RATIONAL TESTING

Investigating recurrent respiratory infections in primary care

Philip Wood,[1] Daniel Peckham[2]

Repeated respiratory tract infections in an apparently otherwise well young person should raise suspicions of underlying immunodeficiency or other respiratory disease

[1]Department of Clinical Immunology, St James's University Hospital, Leeds LS9 7TF
[2]Department of Respiratory Medicine, St James's University Hospital
Correspondence to: P Wood
philip.wood@leedsth.nhs.uk

Cite this as: *BMJ* 2009;339:b4118
doi: 10.1136/bmj.b4118

This series of occasional articles provides an update on the best use of key diagnostic tests in the initial investigation of common or important clinical presentations. The series advisers are Steve Atkin, professor, head of department of academic endocrinology, diabetes, and metabolism, Hull York Medical School; and Eric Kilpatrick, honorary professor, department of clinical biochemistry, Hull Royal Infirmary, Hull York Medical School

The patient

A 29 year old man presents to the surgery with a third episode of respiratory tract infection in three months, having had one admission to hospital with proved pneumococcal pneumonia five months ago. He is a previously well non-smoker who does not have asthma, any previous diagnosed chronic medical condition, or recent history of foreign travel.

He has no weight loss or night sweats. On examination he has bilateral basal crackles in the lungs, normal tympanic membranes, no facial tenderness, and no lymphadenopathy or splenomegaly. A full blood count is normal; random and fasting blood glucose, urea, creatinine, and liver enzymes are all normal, and urinalysis is negative for blood and protein. Sputum culture identifies the presence of *Haemophilus influenzae.* A chest radiograph is reported as normal.

What is the next investigation?

In 2007 the reported prevalence for acute respiratory infections in the United Kingdom was 1599/10 000 population, with peaks in early childhood and in people over 75 years of age. In contrast, the reported prevalence for pneumococcal pneumonia, and for pneumonia due to other causes, was 2/10 000.[1] Upper respiratory tract infections are therefore common but are highly unlikely to indicate an underlying medical condition when they occur in isolation. There are no data on what constitutes a "normal" frequency of respiratory infections, and the characteristics of episodes of infection need to be considered.

Patients may have concerns over recurrent infections and their immunological competence. When infections are severe, persist despite standard therapy, recur after treatment is finished or at an unexpected frequency, or where the isolated organism is unusual within the clinical context, further investigation for underlying causes is warranted. Outside these situations, immunodeficiency is unlikely.

Repeated infections with encapsulated bacterial pathogens such as *Haemophilus influenzae* and *Streptococcus pneumoniae* are common in chronic obstructive pulmonary disease, asthma, and bronchiectasis. *H influenzae* is a common cause for community acquired pneumonia, but recurrent infections are unusual in a young, healthy non-smoker. Thus repeated infections with these organisms should prompt investigations for possible underlying immunodeficiency.

When evaluating patients with recurrent infection, use the acronym SPUR (severe, persistent, unusual, or recurrent) to prompt appropriate investigations for underlying causes. In this case scenario, chronic medical conditions such as diabetes or renal disease, which are associated with an increased tendency to recurrent infection, are effectively excluded by appropriate initial laboratory investigations. The clinical picture does not suggest immunodeficiency involving cellular immunity (most commonly resulting from infection with HIV), although a history of high risk sex or of misuse of intravenous drugs may indicate the need for screening. Secondary antibody deficiencies result most commonly from immunosuppression in lymphoid malignancy or more rarely from protein loss from either the renal or gastrointestinal tracts. Lymphoid malignancies should be considered but are unlikely in the absence of weight loss, fevers, lymphadenopathy, or splenomegaly and with a normal full blood count. The primary antibody deficiency syndromes are a group of rare disorders with a prevalence of around 1 in 50 000 which can present at any age and are characterised by the inability to produce clinically effective antibody responses to infection. With these disorders, delay in diagnosis remains a problem and contributes to chronic disease.[2]

