LESSON OF THE MONTH

One patient, two unusual conditions and three basic lessons

J M M Gardner-Medwin, R J Powell

Case report

A 54 year old woman presented with Raynaud's phenomenon, stiff fingers, and generalised thinning of her hair. She had a long history of pain in the knees and a past history of asthma controlled with inhalers. Examination revealed active digital vasculitis, marked facial telangiectasia, difficulty in fully opening her mouth, and osteoarthritis of the knees, subsequently confirmed radiographically. She was strongly positive for antinuclear antibody, and was anti-Sm positive, with a further undefined extractable nuclear antibody, but was negative for double stranded DNA. The table lists other initial investigations from 1989. A quadriceps muscle biopsy specimen taken for investigation of the increased creatine kinase (CK) concentration (462 U/l) showed only type 2 atrophy and small vessel thickening. An undifferentiated connective tissue disease was diagnosed, and treated with oral prednisolone and continuing azathioprine treatment at a starting dose of 100 mg/day, with a good clinical response, resolution of the vasculitis, and a return of the CK concentration to 156 U/l.

After two years, the digital vasculitis recurred and responded to an increase of the dose of azathioprine to 200 mg/day, but this was subsequently withdrawn because of suspected drug induced neutropenia (1.58 x 10^9/l). The patient received no drugs during the next six months as she declined to transfer her medical care to Spanish physicians during her annual visit over the winter months to the southern coast of Spain. She returned prematurely to England at Christmas 1991 with active digital vasculitis (table), and restarted azathioprine 150 mg/day. When her condition improved she defaulted from follow up, but presented again in June 1992, confined to a wheelchair.

The patient considered that her knee osteoarthritis was responsible for her progressive inability to participate fully in pursuits she enjoyed, sport loving family, and had consulted a private orthopaedic surgeon who undertook synchronous bilateral knee replacements. After her operation, she remained confined to a wheelchair, having failed to regain an ability to walk. When she presented in June 1992, examination showed a profound proximal myopathy such that she was unable to rise from sitting or initiate any upper arm movement. The investigations (table) included a repeat needle muscle biopsy specimen that showed large numbers of atrophic fibres, focal necrosis, the occasional regenerating fibre, marked thickening of the small vessels, and obliteration of small arterioles, with prominent endothelial activation and one focus of active lymphocytic vasculitis. She was treated with intravenous cyclophosphamide plus methylprednisolone and physiotherapy, with some improvement, but remained disabled by the proximal myopathy.

In March 1993, further digital vasculitis was treated with prednisolone and methotrexate (maintenance dose of 20 mg/week). In late April 1994, a blood count (table) was received from Spain. The patient was requested to stop taking methotrexate, and return to the UK immediately. On arrival 25 days later, she had become increasingly bizarre, paranoid, and angry, to the extent that her general practitioner admitted her to hospital under Section 4 of the Mental Health Act and she was

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Case history of laboratory findings

