who require further information regarding the policy.

Whilst eight doctors' grades were unknown, the majority of antibiotics audited were prescribed FY1 doctors and Senior House Officers (SHO).

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Figure 3 shows the number of drug charts with the duration documented (Criterion 2) according to the prescriber's team, and Figure 4 shows the grade of doctors that documented duration.

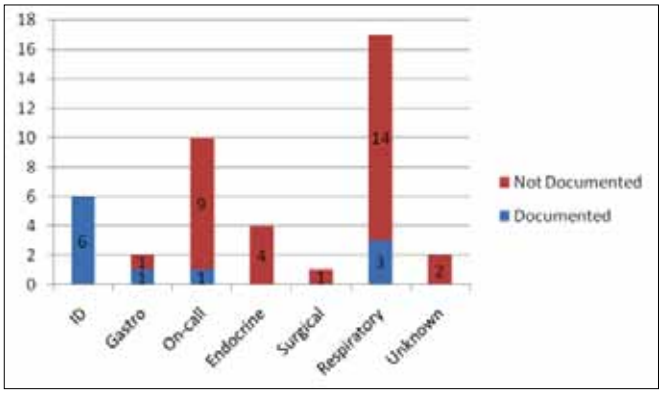

Figure 3. Duration documented according to prescriber's team.

The duration of antibiotics was not documented in 31/42 (74%) cases.

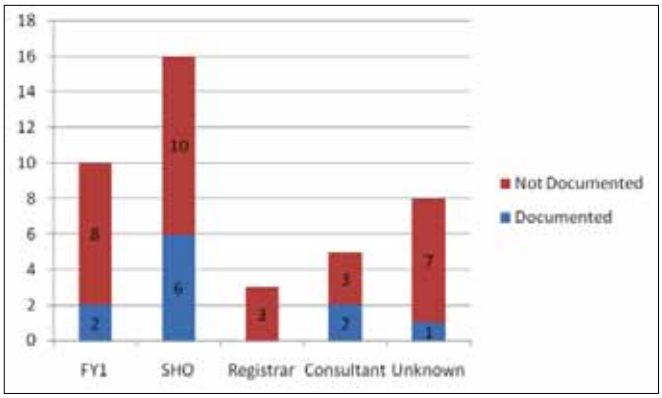

Figure 4. The grade of doctor documenting Duration

Only 7/42 (17%) drug charts had both the indication and duration of antibiotic documented.

The allergy box was completed correctly (Criterion 3) in 41/42 (98%). One chart had "not known" documented in the allergy box and had been in use for three days.

Evaluating the appropriateness of the antibiotics prescribed (Criterion 4) was a difficult task as very few had the indication documented, but after review of the notes 39/42 (93%) patients were prescribed appropriate antibiotics. Five antibiotic regimens had been prescribed after discussion with microbiology. Of the three prescribed inappropriately, one patient was prescribed an antibiotic contrary to the guideline and two patients did not have a clear indication documented on the drug chart or in the notes and so were classed as an inappropriate prescription.

Intervention and Re-audit

Following the initial audit, a teaching session was conducted for the Foundation Year (FY) 1 doctors to review the audit result and highlight the importance of clear prescribing as part of their educational programme about antibiotic therapy.

The re-audit was conducted around five weeks after the teaching session with the assistance of three FY1 doctors. The audit included the two medical wards as before and additionally a surgical ward, within the same hospital using the same method.

Re-audit Results

Overall 52 patients were prescribed antibiotics. The documentation of indication had improved to 32/52 (62%) from 20%. Although most marked for FY1 doctors, improvement was across all grades of doctors.

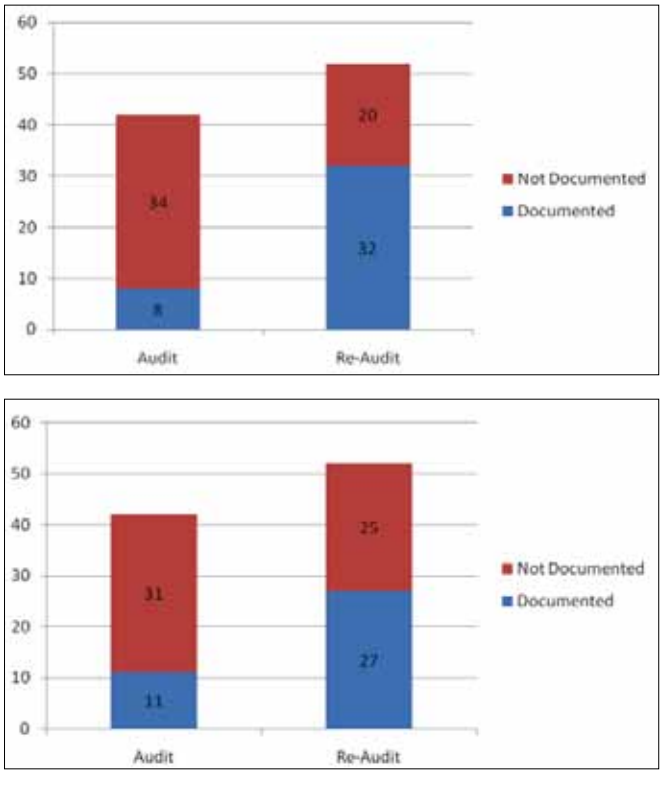

Figure 5. Documentation of indication after the FY1 teaching

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The documentation of duration also improved compared to the original audit with 27/52 (52% from 26%.

The documentation of allergy status had improved, with all 52 charts correctly completed.

The antibiotic regime prescribed was in accordance with guidelines or microbiology advice for 45/52 (87%) patients, with seven prescriptions' indication remaining unclear after reviewing the notes.

Discussion

Clear documentation on drug charts is good practice as it allows physicians to review and rationalise treatment more easily. It enables antibiotic courses to be continued for the appropriate duration to achieve optimum treatment of infection whilst reducing the chances of antibiotic-related side effects associated with inappropriately long courses. Due to the inevitable increase in handovers between doctors during recent years, clear documentation allows easier communication between teams.

The majority of antibiotics are prescribed by junior doctors. A possible reason for not documenting indication or duration includes not being aware of the need to do so within the Trust, an issue aggravated by rotation of junior doctors through different Trusts. It may also be due to the lack knowledge about antimicrobial therapy and simply carrying out instructions from senior colleagues.

The teaching session for FY1 doctors appeared to have a positive impact on prescribing but interestingly this was not confined to the FY1 doctor's prescriptions. There was improvement in other grades. It is possible that the FY1s who had attended the teaching session influenced prescribing to more senior members of the team.

The use of antibiotic guidelines and consultation with the microbiologists was appropriate for the majority of cases. In others the antibiotics used may have been appropriate but there was poor documentation in the case notes. Ensuring indication is entered on the drug chart should help clarify this.
Audit Conclusion and Recommendations

Recommendations to improve the prescription of antibiotics within the hospital include;

- All new doctors to be educated at induction on the importance of documenting indication and duration of antibiotics, including dating the prescription from the first administration within that course.
- All new doctors to be informed at induction of how to access paper and online versions of the hospital antibiotic policy.
- Ward pharmacists to review and question any antibiotics that do not have an indication or duration documented.
- All allergy statuses to be completed fully and any unknown allergy statuses to be confirmed within 24 hours.
- Further audits to be completed in 6 and 12 months time to assess the effect of these recommendations on antibiotic prescribing.

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Authors

Elizabeth A. Hudson MBChB
Core Medical Trainee,
St. James' University Hospital, Leeds.

Philip Stanley MD, FRCP, DTM&H
Consultant in Infectious Diseases,
Bradford Royal Infirmary

Correspondance

elizabeth-hudson@hotmail.com

RESEARCH FELLOWSHIPS IN INFECTIOUS DISEASES

P Collini and DH Dockrell

Research fellowships in infectious diseases.
Training & Teaching.

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Authors

David H. Dockrell MD, FRCPI, FRCP (GLAS), FACP
Wellcome Senior Clinical Fellow
Professor Of Infectious Diseases
Department Of Infection And Immunity
University Of Sheffield & Honorary Consultant
Department Of Infectious Diseases
And Tropical Medicine, Sheffield Teaching Hospitals

Paul Collini MBCHB, BSC, DTM&H, MRCP (London)
MRC Clinical Training Fellow
Department Of Infection And Immunity
University Of Sheffield & Honorary SPR
Department Of Infectious Diseases And Tropical Medicine
Sheffield Teaching Hospitals

Correspondance

David H. Dockrell
Academic Unit Of Respiratory Medicine
Department Of Infection And Immunity
The University Of Sheffield Medical School
Beech Hill Road
Sheffield
S10 2RX UK

Tel: +44 (0)114 271 2160 18
Fax: +44 (0)114 226 8898 19
Email: d.h.dockrell@sheffield.ac.uk

Paul Collini
Academic Unit Of Immunology & Infectious Diseases
Department Of Infection And Immunity
Room LU108, L Floor
The University Of Sheffield Medical School
Beech Hill Road
Sheffield S10 2RX UK

Email: p.collini@sheffield.ac.uk

CLINICAL ASPECTS OF LYME DISEASE

T Blake, N Bhadauria

Clinical Aspects Of Lyme Disease. Patient Management.

Abstract

This article presents a brief history of a patient presenting in the early stage of Lyme disease, an emerging infectious disease in Europe. The reader is directed towards making a clinical diagnosis. Consideration should be given to rashes (including atypical ones), evolution of symptoms, investigations, treatment and prevention.

Clinical case summary

A 31 year old Primary School Teacher from Berkshire presents with a circular red rash over his right upper arm. Over the course of the next few weeks the rash expands rapidly to leave a Bull's eye appearance, as represented in Figure 1. He had suffered "flu" type symptoms however the rash had given him no ill effects. He does not recall any preceding insect or tick bites. Six weeks before this he had spent the day walking through parkland at a nearby historic country house. His past medical history is unremarkable.

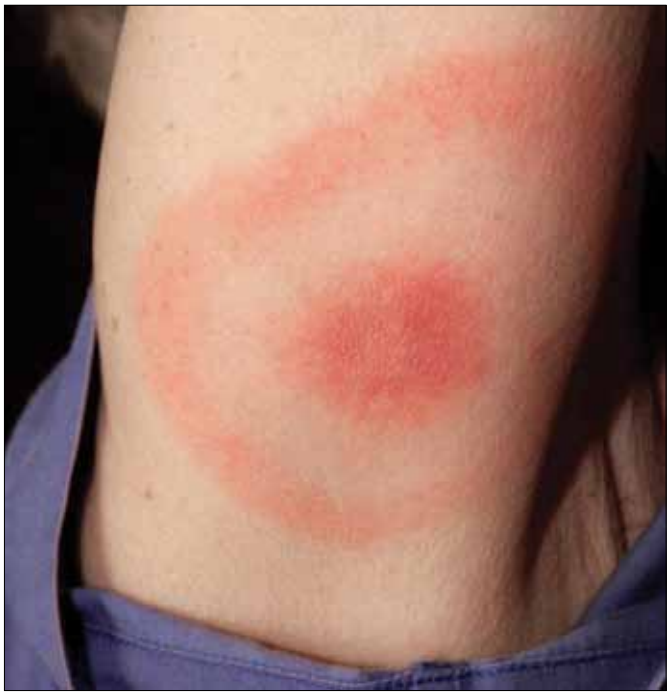

Figure 1: Erythema chronicum migrans

What would be your differential diagnosis of this rash?

The hallmark skin lesion in early Lyme disease is termed Erythema chronicum migrans or Erythema migrans (EM). This circular rash radiates from the site of the infectious tick attachment. In its most characteristic form it is a macular erythematous lesion that expands rapidly (2-3cm per day) up to 70cm in diameter. In around 40% of cases there is central clearing of the lesion to produce a target or bull's eye rash. EM tends to be asymptomatic. Rarely, patients may complain of pain or itching.

The seasonal occurrence of EM in late spring and summer, the morphology of lesions, and the paucity of associated symptoms of pain and itch are useful distinguishing features.

Table 1 sets out more common skin disorders that can be mistaken for EM.

	Seasonal occurrence	Symptoms	Morphology
Erythema chronicum migrans	Yes	Rare (pain or itch)	Uniform erythema, Bull's eye rash
Tinea corporis	No	Itch	Ringlike
Cellulitis	No	Pain	Homogeneous erythema
Hypersensitivity to insect or tick bite	Yes	No	Uniform erythema
Contact dermatitis	No	Itch	Linear
Spider bite (outside UK)	Yes	Pain	Necrotic
Urticaria	No	Itch	Raised
Pityriasis rosea	No	Itch (mild)	Oval
Fixed drug eruption	No	Burning	Plaque, well-demarcated
Granuloma annulare	No	No	Central clearing
Erythema multiforme	No	Variable (viral)	Target lesion

Table 1: Differential diagnosis of Erythema chronicum migrans

CLINICAL ASPECTS OF LYME DISEASE

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The most common misdiagnosis of EM is a hypersensitivity reaction to an insect or tick bite. Nevertheless, these skin reactions tend to develop rapidly, are often itchy, and are usually smaller than EM.[1]

Diseases that may mimic the systemic manifestations of Lyme include the following:

Infections

Viral
Parvovirus B19
West Nile virus

Bacterial
Relapsing fever
Syphilis
Leptospirosis
Mycoplasma
Infective endocarditis
Meningitis

Non-infectious
Gout
Psoriatic arthritis
Systemic lupus erythematosus
Vasculitis
Thyroid disease
Metabolic disorders (vitamin B12 deficiency, diabetes mellitus)

Introduction to Lyme disease

Lyme disease is an emerging tick-borne disease due to systemic infection with the spirochaete *Borrelia burgdorferi*.[2] Bacteria gain entry into the skin after the host is bitten by an infected *Ixodes* tick. Most European cases are caused by *Borrelia afzelii* and *Borrelia garinii*, whereas *Borrelia burgdorferi sensu stricto* is the main cause of Lyme disease in the United States.[3]

Descriptions of the dermatological manifestations of Lyme disease date back to 1883 in Europe, then referred to as Acrodermatitis chronica atrophicans (ACA). In 1912 a Swedish dermatologist coined the term Erythema Chronicum Migrans, now shortened to Erythema Migrans (EM). It was not until the early 1970s that the disease was recognised in the Unites States. Following an outbreak of a number of cases of ECM with associated joint swelling in Lyme, Connectitut, the disease got its name. In 1981 the causative organism was discovered by Willy Burgdorfer. ACA is still described in late stages of *Borrelia afzelii* Lyme disease. It is a progressive fibrosing skin condition and has a predilection for the extremities, particularly extensor surfaces (see Figure 2).5

Figure 2: Acrodermatitis chronica atrophicans

How common is Lyme disease?

