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Case Report

Acute Myeloid Leukemia with Myelodysplasia-Related Changes in a Patient with Crohn's Disease Treated with Immunosuppressive Therapy

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Keywords

Crohn's disease · Immunosuppressive therapy · Anti-tumor necrosis factor · Acute myeloid leukemia · Myelodysplasia

Abstract

We report a case of acute myeloid leukemia with myelodysplasia-related changes in a patient with Crohn's disease. The patient was diagnosed with Crohn's disease at the age of 47 years and was treated with the tumor necrosis factor α inhibitors adalimumab and infliximab, and a short course of azathioprine. Four years later, the patient developed acute myeloid leukemia with myelodysplasia that involved mainly erythropoiesis. Crohn's disease is associated with an increased risk of cancers including hematological malignancies. Cancer surveillance including hematology assessment is warranted to monitor the patients on immunosuppressive therapy.

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Case Report

A 47-year-old male patient initially presented with recurrent abdominal pain, diarrhea, low fever, bloody stools, and oral ulcers in November 2012. He had a 10-kg weight loss over the previous 8 months. His blood counts were essentially normal except for mild anemia. He was admitted to the hospital for perianal fistula, which was treated by surgical repair procedure. The diagnosis of Crohn's disease (CD) was made by colonoscopy and biopsy. The findings included multiple inflammatory lesions and narrowed lumen in the ileum and colon. The ileum biopsy showed characteristic superficial ulceration and transmural inflammation (Fig. 1a, b).

The patient was treated with adalimumab with an initial dose of 160 mg, followed by a weekly dose of 60 mg for a total of 12 weeks. He also had a course of azathioprine (50 mg/day) for 8 days, which was discontinued because of febrile neutropenia. His symptoms were significantly improved with the treatment. However, his CD recurred in 2 years. The treatment was switched to infliximab, and he remained to have intermittent flares of CD that was controlled by infliximab treatment.

Four years after CD diagnosis, the patient was found to have severe anemia. At this point, a blood test revealed hemoglobin of 52 g/L, WBC 25.8 × 10^9/L with immature cells, and platelets 35 × 10^9/L. Bone marrow aspirate revealed 21% blasts, and significant myelodysplastic changes involved mainly in erythroid hematopoiesis. Iron staining of the marrow specimen showed abnormal erythroid sideroblasts and ringed sideroblasts (Fig. 1c, d). Cytogenetic karyotype analysis showed a clonal abnormality of loss of chromosome 7. The diagnosis of acute myeloid leukemia (AML) with myelodysplasia-related changes was made accordingly. After discussion about leukemia treatment, the patient declined chemotherapy for AML, and he was discharged after supportive therapy including blood transfusion.

Discussion

The patient in this report developed therapy-related AML (t-AML). Although t-AML occurred mostly in patients who had previously been treated with cytotoxic drugs for solid tumors or hematological malignancies, it was also seen in non-neoplastic disorders following immunosuppressive therapies. Inflammatory bowel diseases, including CD and ulcerative colitis, have been reported to have an increased risk of hematological malignancies, including acute leukemia, myelodysplasia, and lymphomas [1]. The first description of AML in patients with inflammatory bowel disease was reported in 1980, which identified 5 AML cases among 400 ulcerative colitis patients [2]. In a recent population-based study, using a territory-wide registry in Hong Kong, the risk of acute leukemia was found to be almost 6 times higher in Chinese patients with CD than the general population [3]. With a trend of increasing incidence of inflammatory bowel diseases in Asia [3], it is important to assess complications of disease and to include blood cell counts for surveillance of hematological malignancies.

Our patient was treated for his CD with anti-tumor necrosis factor (anti-TNF) agents including adalimumab and infliximab, and a short course of azathioprine. Anti-TNF is increasingly used for treating CD. It is noteworthy that, similar to our case, there have been reports of acute leukemia in patients with CD or other autoimmune diseases with the use of anti-TNF drugs [4–7]. These cases may raise a concern of anti-TNF drugs potentiating leukemia. Furthermore, anti-TNF therapy is often used in combination with azathioprine. It has been suggested that combination therapy is associated with a higher risk of cancer than anti-TNF or

thiopurine drug alone [8]. However, it remains difficult to define the mechanism of t-AML in CD because there are multiple host and environmental factors, which may be implicated in the development of leukemia.