Measurement of serum immunoglobulins

When recurrent upper or lower respiratory tract infections seem unusual and when there are no obvious predisposing factors, serum immunoglobulins are important investigations to add to other baseline tests in order to exclude an antibody deficiency state as a cause for respiratory tract infections (table). The serum concentrations of the major serum immunoglobulin classes (IgG, IgA, and IgM) are age related, and in current definitions of primary antibody deficiency, two of these immunoglobulins are more than two standard deviations below the reference range for the testing laboratory.[3] Measurement

Reported incidence of the common primary and secondary causes of hypogammaglobulinaemia

Condition	Population incidence (per 100 000)	Comments
Primary[10]:		
Common variable immunodeficiency disorders	1.7	Presentation at all ages
Secondary[11]:		
Chronic lymphocytic leukaemia	4.1	Rare under age 50
Myeloma	6.3	<2% under age 40 at diagnosis
Non-Hodgkin's lymphoma (all types)	16.7	Low grade disease presenting with secondary hypogammaglobulinaemia; rare under age 30

LEARNING POINTS

When evaluating a patient with recurrent infection, consider the acronym SPUR (severe, persistent, unusual, or recurrent) to prompt investigations for underlying causes

In unusual recurrent upper or lower respiratory tract infections with no obvious predisposing factors, check serum immunoglobulin (IgG, IgA, and IgM) and carry out electrophoresis of serum and urine as well as baseline investigations such as fasting serum glucose, full blood count, and renal function

The primary antibody deficiency syndromes are a group of rare disorders characterised by the inability to produce clinically effective antibody response to infection—delay in diagnosis remains a problem and contributes to chronic disease

Recurrent lower respiratory tract infections in a young person with normal immunoglobulin concentrations and electrophoresis results should prompt referral to a respiratory physician to exclude respiratory disease such as bronchiectasis and cystic fibrosis

of serum immunoglobulins is a relatively inexpensive test for this group of disorders. Patients with low concentrations of immunoglobulin are at risk of life threatening infection with encapsulated bacteria, particularly pneumonia,[4 5] and should be referred to a clinical immunology service for further evaluation and management. Although the lower limits of reference ranges vary with age and between laboratories, most patients subsequently diagnosed with primary antibody deficiency have an IgG concentration ≤3 g/l, with an IgA concentration < 0.1 g/l, and an IgM concentration <0.25 g/l,[6 7] and over 90% of patients with the commonest type of antibody deficiency, common variable immunodeficiency, have an IgG concentration <4.5 g/l at diagnosis.[8] These levels are considerably below standard age related reference ranges.

Some people with recurrent sinopulmonary infections have immunoglobulin levels only marginally below standard reference ranges. Further investigations may be required to elucidate the reason for recurrent infections, but patients can have greatly reduced humoral immunity without marked reduction in serum immunoglobulins. In these situations, clinical advice should be sought from a medical immunologist experienced in assessing such patients.

Serum and urine electrophoresis

Serum and urine electrophoresis should be requested in adults to screen for the presence of serum paraproteins or urinary free light chains. These indicate monoclonal immunoglobulin production, which occurs in conditions such as myeloma, low grade B cell non-Hodgkin's lymphoma, and other B cell lymphoproliferative disorders (table). Secondary hypogammaglobulinaemia can occur in these conditions and in chronic lymphocytic leukaemia, resulting in recurrent infections. Such diseases would be unusual at the age of the patient in this case, but incidence increases with advancing age, and these diseases should be excluded in people over 40.

Specialist respiratory evaluation

Repeated respiratory tract infections in an apparently otherwise well young person should also raise suspicions of other respiratory disease such as bronchiectasis, cystic fibrosis, and ciliary dyskinesia. It is essential to take a detailed medical history, with special attention to childhood illnesses such as early childhood pneumonia, pertussis, and measles, as these may increase the likelihood of bronchiectasis.[9] Family history should note the presence or absence of inherited diseases such as cystic fibrosis. Other clinical features that should alert clinicians to a respiratory cause for recurrent infections are a constant runny nose, chronic rhinitis, nasal polyps, sinusitis, agenesis of the frontal sinuses, recurrent ear infections, and deafness. Referral to respiratory services should be undertaken for further specialised investigations if serum immunoglobulin concentrations are normal and there is no evidence of serum or urine free light chains.