The Health Protection Agency (HPA) estimates that there are around 1,000-2,000 cases of Lyme disease in the UK each year. Latest provisional figures show that there were 953 laboratory-confirmed cases in England and Wales in 2010. Some cases are diagnosed clinically. Increasing incidence is thought to be due to better detection of disease. In addition it is thought that around 15% of cases were acquired abroad.

Certain parts of the UK have a high population of ticks: Exmoor, the New Forest in Hampshire, the South Downs, parts of Wiltshire and Berkshire, Thetford Forest in Norfolk, the Lake District, the Yorkshire Moors, Scotland, and upland areas of Wales. Nevertheless, incidence of Lyme acquired in the UK remains low compared to other European countries, particularly central Europe and Scandinavia.[6]

CLINICAL ASPECTS OF LYME DISEASE

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Figure 3 shows which countries have reported cases of Lyme disease to date. Note endemic areas are situated in the Northern Hemisphere.

Figure 3: Worldwide reported cases of Lyme

People of all ages and both sexes are susceptible but disease is highest in those aged 24-64 years. Certain occupations are associated with an increased risk: forestry workers, farmers, deer handlers and gamekeepers. Nevertheless, occupationally acquired cases make up the minority. These cases should be reported to the Health and Safety Executive (HSE) under the Reporting of Injuries, Diseases, and Dangerous Occurrences Regulations, 1995 (RIDDOR).[6]

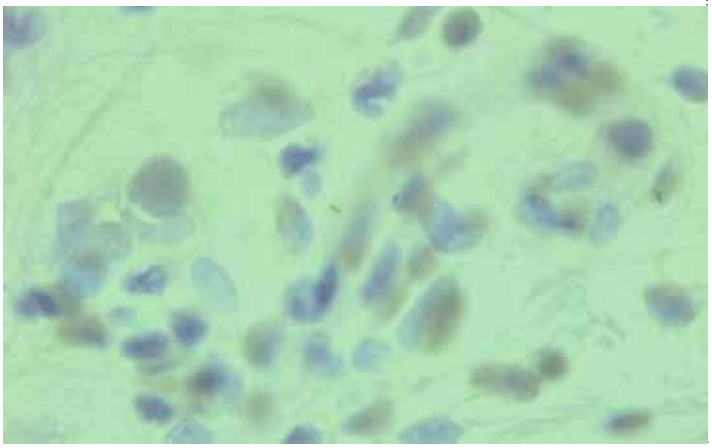
What are the stages of Lyme disease?

Almost any part of the body can become affected by disease; the pathogenesis driven by infection and the body's immune response. Certain organs are more commonly implicated: skin, heart, central nervous system, joints, skin and eyes. The incubation period varies from a few days to one month before symptoms are likely to develop.

The clinical presentation varies according to the stages of disease progression: early localised, early disseminated and chronic disseminated (or late persistent). Nevertheless, there are rarely clear-cut phases and disease should be regarded as a continuum. Asymptomatic infection is also possible. [3]

Early localized or stage 1 (1 to 6 weeks)

In early localised infection around 90% of patients will develop EM at the site of the tick bite. In around one third of cases it is the only manifestation of disease. Other common symptoms at this stage are fever, malaise, headache, arthralgia and myalgia.



Early disseminated or stage 2 (1 to 4 months)

This stage is still considered to represent early infection. A significant proportion (60%) of patients will have a severe flu-like illness with oligoarthralgia. In the US it is more common to develop an inflammatory arthritis with joint swelling. Around 5-8% of patients will develop neurological disorders (neuroborreliosis). These include cranial nerve palsies (commonly facial), meningitis, encephalitis, mononeuropathy, lymphocytic meningoradiculitis (or Bannwarth's syndrome) as well as altered mental status. A minority of patients (10%) will display cardiovascular complaints, including syncope, transient atrioventricular block, myocarditis, or dilated cardiomyopathy. Borrelia lymphocytoma is a purplish nodule that may develop on the earlobe, nipple or scrotum and is found in European cases of Lyme. Figure 4 shows a borrelia lymphocytoma on the cheek of a patient. Rarer complications at this time include hepatitis, orchitis, uveitis and panophthalmitis.

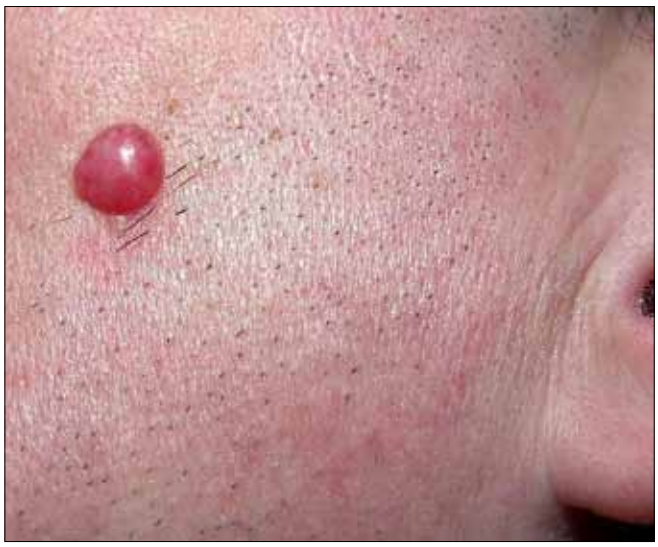


Figure 4: Borrelia lymphocytoma

Late disseminated or stage 3

Chronic symptoms may arise weeks to months after untreated infection. These late manifestations typically affect the central and peripheral nervous system, eyes, joints and heart. Patients may present with a chronic erosive arthritis, usually of the knees. They may also experience chronic pain from secondary fibromyalgia. Around 5% of untreated patients will suffer chronic neurological symptoms, such as polyneuropathy, chronic encephalomyelitis, or cognitive deficits. Frank psychosis has also been recognised.[4]

CLINICAL ASPECTS OF LYME DISEASE

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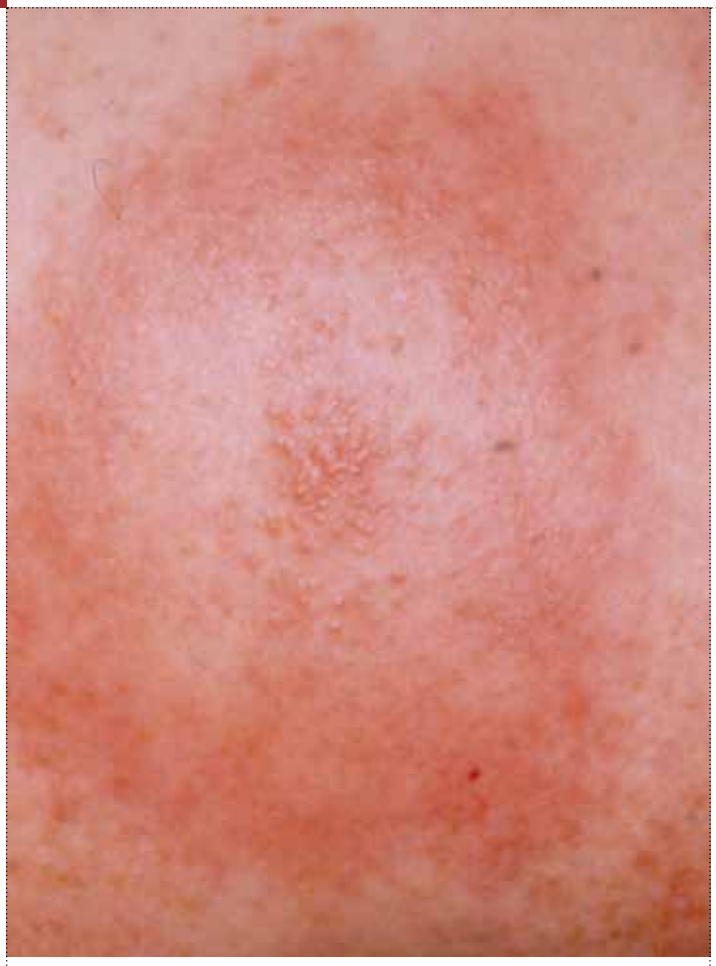

When and how would you test for Lyme disease?

One should always seek advice from a Microbiologist, Infectious Disease Specialist or The Lyme Borreliosis Unit. Serological testing remains the mainstay of diagnostic testing.

Disease is usually diagnosed clinically. If there is a definite history of EM following a tick bite or exposure, then investigation will not be necessary. Serological testing should also not be undertaken in asymptomatic patients.

In Primary Care, testing should be performed in the case of EM without a history of tick bite or exposure, or when there is an isolated unilateral facial palsy (Bell's palsy) and the patient is high risk for tick bites. Where there are suspected complications from Lyme disease such as rheumatological, cardiac or neurological, then it is recommended that specialist advise is sought.

Currently a 2-step process for serological testing is utilised. Initially a screening enzyme immunoassay should be undertaken. If the result is equivocal or there is concern about false positivity (from other spirochaete infections including syphilis, and autoimmune disorders) then one should retest using immunoblot (Western blot). It is important to remember that a negative result does not exclude recently acquired infection. Retesting may be considered after 2-4 weeks if the first sample is negative.[3]

What treatment would you recommend?

It is well known that antibiotics shorten the clinical course and progression of Lyme disease. Antibiotics should be started as early as possible to prevent complications. In most situations oral therapy is adequate. You should ensure that patients are not pregnant or breast feeding before prescribing. Doxycycline should not be prescribed for children under 12 years of age.

There is general agreement among European and American guidelines for choice of antibiotics. In adults, first choice is doxycycline (100 mg twice-daily for 14 days) or amoxicillin (500 mg three times daily for 14 days). Cefuroxime (500 mg twice-daily for 14 days) should be used if there are contraindications to these antibiotics. If you suspect a bacterial cellulitis, you should prescribe 14 days of either co-amoxiclav (500/125 mg three times daily), cefuroxime (500 mg twice-daily), or amoxicillin (500 mg three times daily) with flucloxacillin (500 mg four times daily for 7 to 14 days). [7,8]

Intravenous antibiotics may need to be used in severe cases, as may occur with encephalitis, meningitis, myelitis, vasculitis, optic neuritis, joint effusions and heart block. Third generation Cephalosporins are recommended in such cases.[7,9]

The duration of antibiotics will depend on the manifestations of disease although one should be guided by clinical response. Recent evidence suggests that a two-week course of oral doxycycline is non-inferior to parenteral ceftriaxone in adults and children over the age of 8 who have acute neuroborreliosis (including meningitis) without evidence of encephalitis, myelitis or vasculitis.[9] This is summarised as follows:

Disease manifestation	Duration of treatment
Erythema migrans	Oral regimen 14-21 days
Neuroborreliosis (isolated facial nerve palsy)	Oral regimen 14-21 days
Neuroborreliosis (without encephalitis/myelitis/vasculitis)	Oral regimen 14-21 days
Neuroborreliosis (with encephalitis/myelitis/vasculitis)	IV Ceftriaxone 14 days
Late Neuroborreliosis	IV Ceftriaxone 21 days
Lyme arthritis	Oral regimen 21-28 days
Lyme carditis (with 1st degree block + prolonged PR interval, or 2nd or 3rd degree block)	IV Ceftriaxone 14-21 days
Fibromyalgia	No evidence for treatment

Table 2: Summary of treatment

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What advice would you give about prevention?

Prevention of Lyme disease relates to Environmental and Personal modification. People at high risk of tick-borne infection should be given written information on Lyme. They should be self aware of ticks getting onto their skin and know how to recognise the symptoms and signs of disease. This is particularly pertinent to those working outdoors.

Patients can be directed to Lyme Disease Action (LDA) through their website. LDA is a registered charity raising public awareness of Lyme disease since 2003.

The first step in prevention is tick avoidance. Outdoor workers should be encouraged to wear light-coloured clothes with long sleeves, tuck long trousers into socks and keep long hair under a hat. They may wish to use insect repellents, eg. DEET-containing products. Close inspection of skin should be undertaken after trips outdoors, paying close attention to the skinfolds. Pets should also be inspected for ticks in endemic areas.[3]

Some studies have suggested that the likelihood of tick infection correlates with the duration of tick attachment; infection being unlikely where a tick has been attached for less than 24 hours.[10] A tick that has been feeding for this long will normally appear engorged with blood (Figure 5).

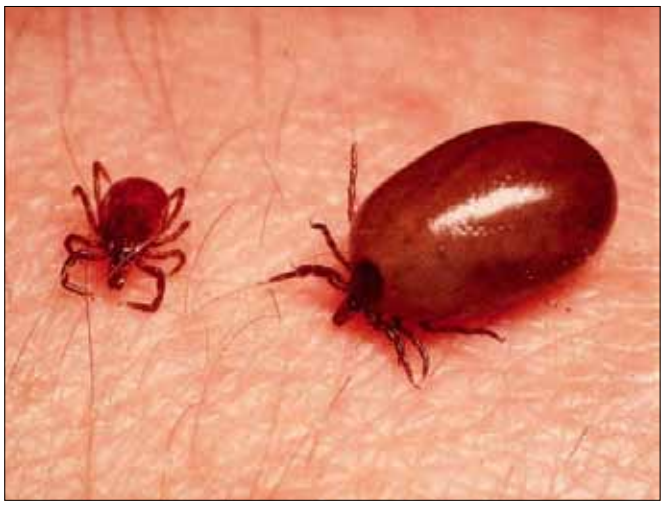


Figure 5: Normal and engorged Ixodes ticks

At the present time, use of prophylactic antibiotics in the UK is not recommended. Nadelman et al (2001) suggested that a single dose of doxycycline within 72 hours of tick removal could prevent the development of Lyme disease. This should be limited to tick bites in certain endemic areas and is not standard practice in the UK.[11] There is no vaccine available at present.

