Case report

A 61-yr-old previously fit lorry driver was referred by his general practitioner in October 1999 to an orthopaedic clinic with a 6-month history of painful hands, shoulders and feet. His general practitioner had treated him with ibuprofen without much improvement. He admitted to a recent history of loss of appetite with loss of two stones (12.7 kg) in weight. His joint pains had been increasing in severity with visible swelling of his fingers and knees. He had no relevant family history. He was an ex-smoker and drank little alcohol.

Physical examination revealed a healthy-looking man with signs of synovitis in the symptomatic joints. The orthopaedic surgeon referred him to the rheumatologist (K.C.). The preliminary blood tests showed haemoglobin of 10.4 g/dl with normal haematocrit, leucocyte and platelet counts and normal serum vitamin B12 and red-cell folate levels. His serum ferritin was 468 μg/l (normal range 18–400 μg/l). He also had transient random hyperglycaemia, which was followed by a normal glucose tolerance test. His rheumatoid factor was elevated at 1:2560. His chest X-ray was normal except for some thickening of the bronchial wall.

He was seen in the rheumatology clinic 2 months later, in December 1999, with classical symptoms and signs of a symmetrical inflammatory polyarthritis suggestive of rheumatoid disease. His knees were drained and injected with methyl prednisolone and local anaesthetic. He was also given intramuscular methyl prednisolone (120 mg) to induce remission of active disease.

Investigations revealed haemoglobin 10.3 g/dl, white cell count 6.4 × 10^9/l, platelet count 449 × 10^9/l and ESR of 100 mm in the first hour. The biochemical screens were all normal, including liver, renal and bone panels. The rheumatoid factor was 2460 IU (normal range 30 IU) and CRP was elevated at 85.1 mg/dl (normal range < 10 mg/dl). The biochemical, serological and microbiological screens including hepatitis A, B and C were all normal/negative. His anti nuclear antibodies, anti DNA antibodies, extractable nuclear antigens, anti cardiolipin antibodies, anti neutrophil cytoplasmic antibodies and cryoglobulins were all negative. Echocardiogram was normal. A cerebrospinal fluid study showed a mild increase in cerebrospinal fluid protein but no oligoclonal band or albumino-cytological dissociation. Electromyography showed severe sensorimotor polyneuropathy of the axonal type with some denervation changes in the peroneal muscles. A skin biopsy confirmed active necrotizing vasculitis, consistent with SRV (Fig. 2).

He was commenced on pulse intravenous methyl prednisolone (500 mg) and cyclophosphamide (500 mg) with some symptomatic improvement, and was discharged home on a 2-weekly regime.

Progress 1: February to May 2000

His disease remained active despite regular intermittent intravenous pulse cytotoxic therapy. The leg ulcers were showing little signs of improvement after about 12 pulses, when a decision to change to daily oral therapy was made. There were also issues about timely intravenous therapies; this prompted oral cyclophosphamide 100 mg/day and prednisolone 30 mg/day, with a favourable clinical response. He was also given cotrimoxazole and folic acid supplements on a regular basis.
The following questions were discussed by R.T. and the audience: (i) What is the most likely diagnosis and what immediate investigations should we do? (ii) What treatment should we offer?

R.T. summarized the case and reminded the audience that this 61-yr-old man clearly had RA, significant weight loss, mononeuritis multiplex and cutaneous vasculitis, and this was suggestive of SRV, but such degree of weight loss was unusual. The personal and family histories of the patient were discussed in detail; both were unrevealing. Sjögren’s syndrome, leprosy and leishmaniasis were discussed as possible causes, but the patient clearly had no clinical features of any of them.

Progress 2: June to September 2000

His disease continued to show signs of clinical and haematological improvement. His regular doses of cyclophosphamide and oral prednisolone were gradually tapered to 50 and 10 mg/day, respectively.

He felt clinically well and his haematological parameters improved. However, cyclophosphamide was discontinued in view of a drop in neutrophil count, which was followed by a rise in neutrophil count to $2.2 \times 10^9/l$ and platelet count to $273 \times 10^9/l$. This improvement continued, and in December his haemoglobin was 12.5 g/dl, white cell count $6.00 \times 10^9/l$, neutrophils $2.9 \times 10^9/l$ and platelets $229 \times 10^9/l$. He underwent no further cytotoxic therapy and was maintained on oral steroid at 10 mg/day.

Progress 3: January to April 2001

He suffered transient symptoms of severe dysuria without haematuria or proteinuria requiring a urology opinion. He subsequently underwent prostatic and bladder biopsy to rule out malignancy. His haematological and biochemical screens were all normal during this time.

