CASE REPORT

EBV-associated colonic B-cell lymphoma following treatment with infliximab for IBD: a new problem?

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SUMMARY

Patients with inflammatory bowel disease who do not respond to steroid therapy often require treatment with immunomodulators in an attempt to achieve a response and maintain remission. However, a major concern and controversy is whether these treatments are putting the patients at a significantly increased risk of developing lymphomas. This case reports a patient with severe ulcerative colitis who had been previously treated with azathioprine and infliximab, and subsequently developed diffuse large B-cell colonic lymphoma.

BACKGROUND

This highlights a rare case of a patient with ulcerative colitis who developed an Epstein-Barr virus (EBV)-driven diffuse large B-cell lymphoma following treatment with anti-tumour necrosis factor (TNF) therapy and a thiopurine.

CASE PRESENTATION

A 65-year-old man was diagnosed with severe ulcerative colitis in 2007. He did not respond to initial intravenous hydrocortisone therapy and required rescue therapy with three doses of infliximab (5 mg/kg) with remission in symptoms and biochemically followed by azathioprine 150 mg daily as maintenance therapy.

Despite maintenance azathioprine he developed a subacute flare in his colitis in January 2012. A flexible sigmoidoscopy demonstrated severe left-sided colitis up to the descending colon. He was prescribed prednisolone 40 mg daily and mesalazine foam enemas and azathioprine was changed to 6-mercaptopurine at a dose of 75 mg daily.

He required further rescue therapy with infliximab. This achieved an initial good clinical response with no diarrhoea or rectal bleeding.

The patient was in remission, however, 3 months later he presented as an emergency with acute abdominal pains. An urgent CT scan of the abdomen demonstrated free intra-abdominal air consistent with bowel perforation. The patient underwent an emergency laparotomy and subtotal colectomy.

OUTCOME AND FOLLOW-UP

The resected bowel was sent for pathology. There was a sigmoid colon tumour at the site of perforation (figure 1). Histology showed the tumour to be comprised of a discohesive malignant cell population with a blastic appearance, in keeping with the morphology of a diffuse B-cell lymphoma (figure 2). Lymphoid nature was confirmed by

Figure 1 Slide demonstrating the perforation of the sigmoid colon at the tumour site.

positivity with leucocyte common antigen and negativity with the epithelial marker AE1/3. The lymphoma was found to infiltrate through the muscularis propria with extensive extramural spread and serosal involvement. Eighteen nodes were sampled and none were shown to be involved by lymphoma. The EBV status was positive and this was then diagnosed as an EBV-driven diffuse large B-cell lymphoma (figure 3).

DISCUSSION

The risk of lymphoma in patients with inflammatory bowel disease (IBD) has generated conflicting results; however, the general consensus is that IBD itself does not cause a statistically significant increased risk of lymphoma.¹⁻⁴ Most population-based studies indicate a risk similar to that of the general population, with one recent study giving an absolute incidence rate of 1.55/10 000 patient-years

Figure 2 Slide demonstrating the diffuse large B-cell lymphoma.

To cite: Allen PB, Laing G, Connolly A, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-200423

Figure 3 Slide demonstrating evidence of Epstein-Barr virus (EBV) latent membrane protein 1 (membranous staining indicating the lymphoma cells harbour EBV).

and a standardised incidence ratio (SIR) of 1.37 (95% CI 0.44 to 4.26).¹ Furthermore, the severity of the disease is not thought to confer an increased risk, unlike in rheumatoid arthritis patients where chronic active inflammation is associated with a higher incidence of lymphoma.⁵

Hospital-based and population-based studies into the effect of immunosuppressive therapy on the risk of lymphoma in patients with IBD have also provided conflicting results with some studies suggesting that those patient with IBD who receive thiopurine treatment are already at an increased risk of developing lymphoma due to the severity of the chronic inflammation associated with their disease.⁶⁻⁷ Beaugerie *et al*⁴ reported that patients' receiving thiopurines for inflammatory bowel disease have an increased risk of developing lymphoproliferative disorders but that these disorders may potentially be a local complication of chronic inflammation of the intestinal mucosa.⁸⁻⁹

However, some evidence supports an increased lymphoma risk directly related to the immunosuppressive effects of thiopurines. Kandiel *et al* published a meta-analysis of patients with IBD treated with thiopurines. Six studies fulfilled their criteria for inclusion and 321 patients had IBD treated with immunomodulators of which 11 developed lymphoma against an expected risk of 2.63 patients. The SIR was 4.18 (95% CI 2.07 to 7.51), demonstrating a fourfold increase in the incidence of lymphoma whereas those patients not treated with thiopurines had a risk equivalent to the general population.¹⁰