Key points

· Lyme disease is a tick-borne infectious disease caused by the spirochaete *Borrelia burgdorferi*
· At least three species are currently known to cause disease in the UK
· Only a small proportion of ticks will carry infection
· Any area in which ticks may be present should be regarded as having a potential risk for disease
· People visiting affected areas especially the southern counties of England, the Lake District and Scottish Highlands should be encouraged to take preventive measures
· Have a high index of suspicion for disease if there has been a history of possible tick exposure
· Early antibiotic treatment works well to control infection

Self Assessment: Best of Five Questions

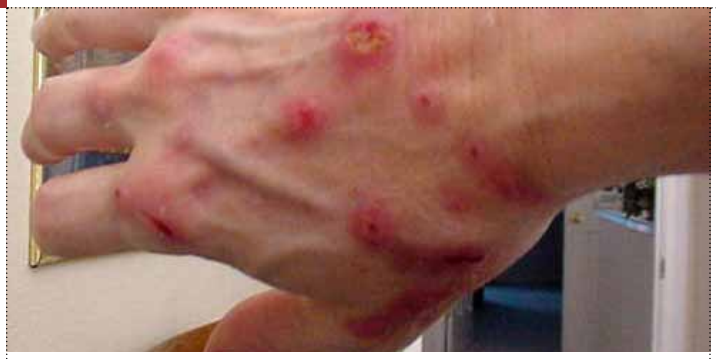
1. What is the rash commonly seen in Lyme disease?
a) erythema multiforme
b) erythema ab igne
c) erythema chonicum migrans
d) erythema marginatum
e) erythema gyratum repens

2. What is the recommended diagnostic test for Lyme?
a) blood culture
b) serology
c) synovial fluid culture
d) CSF analysis
e) skin biopsy

3. What ECG abnormality is seen with Lyme disease?
a) LBBB
b) RBBB
c) AV block
d) Atrial Fibrillation
e) Atrial flutter

CLINICAL ASPECTS OF LYME DISEASE

T Blake, N Bhadauria



4. What is the most common neurological manifestation of Lyme disease?

a) encephalitis
b) mononeuritis multiplex
c) peripheral sensory neuropathy cranial nerve palsies
d) peripheral motor neuropathy
e) cranial nerve palsies

5. What manifestation of Lyme disease is only seen in Europe but not in the USA?

a) fibromyalgia
b) meningoradiculoneuritis
c) acrodermatitis chronica atrophicans
d) lymphocytoma
e) chronic meningoencephalitis

Answers

1. c) Erythema migrans is an erythematous lesion that grows over several days and occurs in Stage 1 of Lyme disease. It can be asymptomatic or it may itch or burn. It often occurs at or near the site of the tick bite. The other rashes do not occur in Lyme disease.
2. b) Antibody detection tests are widely used. When a positive titre is obtained then this is usually confirmed using a Western blot. CSF is only analysed in patients with neurological symptoms and culturing the organism from synovial fluid is rarely effective. B. burgdoferi can be cultured from skin biopsy but this is usually not practical.
3. c) Syncope in Lyme disease is usually due to atrio-venticular block. The level of AV block varies and fluctuates so that the symptoms may be intermittent. The block rarely lasts longer than a week. A temporary pacemaker is rarely required.
4. e) Cranial nerve palsies are common in both the USA and Europe, especially in children. More than half of children with neurological symptoms have a facial palsy. It can be bilateral. The palsy lasts less than 2 months and may begin to resolve even in the first several days.
5. c) and d) A lymphocytoma is a bluish-red nodular lymphocytic infiltrate that typically appears on the earlobe or nipple. It is usually found as part of Stage 2 disease. Acrodermatitis chronica atrophicans (ACA) is a fibrosing skin condition that is seen in late stage European Lyme borreliosis.

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Authors

Tim Blake MBCHB, BSC (Physlology And Pharmacology), MRCP

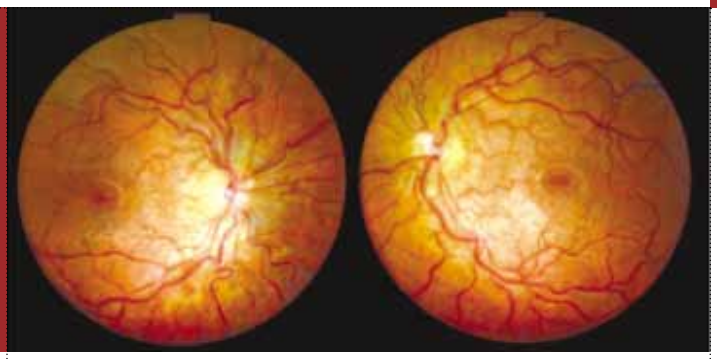
Naveen Bhadauria, MBBS, BSC (Immunology)

Correspondance

South Warwickshire,
NHS Foundation Trust,
Lakin Road, Warwick,
CV34 5BW

HYPERVISCOSITY SYNDROME IN A PATIENT WITH UNDERLYING WALDENSTRÖM'S MACROGLOBULINAEMIA

E Newbold, A Borg



Hyperviscosity Syndrome in a patient with underlying Waldenström's Macroglobulinaemia.
Patient Management.

Abstract

This case based discussion focuses on a 79 year old male with hyperviscosity syndrome found to have an underlying Waldenström's Macroglobulinaemia. This case explores the presentation, investigations and treatment of hyperviscosity syndrome.

Case History

A 79 year old male presented to Accident and Emergency department with severe dyspnoea at rest. He had a 3 month history of progressive exertional dyspnoea associated with anorexia, weight loss of 2kg and night sweats. He had felt increasingly tired and developed non-specific headaches over the last 9 months. He had no significant past medical history.

On examination there were bibasal end-inspiratory pulmonary crackles, bilateral pitting oedema of the legs to the mid shins and JVP was raised to 7cm with a regular heart rate of 110/minute.

What do you think was the cause of this patient's shortness of breath?

The differential diagnosis includes pulmonary oedema or embolus, pneumothorax and lower respiratory tract infection. The clinical features and chest radiograph of this patient are consistent with pulmonary oedema secondary to cardiac failure[1]. (Myocardial infarction was excluded).

Further examination revealed moderate splenomegaly. Hepatomegaly and lymphadenopathy were absent.

What are the causes of splenomegaly?

The causes of splenomegaly can be grouped into various categories including:

	Examples
Congestive splenomegaly	Chronic liver disease
Haematological	Lymphoproliferative and myeloproliferative disorders, haemolytic anaemia
Infections	Glandular fever and other viral infections, endocarditis, malaria, tuberculosis, schistosomiasis.
Connective tissue disorders	systemic lupus erythematosus[1,2].
Splenic tumours and cysts	

The findings of cardiac failure and splenomegaly should prompt the clinician to consider chronic liver disease, lymphoproliferative disorders and endocarditis.

A senior doctor performed ophthalmoscopy because the patient had recently developed headaches and on further enquiry admitted to blurred vision.

What findings does Figure 1 demonstrate?

Figure 1

There are features of:

Retinal venous engorgement and "sausage shaped veins".

These signs on ophthalmoscopy are highly suggestive of hyperviscosity[3].

HYPERVISCOSITY SYNDROME IN A PATIENT WITH UNDERLYING WALDENSTRÖM'S MACROGLOBULINAEMIA

E Newbold, A Borg

Learning point

Ophthalmoscopy led to a diagnosis of hyperviscosity in this patient. Ophthalmoscopy is part of the patient's examination that is often missed. A thorough history and examination is essential to ensure good medical practice and patient care.

Investigations

Routine blood tests showed a normocytic anaemia (haemoglobin 8.0 g/L) and a raised plasma viscosity. Renal and liver function tests were normal apart from a very high total protein and mild hypoalbuminemia.

Learning point

Plasma viscosity (PV) is the gold standard laboratory test for diagnosing hyperviscosity. Most hospitals use the erythrocyte sedimentation rate (ESR) rather than PV for screening. The ESR is usually above 50 mm/1st hr in patients with significant hyperviscosity syndrome.

The high total protein and low serum albumin indicates hypergammaglobulinaemia.

What are the possible causes of Hyperviscosity syndrome?

Hyperviscosity syndrome is due to either a very high level of serum immunoglobulin or increase in the number of red or white blood cells. The table below gives some examples of the causes of hyperviscosity syndrome.

Causes of Hyperviscosity Syndrome	
Increase in immunoglobulins	Increase in cell constituents
Waldenstrom's macroglobulinaemia.	Polycythaemia rubra vera.
Multiple Myeloma.	Leukaemia[4].
Connective tissue disorders.	

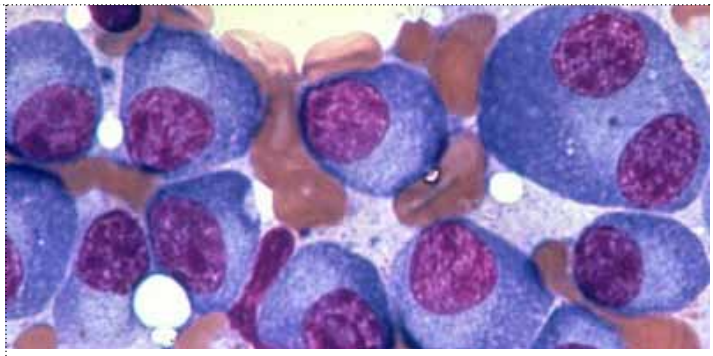
A doctor suggested transfusing this patient with two units of blood to his anaemia.

Why are transfusions not advisable in patients with Hyperviscosity syndrome?

Blood transfusions will exacerbate the total blood viscosity and increase the number intravascular volume.

Haematological investigations were requested which showed:

- Serum protein electrophoresis: IgM paraprotein.
- Serum free light chain assay: monoclonal kappa light chain.
- Bone marrow trephine: extensive infiltration with plasmacytoid lymphocytes.
- Serum LDH: raised.
- Uric acid: raised[4].



The patient's results are diagnostic of Waldenström's Macroglobulinaemia, a type of low-grade non-Hodgkin's lymphoma. This lymphoma produces large amounts of the pentameric IgM immunoglobulin which is highly viscous in the blood. The raised serum LDH and urate levels are suggestive of a high number of lymphoma cells and an increased risk of renal function impairment[2,5].

Treatment

What are the treatment options for a patient with hyperviscosity syndrome and underlying WaldenstrÖm's Macroglobulinaemia?

In the acute situation with raised plasma viscosity levels causing symptoms this patient should be cautiously hydrated and undergo plasmapheresis to lower paraprotein levels and hence plasma viscosity below 3.0 mPa/s. Chemotherapy should be started to treat the underlying lymphoma. Plasmapheresis is done at regular intervals until chemotherapy controls the disease[4,5].

Discussion

Waldenström's Macroglobulinaemia, as features in this case history, accounts for eighty per cent of hyperviscosity patients[5].

Symptoms arise from a reduction in capillary blood flow rate and include neurological disturbance such as headaches, fatigue and confusion and visual disturbances. There are haematological complications with abnormal coagulation resulting in bleeding or thrombosis. High IgM levels are hyperosmotic. This leads to an expanded plasma volume causing a dilutional anaemia and fluid overload with cardiac failure. Mild to moderate renal failure is also common[3,4,6].

Clinical features can suggest a possible diagnosis of hyperviscosity syndrome confirmed with measurement of ESR and later plasma viscosity[6].

Treatment of hyperviscosity syndrome is done by reducing the IgM paraproteinemia by plasmapheresis and chemotherapy for the non-Hodgkin's lymphoma. The principle of treatment of patients with hyperviscosity due to polycythaemia is the same involving regular venesection to reduce the number of red cells. Chemotherapy may be used for the myeloproliferative neoplasm[4].

HYPERVISCOSITY SYNDROME IN A PATIENT WITH UNDERLYING WALDENSTRÖM'S MACROGLOBULINAEMIA

E Newbold, A Borg

Self assessment Questions

1. A 65 year old female is admitted to hospital with a background of multiple myeloma. Which of the clinical features below are suggestive of hyperviscosity syndrome?

a) Recent confusion, constipation, nausea and polyuria with a short history of fatigue and generalised aches and a change in personality.

b) Progressively back pain, with sensory loss and weakness in the legs and new onset of urinary incontinence.

c) Epistaxis with a 2 month history of headache, vertigo and blurred vision

d) Pyrexia with dyspnoea and cough productive of green sputum.

e) Right hip pain with radiological evidence of fracture of the neck of femur

2. A 60 year old female was admitted with symptoms of cardiac failure, recurrent gum bleeding, headaches and noted chest pain on exertion. Her plasma viscosity was found to be 9.4 mPa/s (normal value < 1.74). Haemoglobin was 7.2g/L. A diagnosis of hyperviscosity syndrome is made. Which of the following treatments are most appropriate for her immediate management

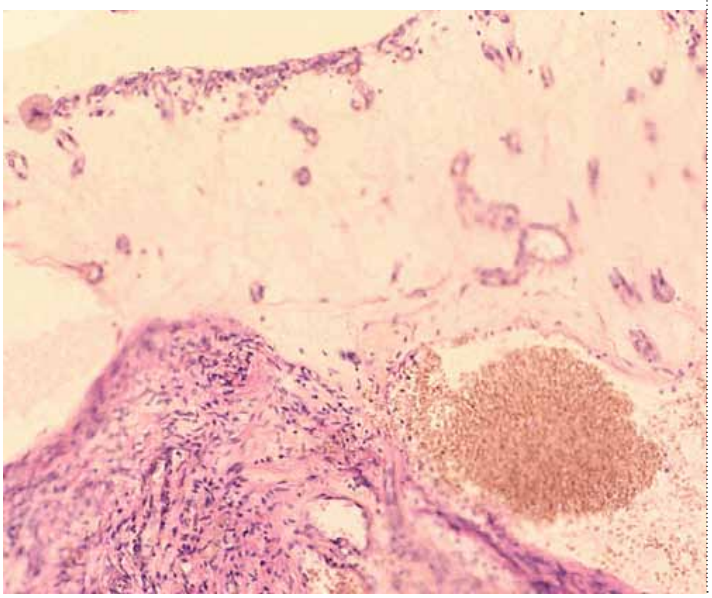
a) IV furosemide.

b) Transfuse the patient with 2 units of blood.

c) Hydrate the patient with intravenous fluids.

d) Plasmapheresis

e) Venesection



Answers

1. Answer C.

The triad of mucosal bleeding, neurological symptoms and visual changes are typical of hyperviscosity symptoms. Answer A show symptoms of hypercalcaemia albeit a number of these symptoms overlap with hyperviscosity. B is spinal cord compression; D is a bronchopneumonia; E is a pathological fracture due to a plasmacytoma.