Progress 4

On 8 June 2001 he was admitted with swinging pyrexia of the quotidian type, with no obvious signs of infection. His temperature was 40°C. There was no hepatosplenomegaly

Fig. 1. (a–c) Clinical presentation of acute vasculitic episode in the casualty department soon after the patient returned from holiday in Spain.
or lymphadenopathy. His joints were quiet and he looked quite ill. An infection screen, including viral, mycobacterial and chlamydial screens, was negative. Repeated tests including all the above and abdominal ultrasound scan, whole-body CT scan and echocardiogram did not reveal any abnormality. His haematology results on admission and subsequently until his death are shown in Fig. 3. Haemolytic and disseminated intravascular coagulation (DIC) screens were negative. Fibrinogen level was 7.5 g/l (normal range 1.5–4.5 g/l).

Further questions were discussed about the cause of pancytopenia and investigations that ought to be done in the clinical circumstances. R.T. summarized that the clinical picture was that of a patient with inactive RA presenting with pyrexia of unknown origin and pancytopenia. He discussed drug-induced myelosuppression, Felty and Evans syndromes as possible causes; peripheral consumption was more likely but Felty syndrome presenting acutely and with pancytopenia was considered to be unusual. Evans syndrome was unlikely as there were no signs of haemolysis.

R.T. commented that in the setting of PUO with pancytopenia, it was important to consider some form of obscure infection, vasculitis and malignancy as the most likely differentials and that a bone marrow biopsy was essential. Discussion from the floor suggested diagnoses of lymphomas, macrophage activation syndrome, myxoma/rhabdomyosarcoma, leishmaniasis and HIV.

The patient was treated with broad-spectrum antibiotics using the neutropenic regimen. He was given blood transfusions but no platelets. A bone marrow biopsy showed hypercellular marrow with adequate megakaryocytes but no normoblasts. No obvious dysplasia was noted (Fig. 4). A tuberculin stain and culture from the marrow were negative. He was treated with blood transfusions for symptomatic anaemia. However, his pyrexia was unresponsive to antibiotic therapy.

He subsequently underwent an indium-labelled white cell scan, which was normal. He was given a steroid pulse (1 g methyl prednisolone) on the suspicion of a flare of his systemic rheumatoid disease. However, his pyrexia continued unabated without any response to any form of therapy.

An interactive discussion took place about persistent pancytopenia and pyrexia and what further investigations should be undertaken to establish the underlying diagnosis. R.T. discussed further investigations, including blood film, white blood cell morphology, PCR for herpes, cytomegalovirus, Epstein–Barr virus, parvovirus B19, HIV test, tuberculin test, early morning urine (EMU) for acid alcohol fast bacilli (AAFB) and blood cultures. K.C. replied that, apart from PCR, all tests had been done and they were negative or normal on repeated testing. Further discussion took place about tumour markers, PET scanning, and duodenal biopsy (to exclude Whipple’s disease). K.C. replied that tumour markers are not particularly helpful as false-positive results are common in connective tissue disorders. Duodenal biopsy was not done as the patient had been reviewed by gastroenterologists and found to have no indication for a biopsy. A PET scan was not requested as it was not available in the NHS.

Progress 5

On 1 July 2001 the patient developed an episode of diarrhoea with acute abdominal distension. X-ray of the abdomen suggested the diagnosis of acute dilatation of the stomach, which was treated with parenteral fluids and gastric suction. Further CT scanning of the abdomen suggested an abnormal texture of the spleen with some enlargement, raising the possibility of haemochromatosis. As his haematology showed no improvement despite various measures, intravenous immunoglobulins were given for 5 days. Again, no improvement was
noted and his haemoglobin, white cell count and platelets continued to decline (Fig. 3). The rheumatologist (K.C.) suggested a laparoscopic biopsy of the splenic tissue, with platelet cover, but the surgeons declined.

Further discussion took place about the final diagnosis and whether anything should have been done differently. R.T. summarized the case again and the current problems, including PUO, pancytopenia and transitory small bowel obstruction in the absence of infection and no response to antibiotics, steroids or intravenous immunoglobulin. R.T. suggested that pure systemic rheumatoid vasculitis and Felty syndrome were unlikely because of pancytopenia, the short course of the symptoms and the lack of response to steroids and intravenous immunoglobulin. Amyloidosis was also unlikely as the history was of short duration and there was no renal involvement. Haemochromatosis and glycogen storage disorders, such as Gaucher disease, were also considered but dismissed as there was no clinical or biochemical evidence.