Outcome

Measurement of serum immunoglobulin in this man showed markedly reduced concentrations of IgG, IgA, and IgM with normal serum and urine electrophoresis. On the basis of these investigations he was referred to the nearest regional clinical immunology service. A diagnosis of a common variable immunodeficiency disorder (CVID) was made on the basis of a typical clinical history associated with hypogammaglobulinaemia and exclusion of other genetically defined primary antibody deficiencies.

Such patients typically have structural lung damage secondary to repeated infections, and high resolution computed tomography of the chest showed minor bronchiectasis. The patient started intravenous immunoglobulin replacement therapy in hospital. After appropriate training he now self administers immunoglobulin by the subcutaneous route at home. He has been taking this treatment for two years and has had no progression of bronchiectasis; he continues to work and leads a full, productive life. A shared care arrangement between his general practitioner and the clinical immunology service ensures prompt treatment of infections and investigation of potential complications of his condition.

The website of the United Kingdom Primary Immunodeficiency Network (www.ukpin.org.uk) provides information and diagnostic algorithms for primary immunodeficiencies.

Contributors: Both authors contributed to the preparation of the manuscript; PW is guarantor.

Competing interests: None declared.

Provenance and peer review: Commissioned; externally peer reviewed.

Patient consent not required (patient anonymised, dead, or hypothetical).

1 Royal College of General Practitioners Birmingham Research Unit. *Annual prevalence report 2007*. London: RCGP, 2007.
2 Wood P, Stanworth S, Burton J, Jones A, Peckham DG, Green T, et al. Recognition, clinical diagnosis and management of patients with primary antibody deficiencies: a systematic review. *Clin Exp Immunol* 2007;149:410-23.

3 Notarangelo L, Casanova JL, Conley ME, Chapel H, Fischer A, Puck J, et al. Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee Meeting in Budapest, 2005. *J Allergy Clin Immunol* 2006;117:883-96.
4 Aghamohammadi A, Moin M, Farhoudi A, Rezaei N, Pourpak Z, Movahedi M, et al. Efficacy of intravenous immunoglobulin on the prevention of pneumonia in patients with agammaglobulinemia. *FEMS Immunol Med Microbiol* 2004 8;40:113-8.
5 Busse PJ, Razvi S, Cunningham-Rundles C. Efficacy of intravenous immunoglobulin in the prevention of pneumonia in patients with common variable immunodeficiency. *J Allergy Clin Immunol* 2002;109:1001-4.
6 Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. *Clin Immunol* 1999;92:34-48.
7 Kainulainen L, Nikoskelainen J, Ruuskanen O. Diagnostic findings in 95 Finnish patients with common variable immunodeficiency. *J Clin Immunol* 2001;21:145-9.
8 Chapel H, Lucas M, Lee M, Bjorkander J, Webster D, Grimbacher B, et al. Common variable immunodeficiency disorders: division into distinct clinical phenotypes. *Blood* 2008;112:277-86.
9 Pasteur MC, Helliwell SM, Houghton SJ, Webb SC, Foweraker JE, Coulden RA, et al. An investigation into causative factors in patients with bronchiectasis. *Am J Respir Crit Care Med* 2000;162:1277-84.
10 Joshi AY, Iyer VN, Hagan JB, St Sauver JL, Boyce TG. Incidence and temporal trends of primary immunodeficiency: a population-based cohort study. *Mayo Clin Proc* 2009;84:16-22.
11 Cancer Research UK. *CancerStats: incidence—UK, 2008*. http://publications.cancerresearchuk.org/WebRoot/crukstoredb/CRUK_PDFs/CSINC08.pdf

