CASE REPORT

Synchronous colonic lymphoma and adenocarcinoma in a patient with Crohn's disease, treated with thiopurine therapy and a TNF α inhibitor: a challenge to Occam's razor

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SUMMARY

A 52-year-old man with Crohn's disease, treated with thiopurine therapy and a tumour necrosis factor (TNF) α inhibitor, attended for surveillance colonoscopy, which revealed a transverse colon mass. Biopsies of this lesion showed a diffuse large B-cell lymphoma. CT scan demonstrated this lesion, an additional caecal mass and multiple metastases. A supraclavicular lymph node was removed and demonstrated metastatic adenocarcinoma, consistent with a synchronous caecal primary. At multidisciplinary oncological, haematological, histopathological, gastroenterological, radiological and palliative care assessment, the metastatic adenocarcinoma was deemed to carry a grave prognosis. Following sensitive discussion, the patient opted for palliative care and died several weeks later. Occam's razor, the principle that 'complexity should not be assumed unnecessarily', is a medical school doctrine. Occasionally, however, dual diagnoses do arise. Recognition, as in this case, may prove critical in informed decision-making, both by doctors and, most importantly, by patients, about prognosis and optimal patient care, especially end-of-life care.

BACKGROUND

The thiopurines—azathioprine and 6-mercaptopurine (6-MP)—play a major therapeutic role in the treatment of inflammatory bowel disease (IBD). However, thiopurine therapy for IBD and for other conditions has been associated with increased risk for lymphoma.

The treatment of Crohn's disease was revolutionised in the late 1990s with the introduction of infliximab, an antitumour necrosis factor (TNF) monoclonal antibody. Since then, clinicians have faced uncertainty regarding the optimisation of efficacy and safety of anti-TNF therapy. The use of immunomodulators, including the thiopurines and methotrexate, concurrently with anti-TNF therapy, may increase response rates, by decreasing immunogenicity against the anti-TNF compounds, or through synergy, by administering two effective medications.^{1–3} However, concerns related to infections and lymphoma risks have dampened enthusiasm for this approach.

It is well recognised that patients with longstanding IBD are at an increased risk of colorectal cancer.⁴ Surveillance colonoscopy for these patients, at regular intervals, according to defined

protocols, is paramount and central to the detection of colonic cancer at an early and treatable stage.⁵

The occurrence of dual colonic malignant processes, synchronous colonic lymphoma and adenocarcinoma, in a patient with Crohn's disease, on thiopurine therapy and a TNF α inhibitor, is highlighted.

CASE PRESENTATION

A 52-year-old man with a 25-year history of colonic Crohn's disease attended for surveillance colonoscopy. His last surveillance procedure had been 5 years earlier. This had shown quiescent disease involving the entire colon. A fiberoptic sigmoidoscopy had been performed during a flare-up 4 years following this, with sigmoid colon biopsies showing active inflammation, but no dysplasia. Rectal biopsies showed quiescent colitis, but no dysplasia.

There was no family history of IBD or colon cancer. His only other medical history was hypercholesterolaemia. Medical therapy for his Crohn's disease was azathioprine and mesalazine. His other medications were calcium and vitamin D supplements, a weekly bisphosphonate and a statin.

The azathioprine had been introduced 16 months prior as a steroid-sparing agent following three flare-ups. Four months later, fortnightly subcutaneous injections of adalimumab, the TNF α inhibitor, were introduced. Therefore, he had been taking azathioprine and adalimumab concurrently for 12 months at the time of presentation. The patient had previously taken azathioprine 9 years earlier, for a period of 6 months. He stopped it after he felt that it was causing lethargy and, after review by the IBD team, it was discontinued.

At review, the patient reported lethargy, anorexia, weight loss and abdominal bloating. Colonoscopy (figure 1) showed an ulcerated, raised lesion in the mid-transverse colon. It was causing stricturing, which prevented advancement of the colonoscope into the ascending colon. Biopsies of the lesion were taken.

CT scan of the thorax, abdomen and pelvis showed synchronous transverse colon and caecal tumours, with retroperitoneal malignant infiltration, causing bilateral hydronephrosis (figure 2). The scan also showed a 1.9 cm pericolic node, posterior and inseparable from the caecal tumour, with

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Figure 1 Fungating lesion in the transverse colon, which distorted the luminal axis. As a result, the scope looped here and could not pass forward.

non-regional peripancreatic and superior mesenteric nodes, a 2.4 cm supraclavicular node and a small pleural deposit on the right lower lobe of the lung.