2. Answer A.

Both diuretic therapy and blood transfusion could worsen the hyperviscosity syndrome. Patients with pulmonary oedema due to hyperviscosity need cautious administration of furosemide starting at 50% of the standard dose. Plasmapheresis is ideal treatment for IgM hypergammaglobulinaemia but is often not readily available in the acute setting.

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Authors

Eloise Newbold MBChB
Foundation Year 1 Doctor

Anton Borg MD, FRCP, FRCPath
Consultant Haematologist

Correspondence

Email: anton.borg@swft.nhs.uk

Acknowledgements

Figure 1 was reproduced from source: Dobberstein H, Solbach U, Weinberger A, Wolf S. Correlation between retinal microcirculation and blood viscosity in patients with hyperviscosity syndrome. Clinical Hemorheology and Microcirculation 1999; 20:31-353.

CASE-BASED DISCUSSION NEUTROPENIC SEPSIS

S Shayler and J Lancashire

Case-Based Discussion: Neutropenic Sepsis. Patient Management.

Abstract

This case based discussion focuses on a 34 year-old female who underwent her second cycle of chemotherapy 10 days ago and now presents with a temperature of 38.5 degrees. The case discusses the assessment, differential diagnosis and treatment of patients who present with neutropenic sepsis.

Case Presentation

A 34 year-old female patient self-refers to the Medical Admissions Unit with a temperature of 38.5°C and feeling generally unwell for the last 4 hours. She complains of lethargy, generalised aches and feeling cold. She completed her second cycle of intravenous chemotherapy 10 days ago.

• Neutropenia is most likely to occur 7-14 days post chemotherapy

• Neutropenia is defined as a neutrophil count of less than 1x10Ð/l. At this level patients are susceptible to infection and the risk increases greatly with a count below 0.5x10Ð/l and a neutropenia of more than 7 days.

• Neutropenic sepsis is a life-threatening emergency requiring immediate intervention (30 day mortality rate of neutropenic sepsis in ITU is 54%). If you suspect neutropenic sepsis, treat without delay.

• Liaise with your hospital's on-call haemato-oncology team early to get specialist input.

History

Your patient is unwell and showing signs of sepsis- rigors, hypotension, tachycardia and pyrexia. You suspect they may be neutropenic because of recent chemotherapy and know that treatment within the first hour of presentation is vital to improving mortality. You take a brief history, obtain intravenous access, take a full set of microbiology cultures and then commence fluids and antibiotics.

After this they are moved to a side room on a specialist haemato-oncology ward where their observations are repeated regularly. Now the patient is stable you are able to take a full medical history, including the following;

• What chemotherapy regime is the patient on? Remember to enquire about previous adverse reactions.

• Have they received any blood products recently?

• Chemotherapy agents such as cytarabine, transfusion reactions and lymphoma and other cancers can cause 'aseptic' fever.

• Have they had any lines inserted/changed or flushed recently? Flushing of colonised central venous lines releases bacteria and their toxins often producing symptoms rapidly.

• Any recent hospital admissions? If so did they have an identified infection and what antibiotics did they receive?

• Any foreign travel? Unlikely, but it raises the possibility of infection with less common organisms.

• Has the patient taken paracetamol or ibuprofen? Remember antipyretics such as these can mask temperatures. Also, some patients are too poorly to mount a febrile response to infection.

Examination

You perform a full systems examination of the patient and include the following; Examination of any lines in situ- Look for erythema at the line exit site or a swelling along the tunnel of a subcutaneous long line as these are a good indication of extra-luminal infection.

Examination of urinary catheter bag- If the patient has a catheter in situ look at the urine quantity and colour.

Skin examination - Do a full examination of the patients skin and consider fungal infections, pseudomonas and varicella zoster.

Mouth examination - Look for ulcers and thrush.

CASE-BASED DISCUSSION NEUTROPENIC SEPSIS

S Shayler and J Lancashire

Genital and peri-anal examination - Look for discharge, erythema and tenderness. PR examination should not be done in the neutropenic patient unless clinically indicated and antibiotics have been given and severe thrombocytopenia corrected.

Eyes - Check fundi for retinal bleeding and signs of infection.

Remember, patients with neutropenic sepsis can look relatively well and may not show obvious signs of sepsis. Despite this however they can deteriorate very rapidly so do not underestimate the severity of their condition.

Investigations

Begin your investigations early so you can obtain results as quickly as possible. Biochemistry/Haematology: Full Blood Count, Liver Function Tests, Urea & Electrolytes, Coagulation screen, CRP, Group & Save, Lactate and an atypical pneumonia screen if indicated. *Remember the white cell count may not be elevated so the CRP is a good marker of infection.*

Microbiology: Blood from all venous lumens and a peripheral vein, urine, stool and sputum cultures for microscopy, culture and sensitivity. You may need to send serial cultures in some cases. Remember to take swabs from any lines in situ if you suspect it is the source of infection.

Radiology: Chest x-ray and abdominal x-ray if indicated. A high resolution CT scan of the thorax should be discussed with the radiologist for patients at high risk of fungal infection, particularly if sepsis persists for more than 72 hours.

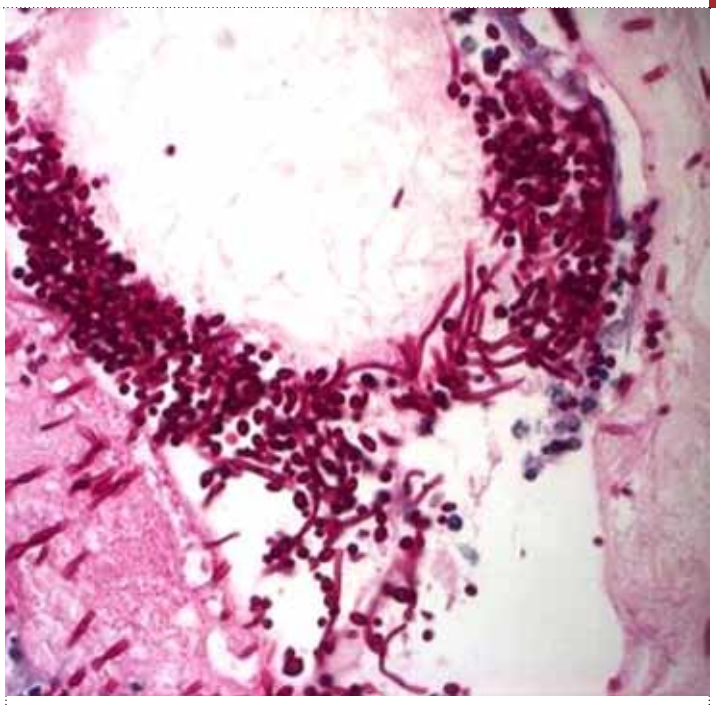
ECG and ECHO if cardiac signs or nail fold, cutaneous vasculitic and retinal infarcts.

Treatment

Remember that treatments can differ between hospitals so it is important to familiarise yourself with local guidelines and if in doubt discuss it with your microbiology team.

A common treatment regime is duotherapy, which involves an antipseudomonal penicillin (usually Tazocin 4.5gms TDS) plus an aminoglycoside (for example gentamicin 3-5mg/kg). It is important to remember that aminoglycosides carry a significant risk of toxicity to both the inner ear and kidney. Consequently they require accurate dosing and close monitoring.

For patients with significant renal impairment, or those already receiving nephrotoxic drugs, an alternative is monotherapy with a carbapenem (commonly Meropenem 1gm TDS).



Discussion

If a patient presents with neutropenic sepsis it is wise to consider why this has developed. In this case the patient has recently undergone chemotherapy so her neutropenia is likely to be due to the myelotoxic effects of the treatment. There are other factors that can exacerbate the severity of neutropenic infection such as the following;

Existing disease ie, renal impairment, diabetes, COPD, HIV
Above 65 years of age
Malnutrition
Reduced serum albumin level
Previous episode of neutropenic sepsis
Combined chemotherapy and radiotherapy
No granulocyte colony stimulating factor used

It is important to consider which organism you are treating;

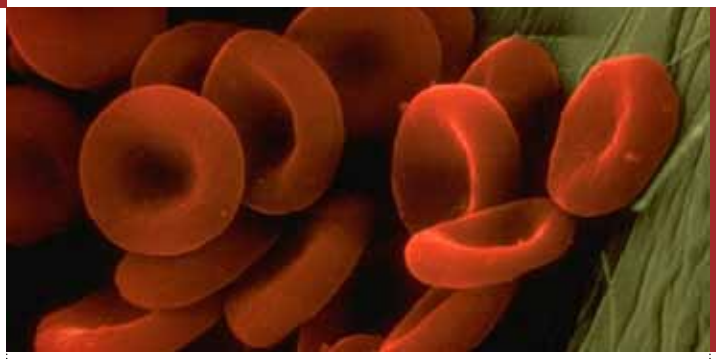
Bacterial: The commonest form of infection in neutropenia. Usually due to gram positive cocci (eg, *Staphylococcus Aureus or Streptococci Viridans) or gram negative bacilli (eg, Escherichia Coli, Klebsiella and Pseudomonas).*

Viral: Herpes simplex infection can cause extensive, painful oral ulcers but response to treatment is good. Other viral infections include CMV, EBV, Influenza, Parvovirus, Hepatitis virus and Respiratory Syncytial Virus.

Fungal: Fungal infections are more likely in patients with prolonged neutropenia who have had broad spectrum antibiotics or are on steroid therapy. Infection with Pneumocystis Jiroveci is an important infection and can cause pneumonitis so prophylaxis against this organism is sometimes prescribed.

CASE-BASED DISCUSSION NEUTROPENIC SEPSIS

S Shayler and J Lancashire



Case-Based Discussion: Neutropenic Sepsis. Patient Management.

Patient Discharge

Following admission and treatment for neutropenic sepsis your patient is stable and ready for discharge. Before she goes you ensure she has clear instructions about monitoring her temperature, prophylactic antiviral and antifungal treatment and a follow-up appointment in the outpatients department. Remember, if your patient remains neutropenic at discharge they should be monitored closely in the Haemato-oncology Day Unit and intravenous antibiotics started at the first sign of infection.

Self Assessment Best of Five Questions

1. A 60 year-old male, who underwent chemotherapy 12 days ago, contacted the chemotherapy suite because he had recorded a temperature of 38.3°C. Despite feeling well, he was advised to attend A&E for further assessment.

How would you have managed this patient?

- Reassured and discharged home
- Advised to see his GP and given paracetamol to control the fever
- Prescribed oral antibiotics and discharged home
- Admitted to hospital for investigation and treatment of possible neutropenic sepsis
- Arranged an appointment for follow-up in the chemotherapy suite the next day

2. A 28 year-old female on the haematology ward informed you that each time her Hickmann Line was used she felt hot, sweaty and shaky. The sister on the ward reported that the patient had spiked several high grade temperatures that coincided with these episodes. You suspect a possible line infection.

How would you have managed the patient?

a. Flushed the line with 0.9% normal saline and continued to use as normal
b. Administered antibiotics through the line as rapidly as possible then use as normal
c. Taken peripheral blood cultures, commenced antibiotics and avoided using the line
d. Remove the line as quickly as possible
e. None of the above

Answers

d.

Although the patient presented to A&E 'feeling well' it was vital to suspect a diagnosis of neutropenic sepsis. Do not be falsely reassured by the lack of symptoms- he was 12 days post-chemotherapy with a documented fever. The correct management was to assume he had neutropenic sepsis until proven otherwise. He required prompt investigation and appropriate treatment.

e.

In suspected line sepsis it is important to determine whether the source is within the line or external to it. Signs of inflammation at the site of insertion may indicate external infection, in which case it may be possible to continue using it. However in this question the scenario points towards a luminal infection, as evidenced by rigors and a fever after the line has been used. In this situation management can vary but may ultimately result in line removal. If the clinical situation allows it is not unusual to try and eradicate luminal infections with intravenous antibiotics. This is done under the guidance of the microbiologists and involves administering antibiotics through each lumen of an involved multi-lumen catheter on a rotational basis.

Authors

Stephanie Shayler BSc (Hons), MBChB, MRCP

Jonathan Lancashire BSc (Hons), MBBS, MRCP

Anton Borg, MD, FRCP, FRCPath

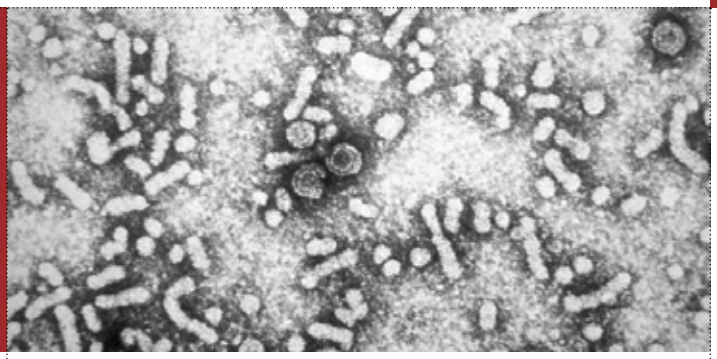
Correspondance

Dr. Anton Borg (Consultant Haematologist)
Haematology; Aylesford Unit, South Warwickshire NHS Foundation Trust, Lakin Road, Warwick, CV34 5BW.

CASE-BASED DISCUSSION – INFECTIVE HEPATITIS

AS Sahota

Case-Based Discussion – Infective Hepatitis. Patient Management.