INTERACTIVE CASE REPORT

A woman with acute myelopathy in pregnancy: case presentation

Reinhard Reuß,[1] Paulus S Rommer,[1] Wolfgang Brück,[2] Friedemann Paul,[3 9] Michael Bolz,[4] Sven Jarius,[5] Tobias Boettcher,[6] Annette Großmann,[7] Alexander Bock,[8] Frauke Zipp,[9] Reiner Benecke,[1] Uwe K Zettl[1]

[1]Department of Neurology, University of Rostock, 18147 Rostock, Germany
[2]Institute of Neuropathology, University Medical Center Göttingen, Göttingen, Germany
[3]NeuroCure Clinical Research Center, Charité Universitätsmedizin Berlin, Berlin, Germany
[4]Department of Gynaecology, University of Rostock
[5]Division of Molecular Neuroimmunology, Department of Neurology, University of Heidelberg, Heidelberg, Germany
[6]Neurology Division, Dietrich-Bonhoeffer Klinikum Neubrandenburg, Neubrandenburg, Germany
[7]Department of Radiology, University of Rostock
[8]Neuroradiology Division, Dietrich-Bonhoeffer Klinikum Neubrandenburg
[9]Cecilie-Vogt Clinic for Neurology, Charité-Universitätsmedizin, Berlin

Correspondence to: R Reuß
reinhard.reuss@neuro.med.uni-giessen.de

Cite this as: *BMJ* 2009;339:b3862
doi: 10.1136/bmj.b3862

This is the first of a three part case report where we invite readers to take part in considering the diagnosis and management of a real patient using rapid responses on bmj.com. In four weeks' time we will report the outcome and summarise the responses

In March 2006, Andrea G, a 23 year old white nulliparous woman who was 17 weeks pregnant, was referred to her local neurology department. She had been experiencing hypoaesthesia of the right leg for seven days and of the left leg for two days. Since the previous day she had also been experiencing a focal weakness of the left leg and an inability to void her bladder adequately.

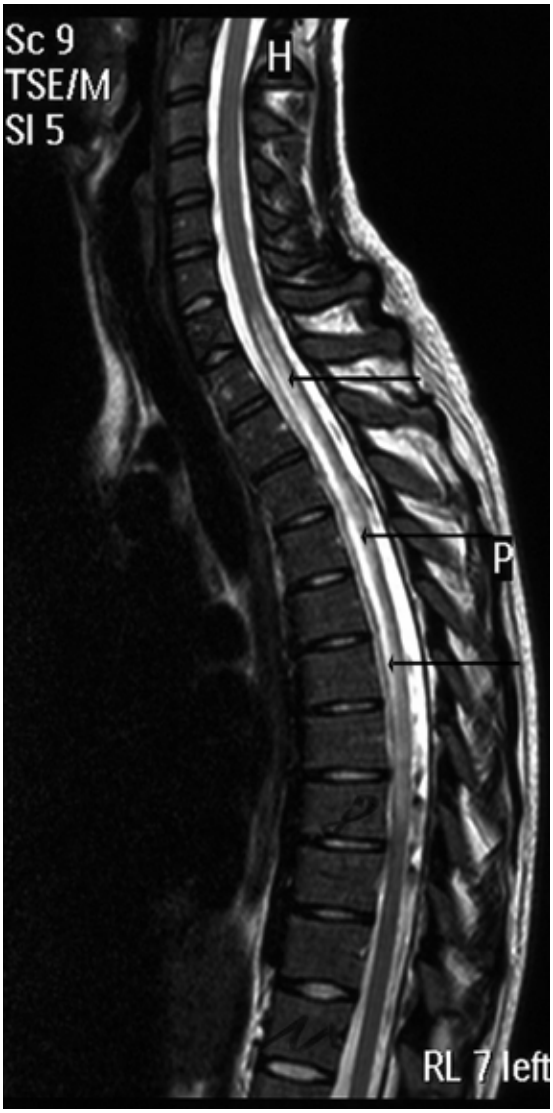
One month earlier she had experienced back pain, which was relieved by physiotherapy. For the past 14 days, she had again been experiencing lumbar pain and pain of the left shoulder. Cardiopulmonary and abdominal examinations showed no abnormality, and her body temperature was within the normal range. She had a hypotonic paraparesis of the legs accentuated on the left side, with bilaterally exaggerated tendon reflexes, non-sustained cloniform Achilles' tendon reflexes, and a normal plantar reflex. Her pain and temperature sensations were diminished on the right from T8 dermatome distally; vibration and position sensation were normal. Anal sphincter tone was normal. She had no meningism. Her mood was slightly depressed.