Azathioprine was used for our patient only for a short course. It was discontinued because of side effects. Azathioprine is a commonly used immunosuppressive agent. There have been many studies on using thiopurine drugs. There have been case reports and small series that implicate azathioprine as a leukemogenic agent [9, 10]. It appeared that a prolonged duration of azathioprine was associated in developing myelodysplasia and AML. In a study of 56 cases of t-MDS-AML, azathioprine had been given for a median of 65 months (range 6–192 months) and a median cumulative dose of 146 g (range 19–750 g) [10]. A mechanism of azathioprine-associated myeloid leukemia is a deficiency in the enzyme thiopurine S-methyltransferase, which may lead to slow the metabolism of the drug and to a higher risk of hematologic toxicity [11]. Our patient received mostly anti-TNF therapy, and azathioprine was administered only for a short course of 8 days. The functional level of the enzyme is unknown in our patient, and it is unclear whether multiple immunomodulatory therapies potentiated the leukemia process.

In conclusion, this case report presents t-AML with prominent myelodysplasia in a Chinese patient with CD. Immunosuppressive therapy and chronic immune-mediated inflammation may be implicated in leukemia. Future studies are required to assess risk factors for the development of hematological malignancies.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors declare no conflicts of interest.

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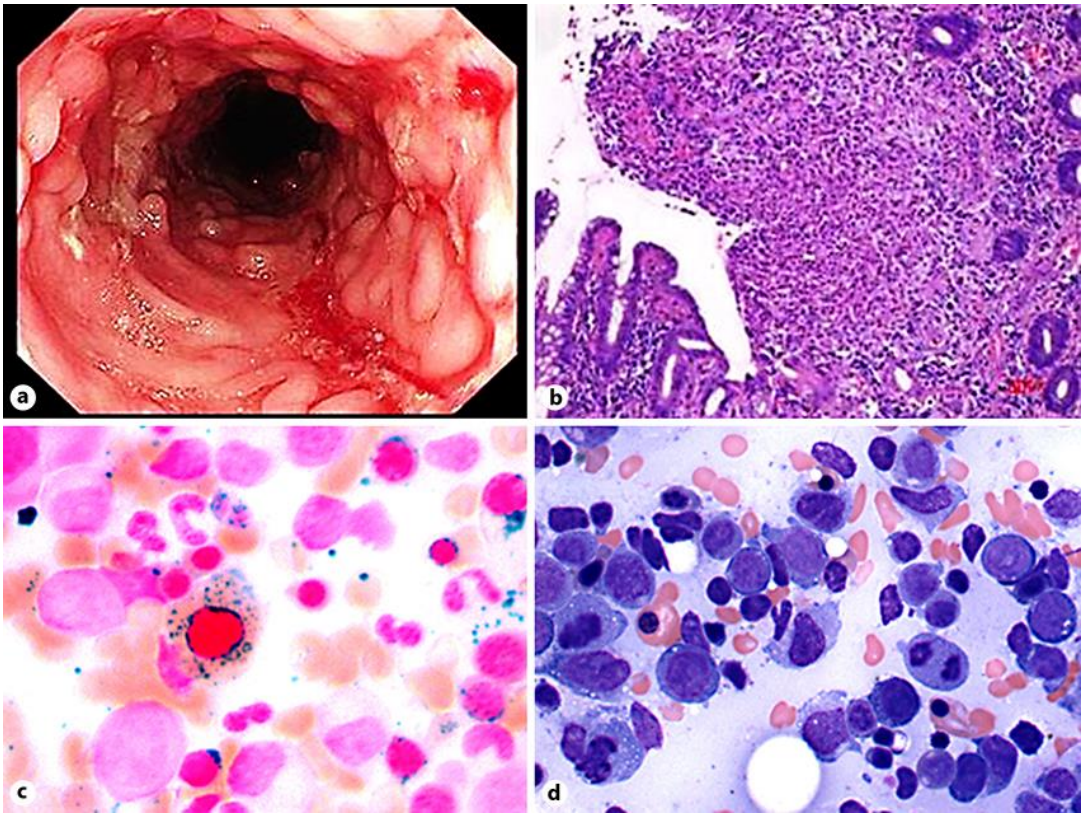

Fig. 1. **a** Endoscopic image of the ileum showed mucosal erythema, ulcerations, and nodular edema in a cobblestone appearance. **b** The ileum biopsy showed surface ulcerations and submucosal diffuse inflammatory infiltrates. **c** Bone marrow smear of Prussian staining showed iron-loaded blue-staining granules in erythroid precursor cells, a large megaloblastoid erythroblast containing numerous iron granules and forming ringed sideroblasts. **d** Bone marrow aspirate showed an increase in blasts and dysplastic cells.