Abstract

This case-based discussion focuses on the presentation of a normally healthy 47-year-old man with jaundice, fatigue and fever following a visit to Thailand. It considers the approach that needs to be taken when dealing with infective viral hepatitis, including comprehensive history taking, assessment of risk, differential diagnosis, investigation, treatment, and follow-up to monitor and manage both acute and chronic complications.

Case History

A 47-year-old businessman was referred to the Admitting Medical Unit by his GP following a finding of abnormal liver function tests (LFTs). 12 weeks previously he had returned from a business trip to Thailand, and for the last 2 weeks had been complaining of worsening fatigue, loss of appetite, vague abdominal pains, loose motions and chills. More recently, he had noticed a yellow tinge to his eyes. He was UK born, Caucasian, normally well, and was accompanied by his wife. The GP letter documented a bilirubin of 63, alanine transaminase (ALT) of 2100, and alkaline phosphatase (ALP) of 156.

What are the possible infective causes of his symptoms?

What would you like to do next?

It is possible that the symptoms and findings are related to the patient's travel, and the markedly raised ALT suggests liver inflammation i.e. **hepatitis.** Acute viral hepatitis is a strong possibility in this case. Many viruses can damage the liver but it is generally accepted that viral hepatitis refers to hepatitis caused by **hepatotropic viruses,** a group that primarily infect the liver. The most significant ones are named **Hepatitis A to E**[1]. If this hepatitis is due to an infection acquired during travel, the incubation period of 12 weeks is not consistent with a diagnosis of hepatitis A or E but would fit with Hepatitis B or C. (See Table 1)

VIRUS	Mode(s) of transmission	Incubation period	Possibility of chronic infection
Hepatitis A	Faecal-oral	2 - 6 weeks	**No**
Hepatitis B	Blood / sex / vertical†	6 – 24 weeks	**Yes** – If acquired in: • adulthood: 5-10% of cases • childhood: >90% of cases
Hepatitis C	Blood / (sex)‡	6 - 12 weeks	**Yes** - 80% of cases (approx.)
Hepatitis D *(deltavirus)*	Blood / sex / vertical - *Transmitted alongside Hepatitis B virus only*	6 – 24 weeks	**Yes**. May exacerbate the course of Hepatitis B infection, including fulminant hepatitis / cirrhosis.
Hepatitis E	Faecal-oral	2-6 weeks	**No.** Acute infection more severe if acquired during pregnancy.

Table 1. Characteristics of the hepatitis viruses[1]

† Vertical transmission is the commonest mode of acquiring Hepatitis B worldwide, but uncommon in UK (<5% cases). Sexual transmission accounts for 50% of cases, but intra-venous drug use remains the most common cause.

‡ In UK, up to 90% of Hepatitis C patients report current or previous intra-venous drug use. Sexual transmission is uncommon. Since the advent of viral screening of blood products in 1991, acquisition from blood products is rare (1%).

However, many other infections and conditions may be responsible. A thorough assessment is essential including a detailed history and examination[2]. Details of all places visited, activities undertaken and precautions taken – before, during, and after travel – should be elicited. Risk factors for infection and transmission should be considered. It is possible that some information will not be volunteered readily, and more sensitive questions may need to be asked in private, away from accompanying friends and relatives.

CASE-BASED DISCUSSION – INFECTIVE HEPATITIS

AS Sahota

Case-Based Discussion – Infective Hepatitis. Patient Management.

History

1) Presenting problem:

• What other symptoms does he have, in particular – *rash / coryza / cough / sore throat / vomiting / diarrhoea / dysuria / change in colour of stool or urine / headache / neck stiffness / arthralgia / joint swelling / penile discharge / night-sweats / weight loss?* These will help identify a systemic or localised infection.

• When did the symptoms begin in relation to his travel – before, during, or after? Different infectious agents have different incubation periods.

• What did he eat and drink - *tap water; treated or bottled water; raw or rare-cooked meat and fish?* Hepatitis A and E are transmitted by the faecal-oral route via poor hand hygiene, infected water, or under-cooked food.

• Where did he eat - *in hotels / reputable restaurants, or from road-side food vendors?*

• Where did he stay - *urban areas, rural areas, or both? In hotels and resorts or with locals?* This may give an idea of local sanitation and standards of hygiene.

• Was anyone *accompanying* him or in close contact also unwell, either *previously or currently?* This may help identify a mode of transmission.

• Did he take any pre-travel *vaccinations or precautions?* Vaccination is available against Hepatitis A and B.

• Did he suffer from insect bites? Was he taking *malaria prophylaxis?* The systemic effects of malaria can cause liver dysfunction but the illness would not typically present in this way.

• Did he partake in any unusual recreational or sporting activities e.g. f*resh-water swimming / jungle treks / direct contact with animals?* This may heighten the possibility of other infections such as leptospirosis.

• Are there any risk factors for acquiring a blood-borne or sexually-transmitted infection which can affect the liver (Hepatitis B, C and HIV) – *current or previous intra-venous recreational drug use; use of unsterilized syringes or needles in a healthcare setting; new tattoos or piercings; unprotected sexual intercourse within the last six months, including with commercial sex-workers or other men?**

*These last questions may be viewed as highly sensitive or embarrassing by both patient and healthcare worker, possibly due to misconceptions, prejudices, or the clinical setting. Asking them may require tact, explanation of their importance, re-assurance of confidentiality, and a private environment, but it is essential they are not avoided.

2) Past Medical History

• Is there any previous history of liver disease – *gallstones / cholecystitis / fatty liver disease / chronic viral hepatitis / cirrhosis?*

• Does he have a systemic autoimmune condition – *rheumatoid arthritis / inflammatory bowel disease / vasculitis / lupus or other connective tissue disease?* These can all involve the liver.

• Does he have *diabetes or hyperlipidaemia?* These are associated with an increased risk of fatty liver disease.

3) Drug history

• Is he taking any regular or new medicines which could be hepatotoxic, including over-the-counter drugs *(e.g. statins / antibiotics / St John's wort)?*

• Is there any risk of intentional or accidental paracetamol overdose?

4) Family history

• Is there any family history of liver disease, particularly chronic viral hepatitis or liver cancer? Hepatitis B is commonly transmitted vertically and can predispose to hepatocellular carcinoma.

5) Social history

• *Alcohol consumption.* This may cause or exacerbate liver disease and infection.

• *Household contacts.* Viral hepatitis may be transmitted horizontally to close contacts (Hepatitis A and E - faecal-oral route; Hepatitis B and C - blood-borne, e.g. blood spillage / sharing of toothbrush or razor). His wife, and any other sexual partner, is also at risk via sexual transmission (Hepatitis B and C).

• *Nature of work / employment*. This is particularly important if his work is in healthcare or involves contact with food.

The patient had no significant past medical, family or drug history, but consumed 35 units of alcohol per week. He travelled alone and did not seek any pre-travel advice as his trip was short, involving only high-quality hotels in the cities. After direct private questioning, the patient revealed that during his travel he had an episode of vaginal intercourse with a commercial sex worker without the use of a condom. He denied any sexual intercourse with his wife since his return.

CASE-BASED DISCUSSION – INFECTIVE HEPATITIS

AS Sahota

Examination – Should Include:

- Hands - clubbing and splinter haemorrhages
- Skin / joints – rash; petechiae; bruising; swelling
- Peripheral stigmata of chronic liver disease – e.g. palmar erythema; leuconychia; asterixis; icterus; spider naevi; caput medusae
- Cervical / axillary / inguinal regions - lymphadenopathy
- Mouth – pharyngitis; candida; ulcers; stomatitis; glossitis
- Abdomen – hepatosplenomegaly; ascites; tenderness
- External genitalia – discharge; ulcers; epididymo-orchitis

On examination he was icteric with no peripheral stigmata of chronic liver disease. There was 3cm tender hepatomegaly with a smooth edge, but no splenomegaly, ascites, lymphadenopathy or rash. He was mildly febrile at 37.8°C, but otherwise not compromised.

What would you do next?

What infection control and public health measures need to be considered?

Until a diagnosis is established, the patient should be isolated in a side-room - he has loose motions and is a returned traveller with fever. Hepatitis A and E virus is shed in the stool and can cause person-to-person transmission. Further investigations then need to be undertaken.

Investigations

1) Blood tests – non-specific

- *Full blood count and C-reactive protein (CRP)* – a raised white cell count and CRP may indicate infection. Malaria can cause anaemia and thrombocytopaenia.
- *Urea and electrolytes (U&E)* – ensure normal renal function.
- *Repeat LFTs* – to look for a trend. Is the hepatic inflammation getting worse or better?
- *Amylase* – pancreatitis may be associated with or caused by liver disease.
- *Coagulation screen* – a coagulopathy, including a raised International Normalised Ratio (INR), indicates worsening synthetic liver function, and may herald fulminant hepatic failure.
- *Blood glucose* – diabetes would increase the risk of certain infections. Hypoglycaemia would be another early indicator of hepatic failure.

2) Blood tests – infection-specific

- *Blood culture* - with clear documentation of clinical and travel details on the request form.
- *Malaria parasite screen* - x3, at least 12 hours apart.
- *Serological tests* (see Table 2)

INFECTION	SEROLOGICAL TEST	EXPLANATION / INDICATION IF POSITIVE
Hepatitis A	○ **IgM antibody**	○ Acute infection
	○ **IgG antibody**	○ Past *cleared* infection and subsequent *immunity*
Hepatitis B	○ **Surface antigen (HBsAg)**	○ *Current infection* – could be acute or chronic. Chronic if still positive *6 months* after initial exposure
	○ **Envelope antigen (HBeAg)**	○ Patient is highly infectious to others
	○ **IgM Core antibody (IgM anti-HBc)**	○ Acute infection -first antibody to appear
	○ **Envelope antibody (anti-HBe)**	○ HBeAg / acute infection beginning to clear (*seroconversion*)
	○ **Surface antibody (anti-HBs)†**	○ *Cleared* infection and subsequent *immunity*. HBsAg no longer present.
	○ **IgG Core antibody (IgG anti-HBc)†**	○ *Cleared* infection. *Chronic* infection if HBsAg still positive. May persist for life
Hepatitis C	○ **Total antibody**	○ Current infection OR previous cleared infection. May persist for life.
Hepatitis D	○ **Total antibody**	○ Only significant / present if co-infected with Hepatitis B (? worse prognosis)
Hepatitis E	○ **As for Hepatitis A**	○ As for Hepatitis A
HIV	○ **Combined antigen / antibody test**	○ Current infection. May not be positive until *12 weeks* post-exposure – consider repeat test.
Other	○ **Epstein-Barr Virus (EBV)**	○ All can cause liver inflammation as part of a systemic infection.
	○ **Cytomegalovirus (CMV)**	
	○ **Dengue**	
	○ **Syphillis**	
	○ **Leptospirosis**	

Table 2. Serological tests in the investigation of infective hepatitis[3]
†Presence of Anti-HBs without IgG anti-HBc suggests previous Hepatitis B vaccination

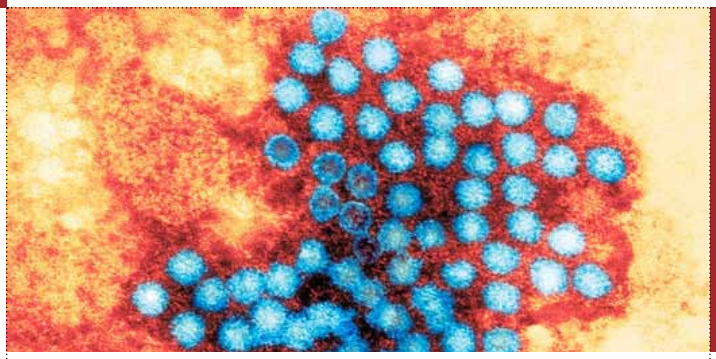
3) Urine dip and microscopy, culture and sensitivity – as part of the septic screen.

4) Chest X-ray (CXR) – bacterial / atypical pneumonia may cause abnormal LFTs.

5) Ultrasound of liver / abdomen – to look for hepatosplenomegaly; focal liver lesions; biliary obstruction.

CASE-BASED DISCUSSION – INFECTIVE HEPATITIS

AS Sahota



Case-Based Discussion – Infective Hepatitis. Patient Management.

The patient had a mild neutrophilia and CRP of 56. Haemoglobin, platelet count, renal function and amylase were normal. INR was raised at 1.3 and ALT was now 3000. The CXR was clear, and ultrasound confirmed hepatomegaly with no focal liver lesions. Viral serology subsequently came back as positive for HBsAg, HBeAg, and IgM anti-HBc. HIV serology was negative.

What is the diagnosis, and how would you manage him?

The serology is consistent with acute Hepatitis B infection[3]. As his LFTs were worsening with development of a mild coagulopathy, he was admitted to the Infectious Diseases Unit.

Management – Ideally With Involvement Of Infectious Diseases Or Hepatology Specialists

1) General management

- Management of acute Hepatitis B is generally supportive. There is no firm evidence for the use of anti-viral therapy[4].
- The septic screen should be completed and reviewed to look for other concomitant infections.
- LFTs, U&E and coagulation screen should be monitored daily to assess for fulminant hepatic failure, an uncommon complication of acute viral hepatitis (<1% of cases of Hepatitis A, B and E; rare in acute Hepatitis C). ALT and bilirubin may take weeks to normalise, but a rising INR, renal impairment and / or a falling blood sugar should ring alarm-bells. If concerned, seek senior input and contact the local Liver Unit.

2) Public health measures

- Infective hepatitis is a notifiable disease, and the Health Protection Agency should be informed[5].
- The patient should be encouraged to explain the diagnosis to his wife, with medical input if necessary. She and all close household contacts need to be screened for Hepatitis B, and if negative vaccinated as soon as possible6. An ethical balance is required between the patient's autonomy and choice to disclose personal information, versus the contact's best medical interests.
- He should be advised that he is currently highly infectious to others. Although all medical staff should already be vaccinated and immune, personal protective equipment should be used for venepuncture and when handling bodily fluids and sharps. All blood spillages should be appropriately cleaned with anti-septic, and toothbrushes and razors should not be shared. Condoms should be used for sexual intercourse.
- He should be referred to Genito-urinary Medicine (GUM) clinic for a full sexual health screen and contact tracing if appropriate. Counselling should also be offered.

