Hepatosplenic T-cell lymphoma following infliximab therapy for Crohn's disease

Musa Drini, Peter J Prichard, Gregor J E Brown and Finlay A Macrae

Tumour necrosis factor inhibitors have revolutionised the management of Crohn's disease, but reports of a possible association between concomitant infliximab and immunomodulator therapy and hepatosplenic T-cell lymphoma (a rare form of aggressive non-Hodgkin's lymphoma) have emerged. We describe the first case in Australia of hepatosplenic T-cell lymphoma in a patient who had been treated with infliximab and immunomodulators for Crohn's disease. **(MJA 2008; 189: 464-465)**

Clinical record

In January 2006, a 39-year-old man of European background presented with severe sepsis of unidentified source. This was complicated by hypotension and multiorgan failure, including renal impairment, abnormal liver function and myocardial injury, and he required intensive care. He had a 13-year history of active perianal and ileal Crohn's disease, which had been treated with prednisolone (varying doses) continuously from 1993, and with azathioprine (2–2.5 mg/kg) from 1993 to 1994 and then continuously from August 1999 (after drainage of a perianal abscess). He had also received three doses of infliximab (5mg/kg) between November 1999 and January 2000, which achieved a partial response. Azathioprine and prednisolone therapy were continued after infliximab therapy, with relatively good control of symptoms. Results of full blood examinations during azathioprine therapy were within normal ranges. On admission, azathioprine therapy was discontinued, but corticosteroids were continued.

Blood cultures grew methicillin-sensitive *Staphylococcus aureus*. Full blood examination revealed mild anaemia (haemoglobin level, 91 g/L; reference range [RR], 130–170 g/L) and mild lymphocytopenia (white blood cell count, 0.6×10^9/L; RR, $4.0–11.0 \times 10^9$/L), but other parameters were initially normal. Biochemical analysis revealed acute renal failure (potassium, 6.5 mmol/L [RR, 3.5–5.0 mmol/L]; bicarbonate, 21 mmol/L [RR, 22–31 mmol/L]; creatinine, 580 μmol/L [RR, 60–110 μmol/L]; and urea, 19.9 mmol/L [RR, 2.5–8.3 mmol/L]). Liver function tests revealed transaminitis (alanine aminotransferase, 432 U/L [RR, < 55 U/L]; aspartate aminotransferase, 2246 U/L [RR, < 50 U/L]; and bilirubin, 53 μmol/L [RR, < 19 μmol/L]). There was also evidence of coagulopathy (international normalised ratio [INR], 2.8 [RR, 0.8–1.3]), grossly abnormal levels of inflammatory markers (C-reactive protein, 218 mg/L [RR, < 8 mg/L]; erythrocyte sedimentation rate, 140 mm/h [RR, 2–14 mm/h]), and elevated troponin I levels (5.24 μg/L; RR, < 0.10 μg/L).

Nine days after admission, the patient developed pancytopenia (haemoglobin level, 78 g/L; white blood cell count, 0.9×10^9/L; and neutrophil count, 0.3×10^9/L [RR, $2.0–8.0 \times 10^9$/L]). This was attributed to drug-induced suppression of bone marrow, and granulocyte-colony stimulating factor (G-CSF) was administered. On discharge, leukocyte and neutrophil levels were normal, G-CSF therapy was discontinued, and follow-up was arranged.

Ten days after the patient was discharged, he re-presented with a 2-day history of fever, malaise and non-specific abdominal pain. Physical examination revealed a temperature of 38.5° C, tachycardia (heart rate, 110 beats/min), and hypotension (blood pressure, 100/60 mmHg); cardiovascular and respiratory systems were otherwise unremarkable. Abdominal examination revealed new hepatosplenomegaly, with no stigmata of chronic liver disease. There was no clinical evidence of lymphadenopathy. Repeat haematological testing revealed pancytopenia: haemoglobin level, 100 g/L; white blood cell count, 0.7×10^9/L; platelet count, 48×10^9/L (RR, $140–400 \times 10^9$/L); neutrophil count, 0.0×10^9/L; and lymphocyte count, 0.5×10^9/L (RR, $1.2–4.0 \times 10^9$/L). A blood film showed atypical lymphocytes and blast cells. Serum lactate dehydrogenase level was grossly elevated at 5351 U/L (RR, 210–420 U/L), and liver function tests showed abnormal results.

Abdominal computed tomography confirmed gross splenomegaly, with the spleen being 24 cm long on its major axis, but no lymphadenopathy. Microscopic examination of a liver core biopsy specimen revealed an atypical lymphoid infiltrate in the sinusoids, especially around central veins (Box), with immunophenotype bcl-2+, CD3+, CD43+, Ki67+, ALK1 –, bcl-6 –, CD5 –, CD10 –, CD20 –, CD30 –, CD79 – and cyclin D1 –. Subsequent genetic studies of a bone marrow biopsy specimen revealed rearrangement of the T-cell receptor γ-chain gene, consistent with hepatosplenic T-cell lymphoma (HSTCL).