<table>
<thead>
<tr>
<th>1989</th>
<th>Dec 91</th>
<th>Jun 92</th>
<th>Mar 93</th>
<th>Apr 94</th>
<th>May 94</th>
<th>Jun 95</th>
<th>Aug 95</th>
</tr>
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<tbody>
<tr>
<td>Haemoglobin (g/l)</td>
<td>122</td>
<td>128</td>
<td>128</td>
<td>126</td>
<td>96</td>
<td>92</td>
<td>130</td>
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<tr>
<td>Reticulocytes</td>
<td>462</td>
<td>0-31</td>
<td>0-31</td>
<td>0-31</td>
<td>0-31</td>
<td>0-31</td>
<td>0-31</td>
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<tr>
<td>Total leucocytes (x 10^9/l)</td>
<td>8-6</td>
<td>4-64</td>
<td>2-24</td>
<td>0-34</td>
<td>331</td>
<td>462</td>
<td>35</td>
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<tr>
<td>Neutrophils (x 10^9/l)</td>
<td>5-0</td>
<td>3-29</td>
<td>0-81</td>
<td>0-31</td>
<td>309</td>
<td>508</td>
<td>35</td>
</tr>
<tr>
<td>Lymphocytes (x 10^9/l)</td>
<td>5-1</td>
<td>3-92</td>
<td>0-7</td>
<td>0-22</td>
<td>260</td>
<td>819</td>
<td>35</td>
</tr>
<tr>
<td>Eosinophils (x 10^9/l)</td>
<td>6-3</td>
<td>4-42</td>
<td>1-31</td>
<td>0-21</td>
<td>246</td>
<td>203</td>
<td>35</td>
</tr>
<tr>
<td>Platelets (x 10^9/l)</td>
<td>1-1</td>
<td>0-64</td>
<td>0-66</td>
<td>0-22</td>
<td>98</td>
<td>92</td>
<td>46</td>
</tr>
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<td>CRP (mg/l)</td>
<td>0-7</td>
<td>0-181</td>
<td>1-34</td>
<td>&lt;6</td>
<td>&lt;6</td>
<td>&lt;6</td>
<td>&lt;6</td>
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<tr>
<td>Total immunoglobulin</td>
<td>1-29</td>
<td>0-261</td>
<td>0-06</td>
<td>0-06</td>
<td>1-72</td>
<td>0-07</td>
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<td>IgA (0-7-3 g/l)</td>
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<td>0-17</td>
<td>0-17</td>
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<td>IgG (1-5-19 g/l)</td>
<td>1-4</td>
<td>1-4</td>
<td>1-4</td>
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<tr>
<td>IgM (0-4-2-7 g/l)</td>
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<td>0-25</td>
<td>0-25</td>
<td>0-25</td>
<td>0-25</td>
<td>0-25</td>
<td>0-25</td>
</tr>
</tbody>
</table>

Normal range. §Values before (pre) and after (post) prednisolone. — = Decreasing to.

CK = Creatine kinase; C3, 4; 1g = complement; CRP = C reactive protein; ESR = erythrocyte sedimentation rate; N/A = not available.
recorded as psychotic by the admitting psychiatrist. She had a fever (38°C), with rigors and marked weight loss. No skin vasculitis, lymphadenopathy, abnormal chest signs, or organomegaly were noted. In view of the marked pancytopenia, repeated blood and urine cultures were performed, but these and viral, toxoplasma, and brucella titres were negative. The table shows the results of other investigations; chest and knee radiographs were unremarkable. Abdominal ultrasound revealed a slightly enlarged spleen, but normal liver and kidneys. The increased CK concentration (1037 U/l) led to a further needle muscle biopsy examination that showed only type 2 fibre atrophy. A bone marrow aspirate was initially reported as hypocellular, with left shift myelopoiesis consistent with a chronic autoimmune disorder.

The patient’s psychotic symptoms preceded initiation of steroid treatment and settled overnight in response to her sedation, with a defer- vescence of the fever. During the next week of admission she developed a palpable liver and spleen. The bone marrow trephine was reported to contain numerous macrophages with cytoplasmic inclusions (usually more than five), consistent with Leishman Donovan bodies. Although initial culture was negative, the parasite was subsequently shown to be Leishmania donovani infantum. There was no history of insect bites for some months before this presentation. The patient was treated with 11 daily doses of liposomal amphotericin B 3 mg/kg, in response to which she made a slow recovery, though treatment was complicated by deranged liver function, hypoalbuminaemia, increasing hepatosplenomegaly, and thrombo phlebitis at the infusion site necessitating central venous access. In addition, she had a persisting pancytopenia marked by a particularly profound neutropenia of 0·05 × 10^9/l and developed an Escherichia coli septicaemia. This was treated with recombinant human granulocyte colony stimulating factor, intravenous ceftriaxone, and gentamicin. A repeat bone marrow sample two weeks after completion of the course of amphotericin showed persistently high numbers of macrophages, though these contained reduced numbers of inclusion bodies (fewer than five) and culture remained negative. At the time of the patient’s discharge from hospital in March 1995, results of laboratory investigations were as shown in the table. At this time the patient’s only medication was prednisolone 5 mg/day, and the hepatosplennomegaly resolved over the subsequent six months.