Malignancy remained a strong possibility but investigations including bone marrow and CT scans failed to show any such evidence. Intravascular lymphomas were also considered but were unlikely.

Leishmaniasis, a parasitic infection transmitted by sandfly bites, is endemic in Spain and was also considered as a possible trigger for the haemophagocytic syndrome. This is a condition characterized by multisystem involvement, fever, splenomegaly/hepatomegaly and pancytopenia. However, it was not seen on bone marrow trephine biopsy. Cytology of the marrow aspirate showed increased macrophages and increased megakaryocytes, and there was no dysplastic changes (Fig. 4).

R.T. made the case for undiagnosed viral/parasitic infection and reactive haemophagocytic syndrome. Further discussion took place about other possibilities, such as Lyme disease, MALToma and trypanosomiasis as possible diagnoses. However, Lyme serology was negative. A splenic biopsy/aspirate was suggested but declined by the surgeons, as discussed earlier.

A few days later his condition gradually deteriorated and he died on 14 July; a limited post-mortem was requested, with consent from the family.

**Limited post-mortem**

Tissues were obtained from the liver, spleen, bone marrow, kidney, heart and brain and stained appropriately. Only the
positive and helpful findings are discussed. The hepatic and splenic tissue were examined, including immunohistochemical studies, which confirmed the presence of CD4⁺ T cells and cytotoxic T-cell granule protein (Figs. 5 and 6). He was negative for B-cell markers. There was no evidence of vasculitis, amyloidosis or haemochromatosis in the tissue examination. The tissues were also examined microbiologically, with negative results.

**Conclusion**

Gamma/delta T-cell lymphoma (γ/δ TCL) represents rare, often aggressive types of T-cell malignancy that are clinically and pathologically diverse [1]. Most γ/δ TCL occur as a hepatosplenic or subcutaneous type. They constitute fewer than 10% of peripheral T-cell lymphomas and occur mostly at extranodal sites in hepatosplenic, subcutaneous or intestinal form. Hepatosplenic γ/δ TCL (γ/δ HSTCL) is recognized as a provisional subset of peripheral T-cell lymphoma in the Revised European–American Classification of Lymphoid Neoplasm (REAL), although a few identified cases of α/β HSTCL appear to have similar clinicopathological characteristics. Histologically, γ/δ HSTCL is characterized by a mixture of small- to medium-sized atypical lymphocytes. To date only about 40 cases of γ/δ HSTCL have been reported. These lymphomas frequently show two non-random chromosomal abnormalities, isochromosome 7q [i (7) (q10)] and trisomy 8 (8q+). Affected individuals are usually young males. Patients commonly present with B symptoms (fever, night sweats, pruritus, weight loss) and hepatosplenomegaly, but not lymphadenopathy. The disease usually follows an aggressive course with a poor response to chemotherapy and a short time of survival. The γ/δ lymphoma has not been reported in the background of seropositive RA. It is believed that this type of TCL can remain localized to the spleen, which may not be obviously enlarged until very late in the disease course, and there may be no nodal involvement. These diseases can present with severe thrombocytopenia with no evidence of bleeding. Systemic vasculitis associated with seropositive non-erosive RA can be a rare presentation of paraneoplastic syndrome due to T-cell γ/δ lymphoma.

This case of apparent seropositive RA of relatively short duration raises many questions about the diagnosis, as there were hardly any convincing radiological signs of RA, although it is unlikely to occur in such short period of time. There is hardly any doubt about the diagnosis of systemic vasculitis and the premortal illness of γ/δ TCL as histological tissues

---

**Fig. 4.** Bone marrow biopsy showing extensive megakaryocytosis with no evidence of dysplasia or marrow infiltration.

**Fig. 5.** Immunohistochemical study of spleen showing positive T-cell markers, CD2 and CD3.
were available to confirm the diagnosis, ante- and post-mortem, respectively.

This 61-yr-old man, who presented with bilaterally symmetrical inflammatory polyarthritis, developed acute systemic vasculitis with positive histology. After appropriate treatment with relevant drugs, the vasculitis went into remission, only to develop the rather uncommon complication of $\gamma/\delta$ TCL. An increased risk of malignancy has been reported in association with vasculitis [2], with an increasing incidence of chronic myelomonocytic leukaemia in about 18% of patients with recognized vasculitic disease, such as polyarteritis [3].

The authors have declared no conflicts of interest.

References


Fig. 6. Immunohistochemical study of spleen showing cytotoxic granular protein characteristic of $\gamma/\delta$ TCL.