3) Follow-up

- Once discharged, the patient should be followed up in an Infectious Diseases or Hepatology clinic.
- He should have regular blood tests and repeat serology at 6 months to look for viral clearance (disappearance of HBsAg), or the development of Chronic Hepatitis B (presence of HBsAg 6 months following initial exposure).
- He should be advised to avoid alcohol and other hepatotoxins until the hepatitis has cleared.
- He should be vaccinated against Hepatitis A if not already immune, to prevent further hepatic damage.

Two days later, his symptoms were settling. His ALT decreased to 2200, bilirubin to 45 and all his other blood tests had normalised. He was discharged home with the appropriate advice. At 6-month follow-up, his ALT was in the normal range. His serology was repeated and showed the following:

- **HBsAg and HBeAg negative**
- **anti-HBe, anti-HBs and IgG anti-HBc positive.**

What does this serological pattern show? (see Fig. 1)

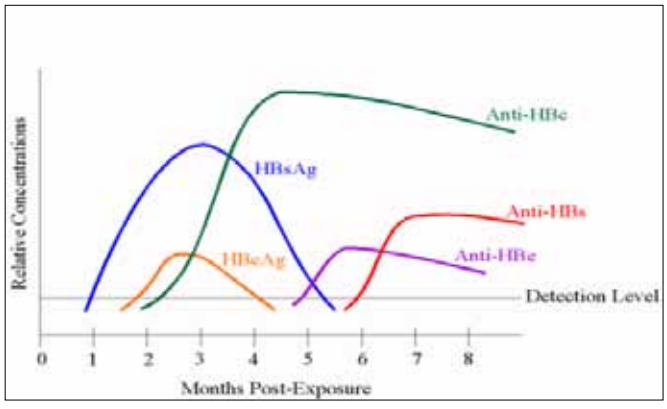


Fig 1. Serological patterns observed during acute Hepatitis B infection

CASE-BASED DISCUSSION – INFECTIVE HEPATITIS

AS Sahota

Discussion

Viral hepatitis encompasses a group of infections which are common and endemic in many countries worldwide (see Fig. 2). They are transmitted by a variety of modalities and have varying incubation periods. Acute infection can cause fulminant hepatic failure (uncommon), vague non-specific symptoms, or often be completely asymptomatic. Whilst some viruses cause self-limiting illness and clear spontaneously, leading to life-long immunity (Hepatitis A and E), others may go on to cause chronic infection (Hepatitis B and C). Left unrecognised and untreated, many years of "silent" chronic infection can lead to cirrhosis, hepatocellular carcinoma, and the spread of infection. This poses a significant public health problem. The diagnosis should always be considered in those from high-risk groups, and returning travellers with relevant symptoms and risk factors.

Fig 2. Prevalence of chronic infection with Hepatitis B virus, 2006[7]

In the case of the patient discussed, the most relevant issues were recognising the features of acute viral hepatitis, taking a thorough travel and sexual history, and assessing risk for public health and infection control. This facilitated appropriate investigations, a correct diagnosis of acute Hepatitis B, monitoring for complications, and prevention of spread. In this scenario the patient cleared his infection, but by ensuring adequate follow-up with specialist teams, the alternative outcome of chronic infection would be diagnosed and managed appropriately. It is essential to check for HIV co-infection in anyone infected with Hepatitis B.

Self Assessment Questions: Best-Of-Five

1) A 25-year-old lady attends a mobile service to donate blood. She has no significant medical history or symptoms, was born in Hong Kong and has been living in the UK for 10 years without any further travel abroad. Her mother died of "liver cancer". Routine blood tests are performed including a viral screen, and results are as follows:

- HBsAg positive; HbeAg negative; anti-HBe positive; IgG anti-HBc positive; anti-HBs negative
- Bilirubin 13, ALT 75, ALP 80, Albumin 34, INR 1.0

Which of the following statements is true?

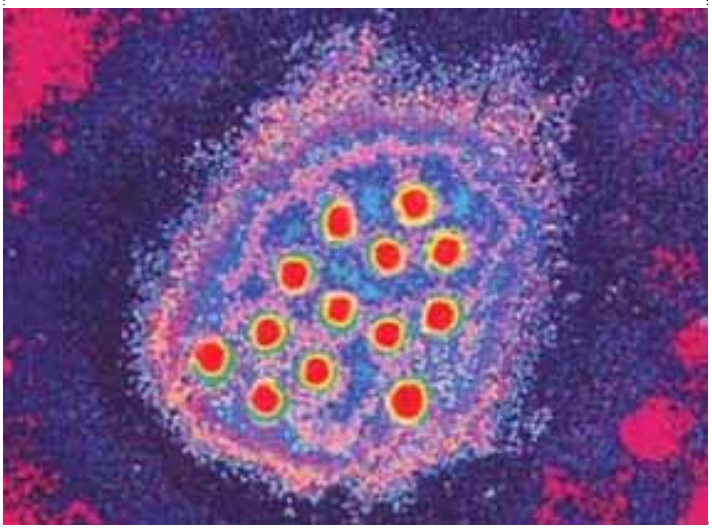
A. She has acute Hepatitis B with resolving liver inflammation
B. She has been vaccinated against Hepatitis B and is immune
C. She has chronic Hepatitis B with on-going liver inflammation
D. She is likely to have acquired Hepatitis B as an adult
E. She is not infectious to others

2) A 37-year-old Caucasian male prisoner is routinely screened for blood-borne infections whilst in prison. He is asymptomatic but suffers from hypertension. He has no significant family history and is married. On examination, the prison doctor notes palmar erythema and possible spider naevi. The blood results are as follows:

- HIV negative; Anti-Hepatitis C antibody positive
- HBsAg negative; IgG anti-HBc positive; anti-HBs positive
- Haemoglobin 13, Platelet count 95, Total white cell count 5.0
- Bilirubin 10, ALT 45, ALP 74, Albumin 25, INR 1.2

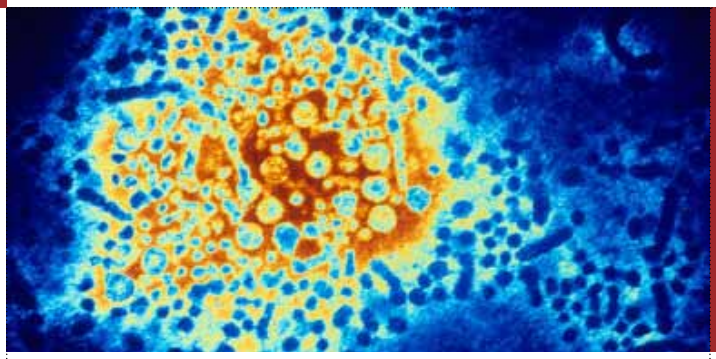
Which of the following statements is most likely to explain these findings?

A. He has acute Hepatitis C
B. He has chronic Hepatitis C with evidence of cirrhosis
C. He is likely to have acquired Hepatitis C sexually
D. He has been vaccinated against Hepatitis B and is immune
E. He has chronic Hepatitis B with evidence of cirrhosis



CASE-BASED DISCUSSION – INFECTIVE HEPATITIS

AS Sahota



Case-Based Discussion – Infective Hepatitis. Patient Management.

Answers

1) C. The history and serology suggests that this lady has chronic Hepatitis B, probably acquired in childhood either vertically or horizontally. Chronic Hepatitis B is endemic throughout China and South East Asia, and her mother probably died of related hepatocellular carcinoma. Unlike Hepatitis B acquired in adulthood, which becomes chronic in the minority, childhood acquisition usually becomes chronic and there is often no recollection of acute illness. The mildly raised ALT suggests on-going low-level hepatic inflammation, which could lead to cirrhosis if left unmanaged. This is not acute hepatitis as evidenced by the presence of IgG anti-HBc and by the lack of symptoms and transaminitis. With on-going infection she is clearly not immune. Although she is HBeAg negative and anti-HBe positive, she remains infectious to others but at a lower risk of transmission. She will need to be assessed further for possible treatment.

2) B. Blood-borne and sexually transmitted infection screens are often routinely performed in prisons due to a history of high-risk behaviour observed in the prison population. This man has evidence of cirrhosis both clinically and on blood tests (thrombocytopaenia, hypoalbuminaemia, coagulopathy), which is currently compensated and asymptomatic. As anti-Hepatitis C antibody is positive, chronic Hepatitis C is the likely cause of the cirrhosis. Unlike Hepatitis B, Hepatitis C leads to chronic infection in the majority. In the UK, intra-venous drug use and needle-sharing is the commonest method of acquisition, usually without distinguishable acute symptoms. Sexual transmission is rare, and there is no vaccination available. In the minority that clear the infection, antibody often remains positive life-long without conferring immunity, so this test cannot be used solely to diagnose current infection. Hepatitis C viral load needs to be detected in serum by polymerase chain reaction (PCR) to confirm the diagnosis and assess the need for treatment. Negative HBsAg in this man indicates that he does not have Hepatitis B. However, the presence of anti-HBs and IgG anti-HBc suggests previous Hepatitis B infection which has subsequently cleared, leading to life-long immunity. In the absence of previous infection, immunity can also be gained by Hepatitis B vaccination, which produces a protective anti-HBs response without any other positive serology.

Acknowledgement

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Author

Amandip Singh Sahota BMedSci, BMBS, DTM&H, MRCP (UK)
ST5 in Infectious Diseases / General Internal Medicine

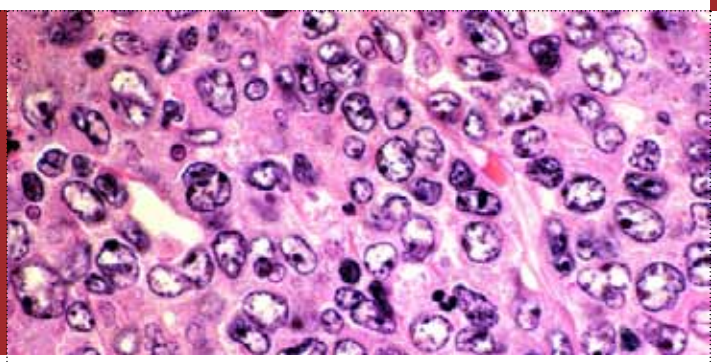
Corresspondance

Department of Infection and Tropical Medicine,
University Hospitals of Leicester NHS Trust,
Leicester Royal Infirmary,
Infirmary Square, Leicester, LE1 5WW
Email: ammo12345@hotmail.com

DIFFUSE LARGE B-CELL LYMPHOMA OCCURRING IN A PATIENT WITH HAIRY CELL LEUKEMIA AND PROSTATIC ADENOCARCINOMA: CASE REPORT AND LITERATURE REVIEW

G Anghel

Diffuse large B-cell lymphoma occurring in a patient with hairy cell leukemia and prostatic adenocarcinoma: case report and literature review. Patient Management.



A 75 year-old man with previous history of prostatic adenocarcinoma was referred for evaluation of pancytopenia in December 2006. A diagnosis of hairy cell leukaemia (HCL) was made. The patient was commenced 2 cloro-deoxyadenosine treatment, attaining a complete remission. Four months later he presented with inguinal & supraclavicular lymphadenopathy, and hypercalcemia. A lymph node biopsy revealed infiltration by diffuse large B cell lymphoma (DLBCL). Though HCL is associated with increase incidence of second malignancies, simultaneous occurrence of DLBCL and HCL remains an uncommon event. A literature review showed only 13 cases have been published to date. The origin and clonal relationship of heavy or light chains immunoglobulin gene's in the two pathologies is also discussed.

Hairy cell leukemia (HCL), initially described as histiocytic leukemia, malignant reticulosis, or leukemic reticuloendotheliosis, represents an uncommon lymphoproliferative disorder. It is defined by the clonal proliferation of abnormal lymphocytes with characteristic cytoplasmic projections, the "hairy cells" originating from a mature but not terminally differentiated activated B cell, and exhibiting specific monoclonal surface immunoglobulins.[1, 2]

It is typically a disease of middle aged males, having a male: female ratio of 4:1. It is characterized by pancytopenia, monocytopenia, splenomegaly but rarely lymphadenopathy. Typically "Hairy cells" express the B-cell activation markers CD103 (HML-1), CD11c, FMC7, CD25, and CD20 and CD22.[2] Association of HCL and other neoplastic disorders, namely high-grade lymphoma, although well described in the literature, remains quite rare [2 - 14]. We describe the case of a 74-year-old man admitted in December 2006 with a swelling of the right orbital region and a recent history of intermittent pyrexia, persistent fatigue, and anorexia. His long-term history was significant for prostatic adenocarcinoma diagnosed in April 2005, in remission after treatment with antiandrogen hormones and agonist analogues of luteinizing hormone–releasing hormone.

On examination, he was pyrexial at 38.2°C. He was pale and breathless. His right orbital region was erythematous and moderately swollen. Peri-orbital erysipelas was diagnosed. The chest and abdomen examination were unremarkable. Laboratory values showed pancytopenia: hemoglobin (Hb) 7.9 g/L; mean corpuscular volume (MCV) 81 fl; white blood cell count (WBC) 2.4 _ 10^9/L; neutrophils 1.25 _ 10^9/L; lymphocytes 0.95 _ 10^9/L; eosinophils 0.2 _ 10^9/L; and platelets 143 _ 10^9/L. Ferritin, serum vitamin B12, and serum folate were normal. A CT scan showed soft tissue swelling overlying the right eye and orbital region with mucosal thickening in the left maxillary antrum, but no signs of orbital collection. The spleen was normal, with no lymphadenopathy present.

A bone marrow aspirate and trephine showed extensive infiltration by a population of small lymphoid cells with the pathognomonic hairy cell appearance. Flow cytometry revealed expression of a monoclonal B cell population, CD19+ B cells, and the equivocal surface immunoglobulins (Igs) lambda and kappa +/-. The phenotype of this population was CD11c (strong), CD20+ (strong), CD22+, FMC7+, CD25+ (strong), CD79b+, CD103+, CD200+, CD5-, CD23-, and CD11a-. Based on these findings, a diagnosis of hairy cell leukemia was made.