One UK-based case-control study was conducted to determine if patients with IBD were at an increased risk of malignancy if they had been treated with azathioprine. Of the 15 471 patients included in the study 435 developed cancer, 15 of these were lymphomas. When reporting 'at ever' versus 'never' use of azathioprine for the risk of developing lymphoma this gave an OR of 3.22 (95% CI 1.01 to 10.18). This study therefore also supports an increase in lymphoma risk for patients with IBD treated with thiopurines.¹¹

A recent French nationwide study published in the *Lancet* that included 19 486 patients identified higher rates of lymphoma in patients currently receiving thiopurines, the risk returned to baseline once treatment was discontinued.⁴

It is very difficult to determine the lymphoma risk associated with the use of Infliximab as a treatment for IBD, as there are very few published cases of patients treated with anti-TNF

monotherapy. The majority of patients have, at some time, also been treated with thiopurines.

The study published by Herrinton *et al* into lymphoma risk with IBD medications, identified an SIR of 5.5 for past use (95% CI 4.5 to 6.6) and 4.4 for current use (95% CI 3.4 to 5.4) of anti-TNF therapy, with or without thiopurines. Seventy-five per cent of patients diagnosed with lymphoma had never been treated with thiopurines or anti-TNF therapy and 4 of the 43 patients had been treated with a combination of infliximab and thiopurines. This therefore shows a statistically significant increase in lymphoma risk in IBD patients treated with anti-TNF therapy, with or without thiopurines. The most common type of lymphoma that patients developed was diffuse large B-cell lymphoma (19 patients).²

Ljung *et al* conducted a population-based cohort study to assess the occurrence of adverse events with the use of infliximab for the treatment of IBD. They included 217 patients in the study, 3 of which developed lymphoma (1 NK-cell and 2 B-cell lymphomas). This gave an overall annual lymphoma incidence of 1.5%. However, it is important to note that 111 (51%) of the patients were receiving concomitant thiopurine therapy.¹²

From our literature search we identified 25 cases of diffuse large B-cell lymphoma associated with the use of infliximab for the treatment of IBD. Of these, four patients had been treated with infliximab and azathioprine, and two with infliximab and 6-MP.¹³⁻¹⁸ It is therefore challenging to evaluate the risk of diffuse large B-cell lymphoma with anti-TNF monotherapy or thiopurine monotherapy for the treatment of IBD as patients are rarely treated with these agents alone, and where they are patient numbers are small.³

A current area of interest is the growing body of evidence to suggest an increased risk of lymphoma in patients with IBD who are treated with thiopurines or infliximab and are coinfectd with EBV infection.¹⁸⁻¹⁹ One theory for the increased incidence of EBV positive-lymphomas in patients with IBD is the use of immunomodulators causing iatrogenic immunosuppression. This is thought to lead to an impairment of cell-mediated immunity allowing proliferation of EBV-infected lymphocytes.³⁻¹⁶

One study, conducted by Vos *et al* reported that 92% of patients (11/12) who developed an EBV-positive lymphoma had been treated with azathioprine or 6-MP, compared with only 19% of patients (4/21) with EBV-negative lymphoma. This suggests a strong link between treatment with thiopurines and the development of EBV-positive lymphoma. The majority of the EBV-positive lymphomas were of the diffuse large B-cell type (none of these patients were treated with anti-TNF compounds).²⁰

From our search, we could only identify four published cases of EBV-positive patients who developed diffuse large B-cell lymphoma following treatment for IBD with azathioprine and infliximab.¹³⁻¹⁵⁻¹⁸ That makes our case, to the best of our knowledge, the first in the UK and a figure which may increase in the future.

This case highlights a rare case of EBV-driven colonic lymphoma in a patient with colitis who was treated with a thiopurine and anti-TNF therapies. There is accumulating data for the potential increased risk of lymphoma with IBD and therefore clinicians should be aware of this potential complication and we need to identify the exact risk and also potential risk factors in prospective databases.

Learning points

- ▶ Be aware of risk of lymphoma with combination therapy of thiopurines and anti-tumour necrosis factor therapy in inflammatory bowel disease (IBD).
- ▶ Avoid combination therapy in high-risk groups of patients, for example, young men and elderly.
- ▶ Epstein-Barr virus-driven lymphoma appears to be increasingly recognised.
- ▶ Colonic lymphoma appears to be very rare and may be under-reported in IBD.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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