CASE REPORT

Macrocytosis in Crohn's disease: a devastating blast

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SUMMARY

A 47-year-old woman with a 36-month history of Crohn's disease with one previous bowel resection treated with azathioprine was found to have a persistently raised mean corpuscular volume (MCV) on routine complete blood count testing. Despite vitamin B₁₂ replacement, her MCV remained elevated. A bone marrow biopsy was performed, which demonstrated myelodysplastic syndrome. Macrocytosis is a common abnormality in patients with Crohn's disease, most commonly due to vitamin B₁₂ deficiency and secondarily due to bacterial overgrowth. However, it is important to recognise that myelodysplastic syndrome is a common under-reported complication of azathioprine therapy. One-third of cases progress to acute myeloid leukaemia with poor prognosis. In patients with suspected myelodysplastic syndrome, azathioprine therapy should be immediately discontinued.

BACKGROUND

Azathioprine therapy is well established for the maintenance of remission of patients with Crohn's disease. There have been no previous case reports of myelodysplastic syndrome (MDS) linked to azathioprine use in the context of inflammatory bowel disease (IBD).

CASE PRESENTATION

A 47-year-old woman with a diagnosis of Crohn's disease was reviewed in gastroenterology clinic and was noted to have a persistently raised mean corpuscular volume (MCV). She had been diagnosed with small bowel Crohn's disease 36 months earlier and had an ileocaecal resection for a fibrotic stricture. She had no other medical history of note and did not drink any alcohol. Following her ileocaecal resection, she had disease recurrence in the terminal ileum, and azathioprine was initiated at a dose of 125 mg.

Complete blood counts performed at the start of azathioprine therapy showed a normal thiopurine S-methyltransferase level, haemoglobin (Hb) of 10.7 g/dL (reference range: 12.0–16.0 g/dL) and MCV of 91 fL (reference: 78–101 fL). Over the next 6 months, her Hb improved to 11.0 g/dL but her MCV had progressively risen to 109.4 fL. The folate level was 3.0 µg/L (reference: 1.8–14.0 µg/L) and vitamin B₁₂ level 93 ng/L (reference: 120–900 ng/L). A standard 3-month course of intramuscular vitamin B₁₂ replacement was initiated; however, her MCV remained high at 113 fL despite a normal folate and vitamin B₁₂. Furthermore, she had developed symptoms of fatigue and complete blood count testing revealed platelets $90 \times 10^9/L$ (reference: $150\text{--}450 \times 10^9/L$),

Hb 10.7 g/dL (reference: 12.0–16.0 g/dL), leucocytes $2.8 \times 10^9/L$ (reference: $3.7\text{--}11.1 \times 10^9/L$).

Bone marrow trephine biopsy was performed following referral to haematology.

OUTCOME AND FOLLOW-UP

Azathioprine therapy was stopped and the patient's fatigue and pancytopenia resolved. The patient continues to be under 3 monthly follow-up by gastroenterology and haematology with regular complete blood count checks and symptom review. Her macrocytosis continues consistent with a diagnosis of myelodysplastic syndrome. There is no evidence of disease progression to acute myeloid leukaemia.

DISCUSSION

MCV is a measure of the volume of the 'average' red blood cell (RBC). A raised MCV or macrocytosis occurs when RBCs have a diameter greater than 8 µm or larger than the size of lymphocytes on a peripheral smear. There are a number of causes for macrocytosis and include the abnormalities of DNA metabolism, a shift to immature (reticulocytes) or stressed red cells, primary bone marrow disorders or lipid abnormalities. In patients who have had small bowel surgery, the most common reason for macrocytosis is the abnormality of DNA metabolism due to vitamin B₁₂ deficiency. Vitamin B₁₂ is absorbed passively in the distal half of the ileum and this process may be impaired following surgical resection. However, it is important to note that deficiencies in B₁₂ can also arise as a result of bacterial overgrowth and coexistent autoimmune disease such as coeliac disease and pernicious anaemia.

Figure 1 A sample of this patient's bone marrow demonstrates severe dysplasia, in keeping with myelodysplastic syndrome.

To cite: Lee LYW, Santharam V, Macfaul G. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-200287

In this case, vitamin B₁₂ levels returned to normal range, but the patient still had macrocytosis and had developed pancytopenia. Initial tests could have included a blood film; however, pancytopenia is an indication for bone marrow examination and the bone marrow trephine biopsy was thus performed (figure 1).

Inflammatory bowel disease is a systemic immune defect associated with a number of extraintestinal manifestations. However, an IBD per se is not associated with MDS. A population-based study from Minnesota of 15 000 patients with IBD was not able to demonstrate an association and did note that the risk of MDS in IBD was negligible (less than 1 case per 100 000 person-years).¹

Azathioprine is well established for the maintenance of remission for patients with Crohn's disease. There was no previous case reports of MDS linked to azathioprine use in the context of IBD.

Azathioprine is used for many medical conditions such as Wegener's disease, multiple sclerosis and post-transplant immunosuppression. Within these specialties, it is widely accepted that azathioprine increases the risk of MDS, and has been classified as a human carcinogen by the International Agency for Research on Cancer.² In a rheumatology cohort of 370 patients who had received azathioprine, the number of cases of treatment-related MDS (t-MDS) was 100-fold higher than the number of cases in an age-matched general population, being elevated to five cases per 100 000 per 10 years. Furthermore, there was a dose-effect with patients at higher doses or on long-term therapy at increased risk.³ In a further review of 25 rheumatology cases of azathioprine-treatment MDS (t-MDS), t-MDS was noted to be predominantly associated with aberrations of chromosome 7, either monosomy 7 or deletions of the long arm and, of concern, 32% of cases progressed to acute myeloid leukaemia with poor prognosis.⁴ In a cohort of 306 patients with t-MDS that had transformed to acute myeloid leukaemia, the 5-year survival was less than 10%.⁵ However, a caveat must be noted as the natural history of t-MDS is not fully understood and there have been case reports of spontaneous morphogenic and cytogenetic remission of t-MDS following the withdrawal of azathioprine therapy.⁶

Learning points

- ▶ Myelodysplastic syndrome must be considered early in the differential diagnosis of blood abnormalities in patients with inflammatory bowel disease being treated with azathioprine.
- ▶ To prevent the treatment-MDS progression, patients with persistent macrocytosis require
 - Immediate cessation of azathioprine therapy;
 - Haematological investigations, including either a blood film or bone marrow;
 - Ongoing follow-up.

Contributors This manuscript was co-written by VS and LL. GM reviewed the manuscript.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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