The patient received a 7-day course of chemotherapy with 2-chlorodeoxyadenosine, (cladribine, 2CdA) at a dose of 0.1 mg/kg/day. He attainined a complete hematological remission (CR), as documented by a repeat bone marrow trephine April 2007.

In May 2007, he presented with an enlarged left supraclavicular lymph node and B symptoms (sweats, weight loss, anorexia?). The laboratory tests showed hypercalcemia at 3.2 mmoL/L, (normal range, 2.3–2.8 mmol/L), and LDH 764 U (normal range, 120–260 U). His full blood count and renal and liver function tests were within normal limits.

A CT scan performed showed enlarged supraclavicular, para-aortic, para-caval, and left iliac lymph nodes. Pathological examination of the 35-_-10-_-5–mm pieces of the left supraclavicular region lymph node revealed diffuse effacement of the normal architecture and replacement by sheets of large cells with poorly defined pale cytoplasm and one to three nucleoli (Fig. 1).

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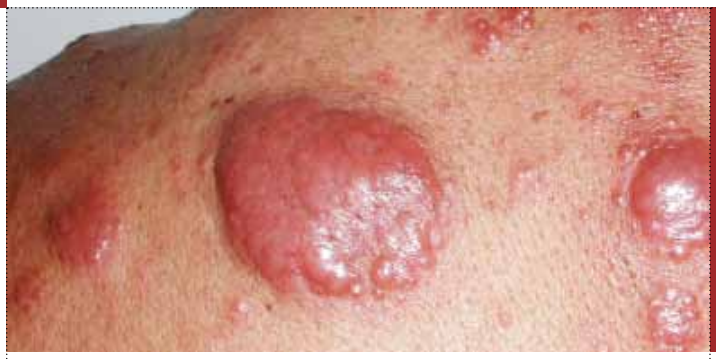

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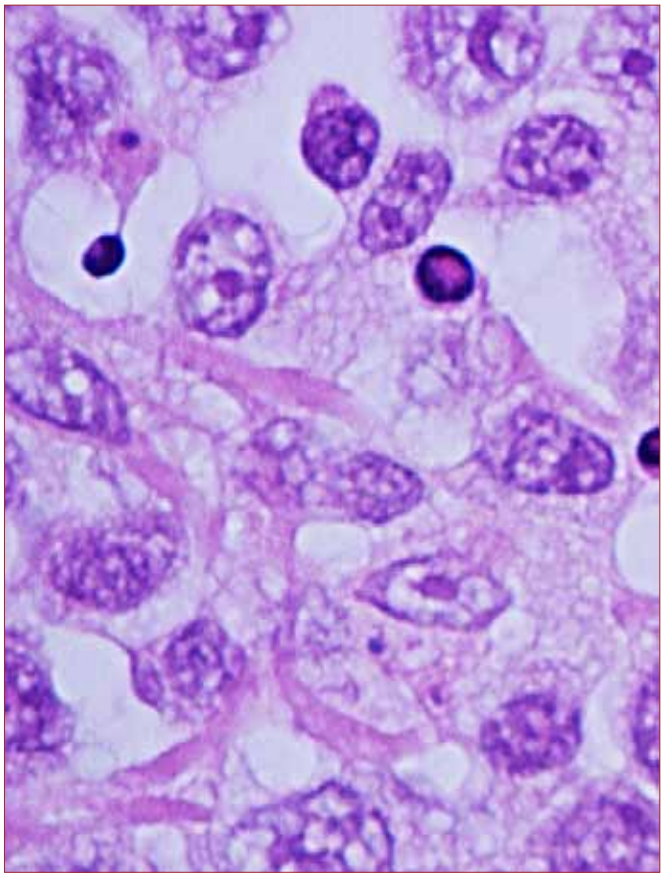

Figure 1. Inguinal lymph node biopsy, showing effacement of the nodal architecture by a diffuse infiltrate of large, pleomorphic lymphoma cells, with large nuclei, distinct nucleoli, and abundant, pale-staining cytoplasm (H&E, original magnification 400X).

Immunohistochemical staining showed the tumor cells to be CD20, CD79a, BCL2 positive. BCL6, and CD10 were negative. MUM1 and p53 were positive in 20% of cells. The proliferative fraction was high at approximately 60% MiB1 positive. The histological features were consistent with diffuse large B-cell lymphoma. The bone marrow aspirate and trephine performed afterward showed minimal infiltration by medium-large lymphoma cells. Studies of the Ig heavy and light chains completed on bone marrow mononuclear cells at later stage using DNA obtained by phenol/chloroform extraction as previously described 8 were unable to demonstrate the same clonal origin of HCL and NHL.

Treatment consisted of CHOP-R (Cyclophosphamide 750mg/sqm, Adriamycin 40 mg/sqm; vincristine 1.4 mg/sqm; prednisolone 100 mg/day for 5 days; and anti CD-20 monoclonal antibody (Mabthera®/Rituximab) for 6 courses). A repeat CT at treatment cessation indicated resolution of the lymphadenopathy, with a tiny residual soft-tissue thickening at the level of the aorta/IVC bifurcation. The results were interpreted as a very good partial response (vg-PR). Consolidation with two further weekly rituximab courses was then performed, and re-evaluation with GDP positron emission tomography (PET scan) is ongoing.

The outcome of HCL has changed significantly with the successful introduction of interferon and purine analogues 2. In addition, with cladribine, patients achieve a sustained complete remission in more than 90% of cases. With the prolonged survival, an increasing number of patients develop malignancies or neoplastic disorders concomitant or secondary to HCL [2-15].

Au et al. [15] demonstrated in a cohort of 117 patients affected by HCL that 30.7% had additional neoplastic disease, while 5% had two or more such disorders. In this study, adenocarcinoma of the prostate existed in eight cases (14.6%), two diagnosed concomitantly with HCL, and six after, at intervals between 3 and 143 months. Standardized incidence ratios to compare the cancer incidence in patients with HCL with that in the general population revealed a significantly higher incidence of prostatic cancers in patients with HCL. Other commonly associated neoplastic disorders were basal cell carcinoma (n=6) or adenocarcinoma of the lung, parotid, caecum, or breast (n=7). The rate of onset of second malignancies was highest in the period up to 2 years after diagnosis, supporting the hypothesis that the cancer risk might relate in part to HCL-associated immunosuppression. However, there are few reports of individual cases of an association of HCL and aggressive lymphoma [2-14].

Federico et al [16] in a large study on 1,136 HCL patients retrospectively analysed (1,022 evaluable) did not support the suspicion that HCL patients have an increased risk of secondary malignancies, although the incidence of non Hodgkin's lymphoma in the entire cohort was 5.3% (95% CI, 1.9 to 11.5) significantly higher than expected. Interferon treatment was not found to induce an oncogenic effect in HCL patients.

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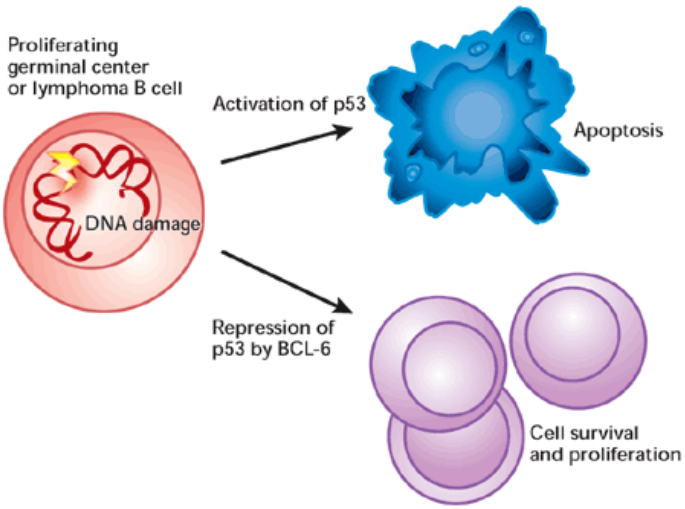

A literature review covering 1979 to 2007 identified 13 reported cases of simultaneous or sequential occurrence of HCL and high-grade lymphoma (Table 1). Median patient age was 62 years (11 males). In two cases [3, 10] the two pathologies were present together at onset; in the remaining patients the median interval between HCL and lymphoma onset was 78 months (range 9–144 months). Outcome data was available for 10/13 cases after a median follow-up of 28 months (range 1–120 months): death from disease progression (n=6); alive with disease (n= 3); and alive with no evidence of disease (n= 1). In three cases outcome and/or follow-up data was not available.

Author and citation number	Year of publication/Source	Age at HCL onset/Gender	_-HCL/NHL onset*	Outcome/F-up**
Adler SS [3]	1979/Cancer	65/F	S^	DDP/ N/A
Fransilla KO[4]	1979/Arch Path Lab Med	62/M	2 y	N/A
Vardiman JW [5]	1979/Cancer	57/M	5 mo	DDP/5 mo
Davis KM [6]	1985/Cancer	63/M	32 mo	DDP/3y
Downing JR [7]	1986/Blood	75/M	9 mo	AWD, 3mo
Arnalich F [8]	1987/Cancer	47/M	4 y	N/A, 4 y
Huang AT [9]	1987/Leukemia	59/M	9 y	DDP/9 y
Lawlor E [10]	1987/Cancer	65/F	S^	AND, 28 mo
Abbondanzo SL [11]	1991/Cancer	62/M	10 y	DDP/1 mo
Lopera GA [12]	1995/J Clin Gastroenterol	54 /M	12 y	AWD/6 mo
Nazeer T [13]	1997/Arch Pathol Lab Med	57 /M	15 mo	AWD /19 mo
Friedline JA [2]	1998/Mol Diagn	62/M	9 y	DDP, 10 y
Tsieh S [14]	2004/Human Pathol	43/M	4 y	N/A, 4 y

Table I. Patients with simultaneous or sequential occurrence of hairy cell leukemia and high-grade lymphoma: a literature review.

**_-NHL - on set: interval between HCL onset and aggressive (diffuse large cell lymphoma)*
*** Outcome/F-up, treatment results, as follows: AND, alive with no disease; AWD, alive with disease; DDP, dead from disease progression.*

F-up, follow-up; F, female; HCL, hairy cell leukemia; M, male; mo, months; N/A, not available; S^, simultaneous (this case represented a simultaneous presentation of HCL with classic B cells, and peripheral T-cell lymphoma with a mixed population consisting of large cleaved/non-cleaved cells with a high mitotic rate and smaller cells); y, years.

Clonality studies in various case reports have yielded conflicting results. Friedline *et al.* [2] described a case of HCL with blastic transformation arising 9 years after HCL onset. The blasts, studied both in bone marrow and peripheral blood, expressed CD34, a stem cell marker, suggesting high-grade transformation. Furthermore, the blast cell immunophenotype was similar to that of the HCL cells, but molecular studies revealed identical heavy- and light-chain gene rearrangement bands in both cell populations pre- and post-transformation.

A similar common origin of the two pathologies was reported in a patient with Ki-1–positive lymphoma developing 10 years after HCL diagnosis [12]. Lymphoma biopsy samples exhibited dual immunohistochemical staining of CD11c and CD22 (Leu 14). No molecular studies for Ig gene rearrangement were performed, but flow cytometry results suggested a common origin.

On the other hand, Downing *et al.* [7] documented a 75-year-old male with HCL who developed diffuse large B-cell immunoblastic lymphoma of the small-bowel 9 months after the initial diagnosis. The HCL expressed the HCL-specific antigens HC-1 and HC-2, which were not common to the lymphoma. Moreover, surface Immunoglobulin light chains were positive for kappa in the NHL only These results were interpreted either as indicating a separate clonal origin of the two malignancies or a clonal evolution of the HCL into the lymphoma. Two patients described in their literature review had concomitant HCL and high-grade lymphoma [3-10].

Hairy cell leukemia is considered to derive from clonal post-germinal center B cells, as documented by Ig gene rearrangement studies and by the somatic hypermutation analysis [1, 7].

The hypothesis that the second-onset cancer risk in these cases might relate in part to immunosuppression takes into consideration the time interval between neoplastic initiation and a clinically detectable tumoral burden, although a few reports describe secondary neoplasms occurring at much longer intervals [2, 12].

It is however to be outlined that most of the large cohort studies (Federico *et al* 16, Kurzock R [17] *et al,*) did not find a statistically significant incidence of secondary neoplasms in patients affected by HCL, apart from lymphoproliferative disorders (LPD). This association apparently was not associated with HCL therapy, either interferone alpha, 2CdA or deoxycoformicin (DCF). Further future molecular studies might be valuable in order to understand the pathway of interconversion from HCL into a LPD.

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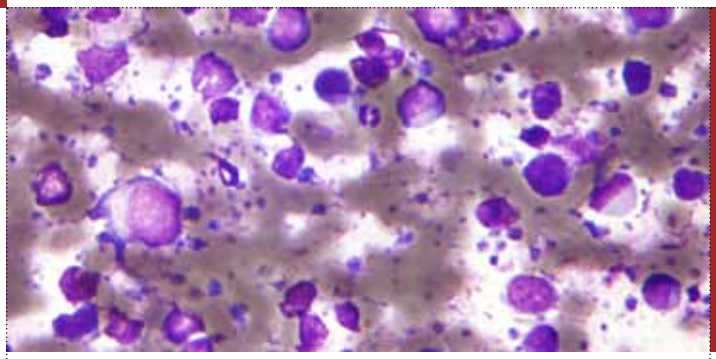

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Plausible mechanisms could arise from continuous antigenic stimuli (e.g., viral, bacterial), inducing further deregulation of the clonal Ig heavy-chain gene and oncogene rearrangements. The antigenic stimuli may induce B-cell proliferation in the pre-germinal center, followed by their transformation into activated pro-lymphocytes that dysregulate the immune response, or by further evolution of cells from germinal to post-germinal–centre cells.

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Author

G Anghel
Consultant Haematologist
United Lincolnshire Hospitals NHS Trust
Lincoln County, Hospital, Greetwell Road

Correspondance

G Anghel
Consultant Haematologist
United Lincolnshire Hospitals NHS Trust
Lincoln County, Hospital, Greetwell Road

A CAREER IN TROPICAL MEDICINE? A CAREER IN THE TROPICS?

N Prevatt

A career in Tropical Medicine? A career in the Tropics? Training & Teaching.