INVESTIGATIONS

Prior to the start of immunomodulatory treatment, hepatitis A, hepatitis B, hepatitis C and HIV were negative. Varicella IgG and rubella IgG were positive. Epstein-Barr virus (EBV) assessment had not been performed. Levels of 6-thioguanine (6-TGN) were normal.

The patient had been having routine blood monitoring while on combination thiopurine/anti-TNF treatment. His last set of routine blood tests was 2 months before he presented for review. His haemoglobin had been stable, with a range 97–109 g/L over the previous 12 months. Within the same period, his white cell counts ranged from 3.4 to $4.3 \times 10^9/L$ and neutrophils from 1.7 to $2.3 \times 10^9/L$. His estimated glomerular

filtration rate (eGFR), throughout the 12 months, including 2 months prior to admission, had been $>90 \text{ mL/min/1.73 m}^2$.

Admission blood tests showed acute changes, with haemoglobin of 61 g/L, white cell count $1.4 \times 10^9/L$, neutrophils $0.7 \times 10^9/L$ and raised creatinine of $178 \mu\text{mol/L}$, with eGFR of $43 \text{ mL/min/1.73 m}^2$. Azathioprine and adalimumab were discontinued and bilateral nephrostomies were inserted. The patient became febrile at 38.4°C and was treated with intravenous antibiotics for neutropenic sepsis.

Histology from the transverse colon biopsies was inconclusive, with one small piece of tissue showing a cellular infiltrate of atypical blastic cells (figure 3A). This was sent away for specialist analysis. Given the possibility that this small sample might not yield a diagnosis, supraclavicular lymph node removal was performed.

Following analysis at the Haematological Malignancy Diagnostics Service, the transverse colon histology demonstrated the atypical lymphoid infiltrate of an EBV-driven diffuse large B-cell lymphoma (DLBCL), which stained positive with CD20 (figure 3B).

Histology from the supraclavicular node showed adenocarcinoma cells, with focal signet ring appearance, staining positive with CK20. This was consistent with colonic adenocarcinoma (figure 3C).

DIFFERENTIAL DIAGNOSIS

- Metastatic lymphoma
- Metastatic colonic adenocarcinoma

The presence of significant systemic symptoms, with the development of a colonic tumour with retroperitoneal tumour infiltration, widespread lymphadenopathy and pancytopenia, in a patient with Crohn's disease treated with thiopurine therapy and a TNF α inhibitor, suggested lymphoma as the primary differential diagnosis.

The development of a colonic neoplasm in a patient with a 25-year history of Crohn's disease suggested metastatic colonic cancer as the main differential diagnosis.

TREATMENT

Discussion at the joint oncological, haematological, histopathological, gastroenterological and radiological multidisciplinary

Figure 2 CT images showing transverse colon (A) and caecal masses, (B) with retroperitoneal infiltration causing bilateral hydronephrosis (C).

Figure 3 High-power view of a small area of the transverse colon biopsy, with many large, slightly pale staining, blastic lymphoid cells (A). Atypical lymphoid infiltrate of diffuse large B-cell lymphoma positive with CD20 (B). Adenocarcinoma cells with focal signet ring appearance positive with CK20 (C).

team meetings confirmed the presence of dual malignancies, namely the DLBCL transverse colon lesion and metastatic caecal adenocarcinoma.

The DLBCL was considered potentially curable. Unfortunately, the metastatic caecal adenocarcinoma was deemed to carry a grave prognosis. Moreover, it was acknowledged that monitoring of treatment would be challenging, in terms of being able to differentiate between the two malignancies on CT scanning.

OUTCOME AND FOLLOW-UP

The potential benefits and complications of chemotherapy for the lymphoma were discussed with the patient and his family. However, after careful consideration, he decided that chemotherapy would have a significant deleterious effect on the quality of the remainder of his life and he declined therapy. He was referred to the palliative care team, which provided holistic patient and family care until he died in the hospice several weeks later.