In August 1995, the patient had a recurrence of vasculitis with increasing weakness, and an increase in the CK concentration to 201 IU/l. A repeat bone marrow biopsy examination did not show parasites on microscopy or culture, and she restarted 30 mg prednisolone and methotrexate 20 mg/week, with a good symptomatic response, and a decrease in her CK concentration.

Discussion
The management of this patient was compromised by her personality and desired life style. We were manipulated into management decisions against our better judgment, in particular the monitoring of cytotoxic treatment from the UK whilst the patient was absent on extended vacations in Spain. The patient’s personality, in combination with the overfocused approach of the private orthopaedic surgeon, led to synchronous bilateral knee replacements in the face of unrecognised extensive proximal weakness and active digital vasculitis, which continued unrecognised during the patient’s rehabilitation in hospital.

In connective tissue diseases, thrombocytopenia, neutropenia, and anaemia, or any combination of these, may be disease related, irrespective of previous drug induced bone marrow toxicity. The use of cytotoxic agents in the management of these conditions demands regular monitoring to detect early signs of bone marrow suppression. Neutropenia with azathioprine is common, whilst methotrexate less frequently causes leucopenia and thrombocytopenia. Pancytopenia with methotrexate is uncommon. Bone marrow biopsying is required to distinguish both between disease and drug effects, and the less common causes of pancytopenia such as infection.

This case demonstrates the relevance of a history of foreign travel, particularly where infection is concerned. Visceral leishmaniasis is endemic on the coast of Malaga and throughout the Mediterranean basin, where the variant Leishmania donovani infantum predominates. The vector is the Phlebotomus sandfly, which is found at the coast, but does not survive at altitude.1 In immunocompetent hosts, 96% of cases of leishmaniasis are subclinical, with the development of lifelong immunity to Leishmania donovani. In the indigenous population, the infection presents as Kala-Azar, and can be characterised by anaemia, often with associated leucopenia and thrombocytopenia, usually related to decreased red cell survival and increased cell sequestration in the spleen.2

In visitors to the endemic area, the onset of leishmaniasis is more likely to be abrupt, with
high fever, and rapid progression of illness with toxaemia, weakness, dyspnoea, and acute anaemia. Immunocompromised hosts are particularly at risk of severe disease, with rapid progression, and appear to follow a clinical course similar to that observed in this patient. Most of the published cases had AIDS or HIV related immunosuppression, and weight loss, high fever, and pancytopenia were characteristic presentations. Notable features were a lack of splenomegaly, and a failure to mount leshmanial antibody production. After treatment, a failure to clear the organism, as revealed by repeat marrow biopsy, was associated with a high incidence of relapse in the immunocompromised host. Among those who are transiently immunosuppressed as a result of taking steroids or cytotoxic drugs, one report of three cases showed that two had moved away from the endemic leishmaniasis area before they were given immunosuppressive treatment and subsequently presented with acute fever and pancytopenia, but not splenomegaly, after the instigation of immunosuppression. These patients did well after removal of the immunosuppressive agents, and the patient we report here was subsequently managed on the minimum possible dose of steroid, to avoid further drug induced depression of her immune system, and to maximise clearance of the parasite. It was with considerable apprehension that we re instituted immunosuppression when the vasculitis returned.

This patient had two unusual conditions: namely, undifferentiated connective tissue disease and visceral leishmaniasis. Careful and detailed preoperative assessment of all patients being considered for bilateral synchronous knee replacements is essential, so that those with reduced upper limb strength, active muscle disease, or both, are identified and appropriate management organised. This patient's case also emphasises the role of bone marrow biopying in the management of bone marrow suppression in patients with connective tissue diseases who are receiving cytotoxic drugs. The reason for the pancytopenia reminds us that foreign travel does not have to be exotic to be relevant.

**The lessons**

- Bilateral synchronous knee replacements should not be considered lightly in patients with poor upper arm function, and a failure of rehabilitation should alert clinicians to review the reasons for poor progress.
- Marrow suppression in a patient receiving cytotoxic drugs is not necessarily attributable to the cytotoxic drugs or the primary condition; a bone marrow examination can be revealing.
- Remember the history of foreign travel when considering causes of infection.

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