Investigating recurrent respiratory infections in primary care

Philip Wood,1 Daniel Peckham2

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

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, 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
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, 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, 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. 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. 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.

**Provenance and peer review:** Commissioned; externally peer reviewed.

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

A woman with acute myelopathy in pregnancy: case presentation

Reinhard Reuß,1 Paulus S Rommer,1 Wolfgang Brück,2 Friedemann Paul,3 Michael Bolz,4 Sven Jarius,5 Tobias Boettcher,6 Annette Großmann,7 Alexander Bock,8 Frauke Zipp,9 Reiner Benecke,1 Uwe K Zettl1

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.
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

---

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

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

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 × 10⁹/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 less than 0.02 × 10⁹/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.

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. Bloodstream infection was proven in 20% 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 or septicaemia 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.


Accepted: 3 November 2008

Adenocarcinoma of colon seen at colonoscopy