DISCUSSION

It is widely recognised that patients with longstanding IBD are at an increased risk of developing colorectal cancer.⁴ Surveillance colonoscopy for these patients, at regular intervals, according to recommended protocols, is paramount and central to the detection of colonic cancer at an early and treatable stage.^{5 6}

The use of the thiopurines, alone or in combination with TNF α inhibitors in Crohn's disease, is associated with an increased risk of the development of intestinal and extra-intestinal malignancies.⁷ Young males, in particular, have a higher risk of developing non-Hodgkin's lymphoma with this combination of treatment. Conversely, the use of TNF α inhibitors alone does not appear to increase the risk of lymphoma.⁸

In a systematic review and meta-analysis, the data suggested that current thiopurine use of at least 1 year may increase the risk of lymphoma nearly sixfold. However, the increased risk appears to revert back to baseline after thiopurines are discontinued. This suggests that immunosuppression is the key factor associated with increasing the incidence of lymphoma. The absolute risk is highest in those older than 50 years. Young male patients (younger than 30–35 years) may also be a high-risk population.⁹ The authors concluded that, for patients of all ages and genders, the risk of lymphoma needs to be weighed against the potential benefits of therapy and that further work is needed to understand how the trade-off of potential benefit and harm varies with age, particularly in the era of combination immunosuppression therapy.⁹

A further meta-analysis has also shown that, in patients with Crohn's disease, there is an increased risk of non-Hodgkin's lymphoma in those treated with combined anti-TNF and immunomodulator therapy.¹⁰ However, dual colonic lymphoma and adenocarcinoma has rarely been documented.¹¹ There are reports of colonic 'collision tumours'. These are tumours containing both lymphoma and adenocarcinoma, with the two histologies remaining distinct.¹² Moreover, the majority of these are not suspected preoperatively, being diagnosed only on histological examination after tumour removal, when the two malignant components are recognised.¹³

It is possible that either or both of the malignant processes found in this patient predated treatment with combined anti-TNF and azathioprine therapy. The patient's previous colonoscopy was 5 years earlier and both tumours could have been developing at any time following this procedure. The fiberoptic sigmoidoscopy, performed 20 months prior to presentation, confirmed the absence of dysplasia in only the sigmoid colon and rectum. The growth of both tumours had probably already

started. The widespread lymphadenopathy and retroperitoneal infiltration at presentation also suggests that these two processes had a more protracted history.

However, there was certainly an acute deterioration in the patient's haematological blood tests and renal function. This may suggest an aggressive, rapidly progressive lymphoma linked to his thiopurine therapy. Additionally, studies examining the influence of duration of therapy have shown that the standard incidence ratio for lymphomas linked to thiopurine use does not increase after the first year of treatment.⁸ Finally, while the increased risk of lymphoma with combined anti-TNF/thiopurine therapy is highlighted, it is also worth pointing out the potential protective effects that they have against chronic inflammation-driven colorectal cancer.⁷

The intricacies of this case highlight the importance of multi-disciplinary assessment. At the joint multidisciplinary gastroenterological, radiological and histopathological meeting, the suspicion of a lymphoma was raised on the basis of the history, examination, blood tests, colonoscopy and CT scan findings. The histopathologists had a high index of suspicion and sent the scanty diagnostic tissue for analysis at the Haematological Malignancy Diagnostics Service, where specialist staining demonstrated the atypical lymphoid infiltrate of an EBV-driven DLBCL. In the meta-analysis, of the 25 thiopurine-exposed patients in whom EBV positivity was tested, 14 (56%) were EBV positive.⁹ Moreover, 32% of all the non-Hodgkin's lymphomas originated in the bowel.⁹

The presence of the synchronous caecal tumour, thought likely to be a cancer, in a patient with a long history of Crohn's disease, together with doubts that there would be sufficient tissue for diagnosis, led to involvement of the ENT surgeons and supraclavicular lymph node removal, with the confirmation of dual malignancies.

This case evoked memories of William of Occam, the fourteenth century philosopher. His teachings centred on the principle that the simplest unifying theory is the one most likely to be true.¹⁴ Known as Occam's razor, the principle that 'complexity should not be assumed unnecessarily' is a medical school doctrine and mantra that is often adopted by doctors to aid in diagnosis.¹⁵ Occasionally, however, dual diagnoses do arise and the more complex solution proves to be the correct one.

Learning points

- ▶ The use of the thiopurines, alone or in combination with tumour necrosis factor (TNF) α inhibitors in Crohn's disease, is associated with an increased risk of the development of non-Hodgkin's lymphomas, particularly in young men. Conversely, the use of TNF α inhibitors alone does not appear to increase the risk of lymphoma in these patients.⁸
- ▶ Surveillance colonoscopy, according to recommended protocols, is essential in patients with longstanding inflammatory bowel disease, so as to detect colorectal cancer at an early stage.
- ▶ The recognition and diagnosis of a synchronous colonic lymphoma and adenocarcinoma proved critical in patient management.
- ▶ Recognition of the limitations of Occam's razor facilitated multidisciplinary team, patient and family decision-making about prognosis and optimal, holistic patient care, especially end-of-life care.

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