Case Report

Crohn's Disease associated lymphoma after treatment with infliximab

S C Kong & G James

S C Kong
(MRCP)
Specialist Registrar in Gastroenterology
Doncaster Royal Infirmary

G James
(MRCP)
Consultant in Gastroenterology
Doncaster Royal Infirmary

Correspondence:
Dr S C Kong
C/o Dr G James' secretary
Doncaster Royal Infirmary
Doncaster DN2 5LT
Tel: 01302-366666
Ext: 3751
Fax: 01302-761208

Abstract

Infliximab (antibody to tumour necrosis factor) has a growing place in the management of refractory and fistulating Crohn's disease. Lymphoma has been associated with the use of other immunomodulatory drugs but far from unequivocally so when they are used in Crohn's disease. A case is described in which use of infliximab was followed by the early presentation of an Epstein-Barr virus-associated anaplastic lymphoma. The possible links between these phenomena are discussed.

Keywords

Case report, Crohn's disease, lymphoma, infliximab, tumor necrosis factor.

Case report

A 25 year old female patient had developed Crohn's disease at the age of 7. She was initially treated with medical therapy. When she was 13 she had needed a defunctioning colostomy and subsequently a colectomy with terminal ileostomy. Unfortunately her Crohn's remained difficult to control despite low dose maintenance steroid with occasional steroid boost, ciprofloxacin, metronidazole and azathioprine. She had recurrent intestinal obstruction requiring 2 laparotomies for excision of intestinal strictures and correction of mesenteric torsion. She had chronic perineal ulceration. She suffered from secondary infertility and was keen to have another child.

In late 1999 the patient sought treatment with infliximab (antibody to tumour necrosis factor-alpha), particularly for her perineal ulceration. Coincidentally she had developed an entero-cutaneous fistula adjacent to her stoma. Infusions of the drug were given at weeks 0 and 2 in February 2000. When she was due for her 3rd infusion (at 6 weeks), she was unwell with a pyrexia of unknown origin, and non-specific gastrointestinal and respiratory symptoms. She improved on a combination of broad-spectrum antibiotics and was discharged home within 3 days. She was admitted again in the middle of April 2000 with diarrhoea, night sweats and abdominal pain. On ultrasound she was found to have thick walled loops of small bowel in her pelvis with very dilated proximal small bowel. She again settled with conservative management and was discharged on 40mg prednisolone daily. She was readmitted within 24 hours having deteriorated. Her symptoms did not settle and laparotomy was required.

Laparotomy showed multiple white nodules (1-7mm) scattered along the small bowel, on the mesentery, on all peritoneal surfaces, and on the right lobe of the liver. Her small bowel was dilated. There was a dense mass in her pelvis. Her ileum led to the mass from which the ileostomy now arose. Attempted dissection of the pelvic mass had to be abandoned because of the risk of injury to other pelvic organs.

Specimens were examined routinely and by immunohistochemistry. The final conclusion was of Epstein-Barr Virus- (EBV) related high grade lymphoma of the large cell anaplastic type (it was not possible to identify whether it was of T or B cell differentiation). She went on to complete 6 cycles of CHOP (cyclophosphamide, doxorubicin hydrochloride, vincristine and prednisolone) chemotherapy. She required admission for septicaemia secondary to leukopenia complicating the 2nd course, but responded well to antibiotics and granulocyte-colony stimulating factor. CT scan at 8 months follow-up demonstrated complete remission.

Discussion

Infliximab, a chimeric monoclonal IgG1 antibody, has been licensed for use in the treatment of refractory Crohn's disease,[1] and European guidelines have been published regarding its use.[1] Various side-effects have been reported including headaches, nausea and upper respiratory tract infection.[1-3] In the short time that it has been used, reports are emerging about a possible relationship between infliximab and the development of lymphoma in Crohn's disease patients. One patient in the Rutgeerts study developed intravascular duodenal B-cell lymphoma 9.5 months after initial treatment with infliximab.[2] Bickston *et al* reported 1 case of intravascular large B-cell type lymphoma and 1 case of thoracic nodular sclerosing Hodgkin's disease which developed after treatment with the

drug.[4] Other cases have also been described.[3,5] Aithal *et al* have calculated the risk of post-infliximab lymphoma as 0.36%.[5] There is difficulty in defining an exact causal relationship between infliximab and lymphoma because of the predisposition of these patients (especially those with rheumatoid arthritis) to develop lymphoma secondary to the intrinsic disease, and possibly also to treatment with other immunosuppressants prior to the infliximab.[4-6] In the present case the very short interval between exposure to infliximab and definite lymphoma symptomatology, makes a causal association unlikely. There are further infliximab trials nearing completion and a growing number of post-marketing surveillance records. These should clarify whether there is a causal relationship between infliximab and lymphoma in Crohn's disease. In the interim, the possible relationship should perhaps be explained to patients prior to treatment with infliximab.

References

1. Schreiber S, Campieri M, Colombel JF, *et al;* Use of anti-tumour necrosis factors agents in inflammatory bowel disease. European guidelines for 2001-2003. *Int J Colorectal Dis* 2001; **16**: 1-11.
2. Rutgeerts P, D'Haens G, Targan S, *et al;* Efficacy and safety of retreatment with anti-tumour necrosis factor antibody (Infliximab) to maintain remission in Crohn's disease. *Gastroenterology* 1999; **117**: 761-769.
3. Hanauer SB Review article: safety of Infliximab in clinical trials. Aliment Pharmacol Ther 1999; 13 Suppl4 : 16-22
4. Bickston SJ, Lichtenstein GR, Arseneau KO, *et al;* The relationship between Infliximab treatment and lymphoma in Crohn's disease. *Gastroenterology* 1999 Dec; **117**(6): 1433-1437.
5. Aithal GP, Mansfield JC. Review article: the risk of lymphoma associated with inflammatory bowel disease and immunosuppressive treatment. *Aliment Pharmacol Ther* 2001; **15**: 1101-1108.
6. Farrell JR, Ang Y, Kileen P, *et al;* Increased incidence of non-Hodgkin's lymphoma in inflammatory bowel disease patients on immunosuppressive therapy but overall risk is low. *Gut* 2000; **47**: 514-519.

may be photocopied & cut

Subscription form

If you already subscribe please ignore this circular

CME Gastroenterology **Publication: 3 per annum** **ISSN: 1367-9015**

Subscription Rates:	Personal Rate:	UK £30; Overseas £60	Trainees £20; (UK only)
(Postage included)	Institutional Rate:	UK £60; Overseas £90	

(Sterling cheques must be drawn on a UK bank account.)

Name

Address

Post Code Country

Telephone email

Please debit my ❑ Access ❑ Visa ❑ Mastercard ❑ Switch

Card no.

Expiry date Switch issue No.

Signature

Date

❑ I enclose a cheque made payable to **"Rila Publications Ltd"**

Amount £ ____________________

Now return your order using one of the following methods

POST: **Rila Publications Ltd, 73 Newman Street, London W1A 4PG, UK**

ONLINE: **www.rila.co.uk** (click on "subscribe")

TELEPHONE: call subscription department on **020 7637 3544**

FAX: **020 7580 7166**