Urine culture showed urinary tract infection with *Escherichia coli* and *Klebsiella pneumoniae*. Cerebrospinal fluid analysis showed no evidence of infection (table). Visual evoked potentials were normal.

QUESTIONS

1 What diagnoses might explain the patient's presentation and the neurological abnormalities that were found?
2 What could account for her magnetic resonance imaging results?
3 What additional diagnostic tests would you suggest?
4 Could pregnancy have a role in her symptoms?

Please respond through bmj.com, remembering that the patient is real and that she and her carers will read the response



MRI (T2 weighted) showing symmetric spinal cord lesions (arrows) extending from C7 to T8

Results of Mrs G's cerebral spinal fluid and serum analysis at presentation

Test	Result	Normal range
Cerebral spinal fluid		
Total cell count (×10⁶/l)	7	<5
Differential cell count (%):		
Lymphocytes:	61	60-70
Activated	3	0
Monocytes:	5	30-50
Activated	3	0
Segmented granulocytes	27	0-3
Eosinophilic granulocytes	1	Rarely detected
Erythrocytes	0	0
Total protein (mg/l)	520	150-450
Oligoclonal bands	Negative	Negative
Intrathecal IgG synthesis	Negative	Negative
Intrathecal IgM synthesis	Negative	Negative
Intrathecal IgA synthesis	Negative	Negative
Glucose (mmol/l)	3.0	2.5-3.9
Lactate (mmol/l)	2.7	1.2-2.1
Serum		
Leucocytes (×10⁹/l)	17.8	4.3-10.0
C reactive protein (mg/l)	10.1	<5
Alanine aminotransferase (U/l)	0.61	0-23
Total protein (g/l)	57.9	55-80

T2 weighted magnetic resonance imaging (MRI) of the spinal cord showed central symmetric lesions spanning from cervical level 7 (C7) to T8, enhancing between T2 and T7 (figure), and excluded a compressive cause. Cranial MRI showed a pineal cyst. MRI in the emergency department had indicated vascular malformation as the reason for her clinical symptoms, but spinal angiography showed no evidence of vascular malformation or occlusion as other non-compressive causes of acute myelopathy. Although fetal organogenesis was complete, Mrs G consented to termination of the pregnancy on medical grounds after being counselled about the risk to the fetus from the high x ray load of procedures such as spinal angiography and use of contrast agent.

We thank A Bock for providing the figure.

Competing interests: None declared.

Patient consent obtained.

Provenance and peer review: Not commissioned; externally peer reviewed.

Accepted: 14 August 2009

LESSON OF THE WEEK

Colonic carcinoma presenting as repeated episodes of enterobacter septicaemia during induction of remission in acute myeloblastic leukaemia

Bassam Odeh,[1] David Bareford[2]

During neutropenic episodes, recurrent septicaemia with gut bacteria should prompt suspicion of underlying gut pathology

[1]Department of Haematology, City Hospital, Birmingham B18 7QH

[2]Department of Haematology, Russells Hall Hospital, Dudley DY1 2HQ

Correspondence to: D Bareford, d.bareford@bham.ac.uk

Cite this as: *BMJ* 2009;339:b4027
doi: 10.1136/bmj.b4027

Patients undergoing curative treatment for acute leukaemia receive several cycles of combination chemotherapy using intravenous cytotoxic drugs given through central venous catheters. As a side effect, each period of treatment is followed by a pancytopenic phase lasting between two and four weeks, when haemoglobin, white cells, and platelets reach very low levels. During this period transfusions of blood and platelets are needed. If the patient becomes pyrexial (neutropenic fever) blood cultures are taken and broad spectrum antibiotics are started while awaiting specific identification of the cultured organism and its sensitivity to antibiotics. Over the past two decades the most common organisms isolated have been Gram positive bacteria, often in relation to the use of central venous catheters.[1] *Staphylococcus epidermidis* is frequently isolated and responds to vancomycin or teicoplanin. Repeated isolation of Gram positive organisms in blood culture often leads to removal of the central line with resolution of the problem. Repeated blood cultures positive for Gram negative organisms are very rare. We report a case in which repeated isolation of a Gram negative organism commonly found in the large bowel eventually led to the identification of a colonic neoplasm.

