CASE REPORT

Adalimumab-induced acute myeloid leukaemia in a patient with Crohn's disease

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SUMMARY

We present a patient with Crohn's disease under treatment with adalimumab who developed acute myeloid leukaemia (AML) with core-binding factor beta gene rearrangement. This case report emphasises the importance of long-term close follow-up of patients receiving adalimumab because of the increased risk of developing AML and other malignancies.

BACKGROUND

Inflammatory bowel disease (IBD) is characterised by chronic inflammation of the gastrointestinal tract and is divided into two clinical disorders: Crohn's disease (CD) and ulcerative colitis. CD can involve any part of the gastrointestinal tract, whereas ulcerative colitis usually affects the colon.¹ Patients with CD often present with abdominal pain and a change in their bowel habits, especially diarrhoea, as a result of malabsorption secondary to small bowel involvement. Perianal disease is not uncommon, affecting one-third of patients.^{2,3} Patients with a moderate to severe disease frequently require antibiotics, glucocorticoids and immunomodulatory therapy to control it. Surgical resection is sometimes needed to manage patients with a small bowel obstruction or neoplastic lesions.⁴ Many targeted monoclonal antibodies have been approved by the US Food and Drug Administration (FDA) in recent years, but long-term complications following usage of these drugs need to be further evaluated. Adalimumab, for example, is an anti-tumour necrosis factor (anti-TNF) monoclonal antibody that was developed

Figure 2 Bone marrow aspirate (Wright-Giemsa stain) showing rare eosinophils with basophilic granules.

and approved by the FDA to treat patients with moderate to severe CD, especially those who do not respond to infliximab, because adalimumab has a high affinity to TNFs.⁵ However, this medication is associated with adverse effects, including headaches, skin rash and an increased risk of infection. Several neoplastic-related events were reported among patients being treated with anti-TNFs, such as lymphoma and malignant melanoma.^{6–8} The first reported case of acute leukaemia in a patient using etanercept was in 2003.⁹ In 2008, a postmarketing study revealed 121 cases of leukaemia (acute and chronic) secondary to TNF blockers. Seventy-four cases were related to infliximab, 39 to etanercept and 12 to adalimumab therapy.¹⁰ However, there were limited data on the cytogenetic classifications and survival rate. In 2009, the FDA reported 44 cases of AML in patients receiving TNF- α inhibitors (for all indications).¹¹ Moreover, several recent case reports have shown an association of adalimumab with acute myeloid leukaemia (AML).^{12–14} On the other hand, adalimumab is thought to be a relatively safe drug on the basis of a recent clinical trial in which it was compared with a placebo.⁵ No association was shown between adalimumab and the development of malignancy, however, because the trial did not follow patients for a long duration. To our knowledge, this case report is the first to describe a patient with CD being treated with adalimumab who developed AML with core-binding factor beta (CBFB) gene rearrangement. This case report emphasises the importance of long-term, close follow-ups of patients receiving adalimumab because of the increased risk of developing AML and other malignancies.

Figure 1 Bone marrow core biopsy (H&E stain) showing 80%–90% cellularity with 20%–30% myeloblasts (orange arrows), abundant eosinophils (green arrow) and frequent mitosis (black arrow).

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CASE PRESENTATION

A 32-year-old African-American man presented with a medical history of CD status after two partial bowel resections several years ago and treatment with adalimumab for approximately 1 year. He was refractory to azathioprine, which he received for 2 years, and was stopped for 7 months before adalimumab was administered. He was also refractory to treatment with mesalamine and steroids. He had initially presented to an outside hospital, reporting cough, chest tightness and subjective fever for several days. The patient was in his usual state of health until his recent symptoms occurred. His chest X-ray showed a lingular opacity consistent with possible pneumonia. He was diagnosed with community-acquired pneumonia and discharged home with levofloxacin.

However, he was prompted to return to the emergency department because his laboratory test showed pancytopenia with evidence of blast cells in the differential count, which was concerning for acute leukaemia. He was initiated on broad-spectrum antibiotics and transferred to our centre for further care. On arrival, the patient was febrile at 38.5°C but haemodynamically stable.