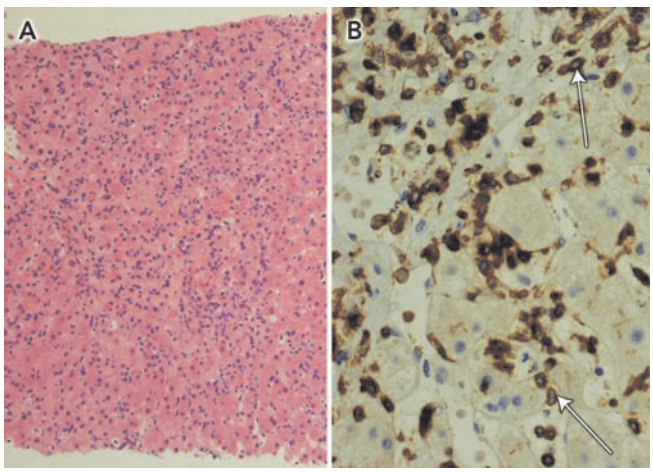
The lymphoma was treated with one cycle of cyclophosphamide, mesna, dexamethasone, doxorubicin and vincristine, which achieved a partial response, but subsequent salvage chemotherapy with ifosfamide, carboplatin and etoposide did not arrest disease progression. In June 2006, the patient received a sibling allogeneic bone marrow transplant, after conditioning with etoposide and total body irradiation.[1]

The patient remained largely free of disease after transplantation, with monitoring on an outpatient basis and adjustment of immunosuppression as clinically indicated. However, in April 2007, he was hospitalised for investigation of diarrhoea and worsening liver function. He underwent colonoscopy and biopsy of a caecal polypoid mass; results of histological examination were consistent with recrudescence of HSTCL. Positron emission tomography showed multiple sites of relapse. A palliative approach was adopted, and the patient died in June 2007.

Discussion

We describe the first case, to our knowledge, in Australia of HSTCL in a patient with Crohn's disease who had been treated with infliximab and immunomodulators. Inhibitors of tumour necrosis factor (TNF) such as infliximab have shown great efficacy in the treatment of luminal and fistulising Crohn's disease, as well as ulcerative colitis.[2] Infliximab is a chimeric (human/murine) monoclonal antibody that binds to human TNF-α. It was approved by the United States Food and Drug Administration (FDA) in 1998 for the treatment of moderate-to-severe Crohn's disease when response to immunomodulator therapy is inadequate. More recently, the FDA has expanded the indication to include ulcerative colitis refractory to conventional treatment.

Liver core biopsy specimen of a patient with Crohn's disease, following infliximab and immunomodulator therapy



*Low magnification (**A**: haematoxylin and eosin stain; original magnification, × 10) and high magnification (**B**: CD3 stain; original magnification, × 40) views of a liver core biopsy specimen, showing prominent atypical lymphoid infiltrate in the sinusoids and around central veins, and occasional red cell extravasation. The high magnification shows strong CD3 staining (arrows), findings consistent with hepatosplenic T-cell lymphoma.* ◆

In Australia, the Pharmaceutical Benefits Advisory Committee recently approved TNF inhibitors for the treatment of Crohn's disease. However, the safety of such biological therapy is a concern: a recent meta-analysis reported a threefold increase in the risk of malignancy (solid and haematological) with the use of anti-TNF therapy in rheumatoid arthritis patients.[3] This increase may be partly due to severity of disease or to other aspects of disease management. Interestingly, to date there have been no reports of HSTCL in rheumatoid arthritis patients. The TREAT (Crohn's Therapy Resource, Evaluation and Assessment Tool) registry, which monitors over 3000 patients with Crohn's disease who have been treated with infliximab, has not reported an increased incidence of lymphoma.[4] However, it is estimated that a substantially larger number of patients would need to be monitored to detect a significant increase in a rare adverse event, such as lymphoma.[5] Between 2000 and 2006, the Adverse Drug Reactions Advisory Committee received 319 reports involving anti-TNF therapy, including five cases of lymphoma.[6]

HSTCL is a rare form of aggressive non-Hodgkin's lymphoma that comprises 5% of peripheral T-cell lymphomas. Reports of approximately 120 cases have been published worldwide. Eight cases of HSTCL have been identified from the post-marketing infliximab safety database run by the FDA, which seems more than expected, all in young men with a history of Crohn's disease and concomitant use of azathioprine or mercaptopurine.[7] In addition, there have been 15 reports of "T-cell lymphoma" in patients treated with infliximab, but data from the Adverse Event Reporting System were limited.[7] Furthermore, there have been no reports of HSTCL associated with other anti-TNF therapies (eg, etanercept and adalimumab) used for any indication.[7] Of note, there have been four reports of HSTCL in patients who received azathioprine or mercaptopurine alone for 4–6 years.[8]

The case we describe differs substantially from previously reported cases of HSTCL associated with concomitant infliximab and immunomodulator treatment in Crohn's disease. To our knowledge, it involves the oldest patient and longest lead time (72 months) reported to date. Patients in most other cases have been younger than 22 years, with a lead time of less than 58 months[7] (unpublished data, Centocor, Horsham, Pa, USA).

Recent data suggest an association between lymphoma — especially HSTCL — and concomitant use of infliximab and immunomodulators in Crohn's disease. However, the mechanism of this possible association remains unclear. The use of biological therapy as a "bridge" to stabilise the disease, while waiting for immunomodulators to become clinically effective, may need to be considered with increased caution. Immunomodulators might need to be avoided after infliximab therapy, and alternative treatments considered. These may include maintenance with ongoing biological therapy alone, use of newer anti-TNF therapy, or earlier surgery (especially in young men). Until further evidence emerges, long-term surveillance of patients who have used biological therapy is warranted. In particular, biological therapy should be used cautiously in the management of refractory inflammatory bowel disease. The decision to use infliximab should be tempered by observations of an association with HSTCL, and strategies for long-term maintenance therapy need to be developed.

Competing interests

None identified.

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