Case report

A white man aged 60 presented to his general practitioner with tiredness and lethargy. A full blood count indicated acute myeloid leukaemia with a haemoglobin level of 55 g/l, white blood cell count of 8×10^9/l, platelet count 35×10^9/l, and a peripheral blood film showing the presence of myeloblasts. He was promptly admitted for further investigation and treatment.

His symptoms on admission were feeling unwell and profoundly tired. He had also noted a small fine rash on his legs. He had occasionally noted recent small amounts of rectal bleeding but on direct questioning reported no constipation, melaena, or change in his bowel habit.

On examination the patient was pale, apyrexial, and normotensive. Lymphadenopathy and organomegaly were not present but petechiae were noted on both legs.

Results of liver and renal function tests, lactate dehydrogenase, and coagulation screen were normal. Bone

marrow morphology and immunophenotyping were consistent with acute myeloblastic leukaemia. Molecular studies and cytogenetics confirmed acute myeloblastic leukaemia (WHO classification—acute myeloid leukaemia with t(8;21)(q22;q22) (AML1/ETO)).[2]

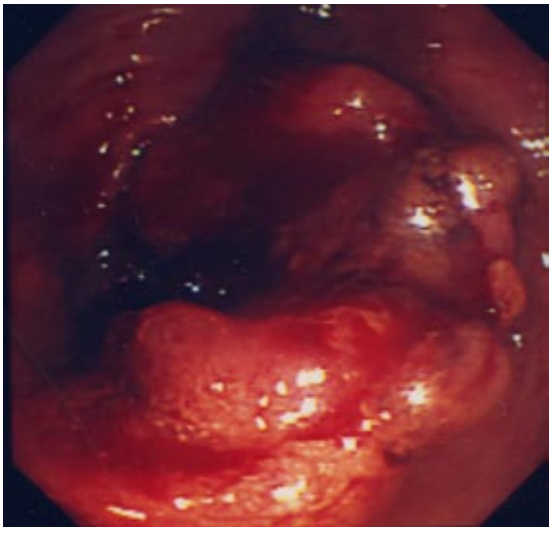
The patient consented to enter the current MRC/AML15 trial (www.aml15.bham.ac.uk, ISRCTN 17161961) and after insertion of a central venous catheter he underwent cyclical chemotherapy. The first cycle consisted of daunorubicin and cytarabine administered intravenously over ten days with gemtuzumab ozogamicin. After recovery of blood counts he proceeded to the second cycle of daunorubicin and cytarabine over eight days, followed by two further cycles of high dose cytarabine as consolidation. His treatment was completed within six months. He entered complete haematological remission after the first two courses but molecular analysis indicated minimal residual disease at the molecular level after completion of the fourth cycle.

After the first cycle of treatment his neutrophil count fell as expected and during this period of neutropenia (at a neutrophil count of less than 0.02×10^9/l) he developed a Gram negative septicaemia with a species of enterobacter. He responded promptly to meropenem and gentamycin. After the second cycle of chemotherapy he again developed a neutropenic sepsis (at a neutrophil count of 0.05×10^9/l) and blood culture grew the same species of enterobacter. This episode responded promptly to the same intravenous antibiotics.

Septicaemia with the same species of Gram negative organism developed again during the neutropenic period associated with the third and fourth cycles of chemotherapy, and both these episodes also responded promptly to intravenous antibiotics.