INVESTIGATIONS

His laboratory tests results were pertinent for pancytopenia with an absolute neutrophil count of 244. He was continued on spectrum antibiotics and started on empiric antiviral and antifungal coverage. His bone marrow biopsy showed 20%–30% blasts with an increase in eosinophils indicative of AML (figure 1). The bone marrow aspirate showed rare eosinophils with basophilic granules (figure 2). These findings were highly suggestive of AML with CBFB, also called AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);CBFB-MYH11, per the latest 2016 revision to the WHO classification of myeloid neoplasms and acute leukaemia. These findings were confirmed by a subsequent fluorescence in situ hybridisation study. The patient continued to spike fevers despite receiving vancomycin and cefepime and, therefore, underwent a CT scan of the chest, abdomen and pelvis. The results showed tree-in-bud nodularity and multifocal infiltrates, most prominent in the left lung, which was concerning for mycobacterial and fungal infections, especially in the setting of chronic immunosuppression.

TREATMENT

Despite the patient's persistent fevers, broad-spectrum antibiotics were discontinued, in accordance with infectious team recommendations, as the patient's condition was not consistent with acute bacterial infection. A bronchoscopy with bronchoalveolar lavage was performed, and the samples tested negative for acid-fast bacilli and *Pneumocystis jirovecii* but positive for atypical cells, which raised further suspicion of leukaemic pulmonary infiltrates. A repeat bronchoscopy with biopsy, however, showed no evidence of neoplasm, granuloma or significant inflammation.

OUTCOME AND FOLLOW-UP

The patient continued to do well without antibiotics and was subsequently started on induction chemotherapy, followed by four cycles of consolidation chemotherapy with high-dose cytarabine. He developed neutropenic fever and required hospitalisation twice through the course of chemotherapy. A subsequent bone marrow biopsy revealed that the patient had achieved remission.

DISCUSSION

Malignant diseases, including lymphoma and malignant melanoma, have been shown to be associated with long-term use

of anti-TNF therapy.^{6–8} Several studies have demonstrated that TNF has a significant role in controlling cell proliferation, differentiation and apoptosis, especially in malignant cells.^{15 16} Moreover, studies have shown an increased risk of haematological malignancies among patients with IBD compared with the general population.^{12 13} A core-binding factor beta gene and the protein regulates a host of genes required for haematopoiesis. Rearrangement in this gene is linked to acute myeloid leukaemia of the M4Eo subtype. TNF- α causes immune suppression by suppressing the TNF superfamily of proteins. The FDA in its postmarket reports showed an increase incidence of leukaemia in patients with CD using TNF- α blockers. The FDA did not publish the subcategory of these reported cases of leukaemia based on WHO classification. Data on leukaemia and its subcategories are needed to strongly link this particular chromosomal rearrangement to the use of anti-TNFs in CD. Interestingly, a recent study showed that the odds of developing myeloid neoplasms in patients with IBD increased in those receiving thiopurine monotherapy or in combination with TNF- α inhibitors compared with patients who were receiving TNF- α inhibitor monotherapy.¹⁷ Our case describes the development of AML in a patient with CD who had been treated with adalimumab for 1 year. He likely developed AML because of the extended period receiving adalimumab, with the possible contribution of past exposure to thiopurines. Nonetheless, this occurrence might have been coincident with the development of AML.

Clinicians should be aware that adalimumab can increase the risk of malignant diseases. Therefore, patients receiving this medication who develop an unexplained fever should be evaluated for malignant disease, including leukaemia. Further studies should assess the factors that increase the risk of malignancy among patients who are being treated with adalimumab to determine which patients should avoid it.

Learning points

- ▶ Adalimumab is an anti-tumour necrosis factor monoclonal antibody that was developed and approved by the US Food and Drug Administration to treat patients with moderate to severe Crohn's disease.
- ▶ Studies show an increased risk of haematological malignancies among patients with inflammatory bowel disease compared with that in the general population.
- ▶ Recent case reports have shown an association of adalimumab with acute myeloid leukaemia; long-term monitoring for side effects, including the development of therapy-related acute myeloid leukaemia, is needed.

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