Many junior doctors are interested in Tropical medicine and want to work in a more 'needy' African setting. Dr natalie prevatt describes ways to take time out of UK speciality training.

For generations pioneering doctors have gone to the other 'side' of the world in search of adventure, armed with their medical degree and this daft desire to make a difference.... The question is; are you going to be one of them?

Motivation

In foundation training I was mocked for wanting to 'change the world' but now I have started my overseas work I find I am surrounded by people who understand and share my motives. What are my motives? They are complex, firstly a desire to treat sick needy patients rather than to stay here and be bogged down with interminable notes and word-processed discharge summaries. Secondly I wanted to see some tropical diseases, and thirdly, I wanted to experience other cultures- have some good old-fashioned adventure with like-minded people. My friends will say I wanted a tan.
You will have reasons of your own, and it's probably something you've thought about for a long time.

Taking time out... all about timing?

You will frequently hear about doctors who spent their whole junior career in the NHS waiting to go to work in Africa, but then got stuck at home with 2.4 children and a mortgage. Then there are those doctors who planned it for years only get to the developing world, sleep on the floor for a week and realise they hate it. For this reason I decided it was best to see if it was really what I wanted early on...

In 2008 The Gold Guide was published as a doctors reference guide to NHS Specialty Training (ST). The Gold Guide includes rules about time out of training to work abroad that had been recommended in the 2007 report by Lord Crisp. The Crisp report on 'Global Health Partnerships' discussed the UK's contribution to health in developing countries and identified that the NHS needs to give up its doctors both for long-term overseas work and for humanitarian aid crises. Lord Crisp also recommended that NHS pension contributions continued to be paid while doctors were working abroad, and that safeguards would eventually be put in place to ensure re employment of NHS staff when they returned. Of course we all have our sights set on ST training posts and the best way to ensure re employment as an ST trainee is to apply for an ST post and then defer entry or to start one and take time out from it at some point after ST1.

The Gold Guide allows time out of the ST program in any specialty for different reasons including time for research (OOPR), for career break (OOPC), for experience not available in the UK (OOPE) and for PMETB approved training overseas (OOPT). I took my time out as a career break (career break can be for anything- if you want to join the circus for a year you can!!) under the heading of a 'clearly identified life goal' because this seemed the easiest way to get to Africa at the time. With hindsight if I had gotten my jobs approved for training I could have been racking up years of my ST.

Despite the procedures in the Gold Guide some people have found it difficult to gain time out of training. This is because deaneries can refuse due to NHS service provision needs. If you are still in the foundation years it may be easier to take time out, and come back to start your speciality training later. It's all a gamble.

There are other ways to work overseas during UK training; because of the difficulties in finding PMETB accredited posts a few of the Royal Colleges have set up year abroad fellowship schemes which count toward ST training. There are also over 100 links between NHS local health authorities and hospitals overseas and you may go for short breaks to visit affiliated sites, usually as study leave.

A CAREER IN TROPICAL MEDICINE? A CAREER IN THE TROPICS?

N Prevatt

A career in Tropical Medicine? A career in the Tropics? Training & Teaching.

The Diploma in Tropical Medicine and Hygiene (DTMH)

There are two ways to go about learning tropical medicine; go to med school in a tropical country, or take the DTMH and learn all the things that are missed out of the UK curriculum.

This DTMH was originally designed to equip mission and army doctors but it now serves a really mixed bunch; from foundation doctors interested in global health to retired GP's looking for an adventure. To take the DTMH exams you now have to have been on a recognized course. I took mine earlier this year at the London School of Hygiene and Tropical Medicine (LSHTM). My life has changed so much since!

In the UK, different DTMH courses run from the London school, the Liverpool school, Sheffield and Glasgow.

The London School (LSHTM) course is 3 months full time, back to lectures 9-5. Lectures cover epidemiology, diagnosis and management of communicable and tropical diseases, under resourced chronic disease management, planning of health services, aid and development, entomology and parasitology, to name but a few. Lectures are of an incredibly high standard. Most lecturers are speaking on their area of specialisation, and are taking time off their day job to teach you; many are world authorities in their own sphere. As such the days are never boring, there is plenty of class discussion and tomfoolery. Ward rounds and Lab sessions reinforce what you have learnt in lectures.

The DTMH course at the London School (LSHTM) runs from 4th January to 31st March. The fees for 2010 are £4,750 (but don't forget the cost of living unpaid for 3 months) and these fees subsidise costs for some African doctors. The course is a multinational affair and you have a chance to make lifelong friends. A lovely side effect of the course is that 70 doctors of different ages and career paths arrive to live without their families and friends for 3 months in the big city. It makes for a great social life, like a second 'fresher's'!

A typical week on the London DTMH involved 3 days of lectures, one day in the practical lab learning; helminthology/entomology/protozoology/parasitology, and one day of small group teaching including some ward rounds.

Tutors are impressive yet down to earth and eager to help with career plans. Most learning takes place during the course hours - there are textbooks but I only used them for reference and to revise from. Days are packed and full of coffee, yet it is the only course I have been on where I desperately didn't want to miss lectures!

The London School exams are run by the Royal College of Physicians (RCP) and held on the last 3 days of March to coincide with the end of the course. They are paid for separately, and cost roughly £200. There are three written papers and one practical. The pass rate is very high.

The course is oversubscribed and places are on first come, first served basis with preference given to developing world candidates. It is advisable to apply early.

Another exciting possibility is that of taking the DTMH in a foreign country where all the diseases are readily available for your learning pleasure. Non RCP- accredited courses are currently available in Thailand and Peru, but the London School itself may be rolling out a new TMH course in East Africa in the next few years.

A CAREER IN TROPICAL MEDICINE? A CAREER IN THE TROPICS?

N Prevatt

Does the DTMH prepare you for a career overseas?

The DTMH tries to prepare you for work in an underdeveloped tropical setting. Although nothing may quite ready you for being left with a seriously ill patient and an out of stock cupboard, it is the best preparation available- I walked into the ward and saw a patient with onchocerciasis last week and I wondered how difficult it would be if I didn't know what that was!

Most NGO's require the DTMH qualification and a few years training in your chosen specialty. There are smaller charities that take foundation doctors and these see the DTMH as a definite bonus. Those who want to do expedition medicine or work for Raleigh International/ other eco-tour companies will find that the DTMH, combined with A and E experience will help get you onto their books!

At the end of the course LSHTM organises a careers fare where various NGO's and charities scout for employees. Most people take the rest of the year (at least!) to go abroad and consolidate their knowledge. I got a post in tropical research and my colleagues have been propelled down a variety of paths; from going back to NHS work, to working in tropical Australia, working in Africa and Asia for VSO/ MSF /Merlin, working in the media, sailing down the Amazon on a 5 man boat-clinic of doctors and dentists...

Does the DTMH prepare you for a career overseas only?

No. Tropical Medicine is a branch of Infectious Disease (ID) medicine in the UK, which is represented in the larger hospitals. The hospitals nearby airports in London do a roaring trade. There are ST rotations in London after core medical and ID training but places are minimal and it is obviously a popular choice. A good deal of medical research is hopefully going to focus on tropical neglected diseases in years to come, and experience of tropical medicine and work overseas is desirable to work for any of the large international agencies such as WHO/UN/Red Cross who also have some first world posts. Work overseas itself usually equips you with new skills and sets you well above your peers in terms of responsibility and management skills.

And finally, in future there may be an electronic exchange where requests for help and disaster relief can be matched to those wanting to volunteer, so that people with overseas experience can work in the NHS and dip out when they are desperately needed.

For DTMH at LSHTM: http://www.lshtm.ac.uk/prospectus/short/stmh.html

For RCP: http://www.rcplondon.ac.uk

For overseas career help: http://www.almamata.net/news/careers

For Gold Guide: http://www.mmc.nhs.uk

For Crisp report: http://www.dh.gov.uk/en/Publicationsandstatistics

Author

Natalie Prevatt, MBbCH, DTMH
ST2 Paediatric Trainee
London Deanery

Corresspondance

Natalie Prevatt
drnatprevatt@hotmail.com

Dr Prevatt is a Wales Deanery Paediatric trainee who is taking an extended career break to work in Africa. She has completed the Diploma in Tropical Medicine and Hygiene and is currently studying for the Diploma of Paediatric Infectious Disease. She is now working as a Research Fellow for Imperial College London in East Africa.

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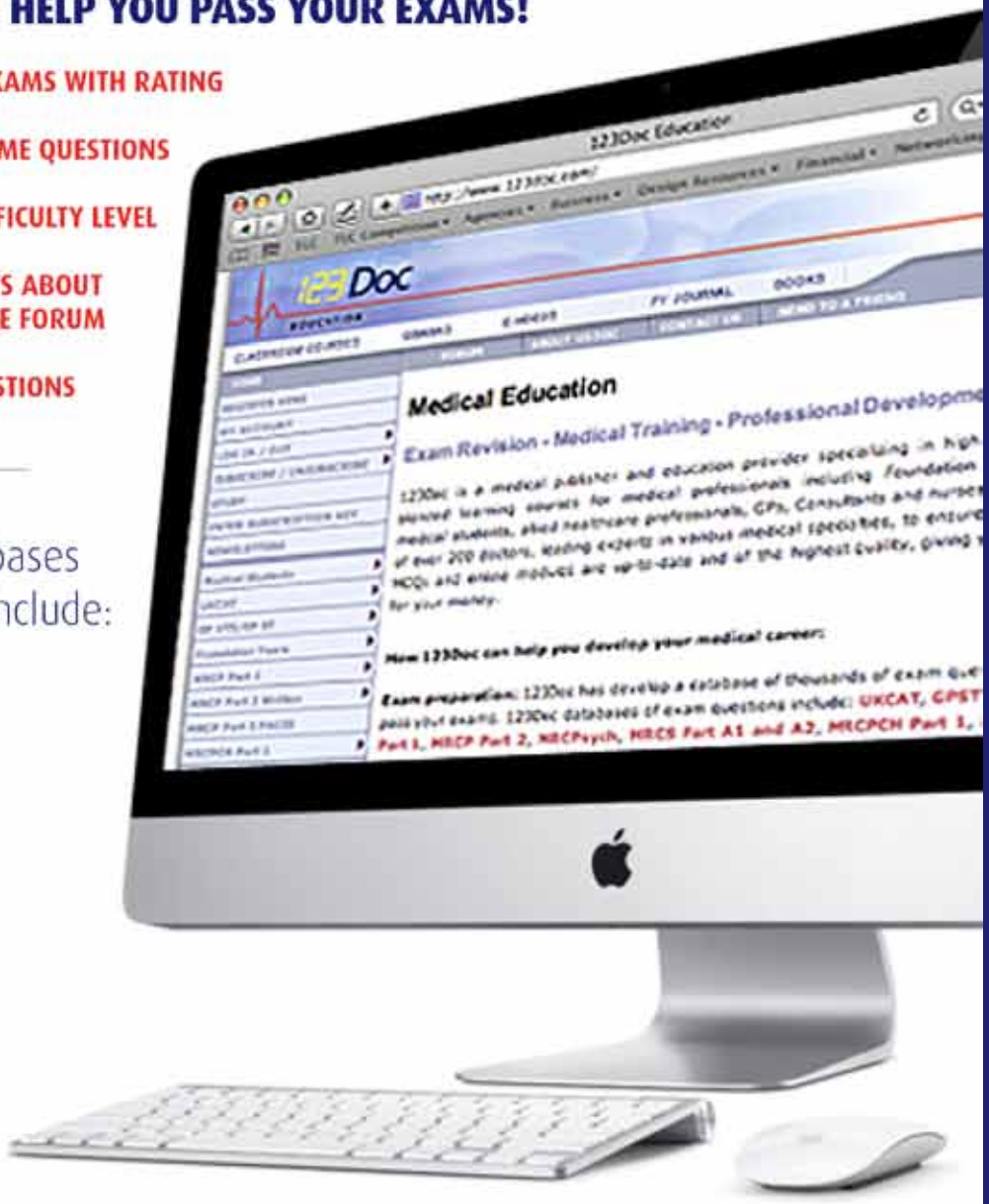

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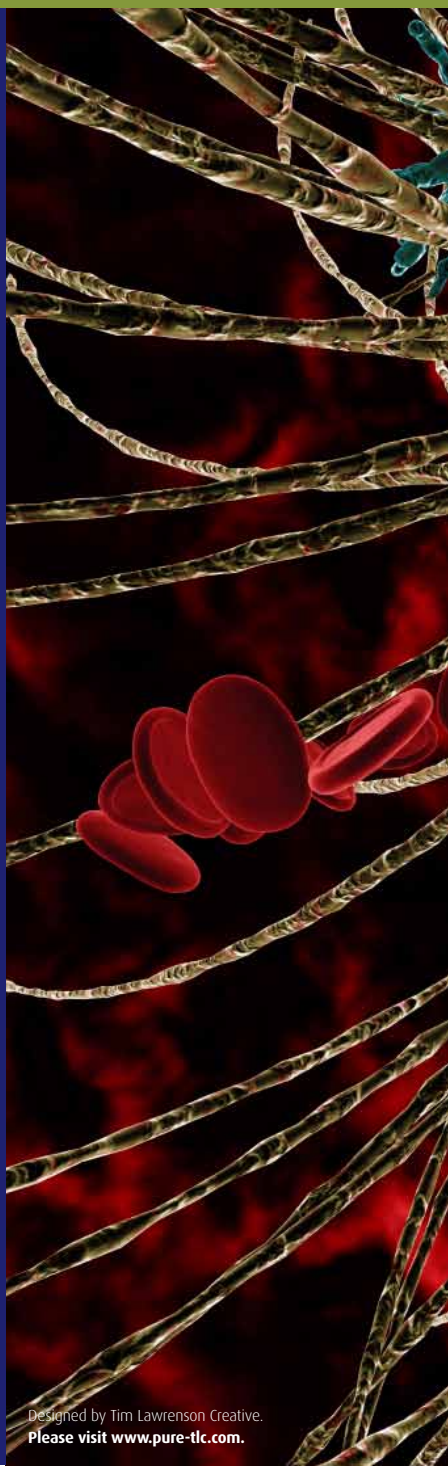

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