This pattern led to a suspicion that underlying gut pathology was causing these repeated episodes, because the organism was likely to be emanating from his gut bacterial flora. The patient was therefore referred to the gastroenterology team for further investigation once he had completed consolidation chemotherapy.

A colonoscopy revealed a moderately differentiated adenocarcinoma of the sigmoid colon (fig). The patient subsequently underwent anterior resection of the rectosigmoid junction without complications. However, staging computed tomography showed a suspicious lesion in the posterior aspect of the right lobe of the liver. The patient eventually had a hemihepatectomy two months later, and the liver lesion turned out to be benign. The patient remains in remission from acute leukaemia and carcinoma of the colon four years later.



Adenocarcinoma of colon seen at colonoscopy

Discussion

This case was different from usual cases of febrile neutropenic episodes after chemotherapy in that an organism was quickly isolated during each episode, was always of the same species, and was a gut associated Gram negative bacteria. A review of 58 patients with acute leukaemia undergoing 119 chemotherapy cycles with a central venous catheter reported that fever occurred in 73% of cycles.[3] Bloodstream infection was proven in 26% of cases with 77.5% Gram positive and 20% Gram negative bacteria (the remaining 2.5% was a case of *Candida* infection). In the case report described above, to isolate the same enterobacter species on four separate occasions without any other type of febrile episode or organism being isolated is quite rare.

The connection between colonic carcinoma and bacteraemia from a gut organism (*Streptococcus bovis*) causing infective endocarditis[4-6] or septicaemia[7-10] suggested the possibility that these repeated episodes might be related to gut pathology. Therefore, although the patient had no specific bowel symptoms before the onset of the acute leukaemia, we investigated his lower gastrointestinal tract. Colonic pathology should be considered when patients undergoing neutropenic episodes have repeated bloodstream infections with a gut bacterial isolate.

Contributors: Both authors contributed equally to the management of the patient and researching and writing the article.

Competing interests: None declared.

Provenance and peer review: Not commissioned, externally peer reviewed.

Patient consent obtained.

1 Rubio M, Palau L, Vivas JR, del Potro E, Diaz-Mediavilla J, Alvarez A, et al. Predominance of gram-positive microorganisms as a cause of septicemia in patients with hematological malignancies. *Infect Control Hosp Epidemiol* 1994;15:101-4.
2 Vardiman JW, Harris NL, Brunning RD, The World Health Organization (WHO) classification of the myeloid neoplasms. *Blood* 2002;100:2292-302.
3 Karthaus M, Doellmann T, Klimasch T, Krauter J, Heil G, Ganser A. Central venous catheter infections in patients with acute leukemia. *Chemotherapy* 2002;48:154-7.
4 Leport C, Bure A, Leport J, Vilde JL. Incidence of colonic lesions in *Streptococcus bovis* and enterococcal endocarditis. *Lancet* 1987;1:748.
5 Waisberg J, Matheus C de O, Pimenta J. Infectious endocarditis fom Streptococcus bovis associated with colonic carcinoma: case report and literature review. *Arq Gastroenterol* 2002;39:177-80.
6 Beeching NJ, Christmas TI, Ellis-Pegler RB, Nicholson GI. Streptococcus bovis bacteraemia requires rigorous exclusion of colonic neoplasia and endocarditis. *Q J Med* 1985;56:439-50.
7 Friedrich IA, Wormser GP, Gottfrid EB. The association of remote Streptococcus bovis bacteremia with colonic neoplasia. *Am J Gastroenterol* 1982;77:82-4.
8 Tabibian N, Clarridge JE. Streptococcus bovis septicemia and large bowel neoplasia. *Am Fam Physician* 1989;39:227-9.
9 McMahon AJ, Auld CD, Dale BA, Walls AD, McCormick JS. Streptococcus bovis septicaemia associated with uncomplicated colonic carcinoma. *Br J Surg* 1991;78:883-5.
10 Varghese GM, Shenoy M, Subramanian S, Peter S, Mathai D. Colonic malignancy with recurrent bacteraemia presenting as pyrexia of unknown origin. *J Int Med* 2004;255:692-3.

Accepted: 3 November 2008