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An undue guest of thrombotic thrombocytopenic purpura with acute myeloid leukemia in an elderly patient with Crohn's disease

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ABSTRACT

Thrombotic thrombocytopenic purpura and acute myeloid leukemia are rarely associated with Crohn's disease. Early recognition of these conditions with timely referral to hematologist is paramount. Acute myeloid leukemia should be suspected despite the absence of blast cells from peripheral blood film. Although is rare, thiopurines like azathioprine have been associated with increased risk of acute myeloid leukemia. Therefore, patients should be given informed consent of this risk prior to initiation of thiopurines therapy.

Keywords: acute myeloid leukemia, azathioprine, Crohn's disease, thiopurines, thrombotic thrombocytopenic purpura

1. INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a rare hematological disorder caused by severe deficiency of the von Willebrand factor-cleaving protease ADAMTS13, which results in the breakdown of platelets with subsequent blood clots formation in microvasculature. It can be due to inheritance (mutation in ADAMTS13) or acquired (autoimmune). Classical presentations include fever, purpuric rash, altered mental status, microangiopathic hemolytic anemia, thrombocytopenia, and renal impairment (Stanley & Michalski, 2019). Acute myeloid leukemia (AML) on the other hand, is hematological malignancies that affect the bone marrow causing production of abnormal myeloblasts, red blood cells, or platelets. Among the known risk factors for AML include underlying hematological disorders (e.g. myelodysplastic syndrome (MDS) and myelofibrosis), congenital disorders (e.g. Bloom syndrome and Fanconi anemia), germline mutations, and radiation exposure and chemotherapy agents. TTP as the initial presentation of AML is extremely rare and to the best of our knowledge, only one case has been reported so far (Kucharik et al., 2020). Here, we describe a rare case of

lethal AML preceded by TTP in an elderly patient with Crohn's disease (CD) who had been on maintenance azathioprine therapy.

2. CASE REPORT

A 78-year-old lady with 3-year history of ileocolonic CD presented to the emergency department with crampy abdominal pain and watery diarrhoea for 2 weeks, consistent with the disease flare. Her disease has been quiescent while on 50mg azathioprine daily for the past 2 years. Subsequent colonoscopy showed moderately active right-sided colitis with terminal ileitis. Intravenous hydrocortisone was initiated along with the increment of azathioprine to 75mg once a day. Magnetic resonance enterography (MRE) was also performed to assess the involvement of the small bowel, which demonstrated inflamed distal ileum with a few deep ulcers (Figure 1).

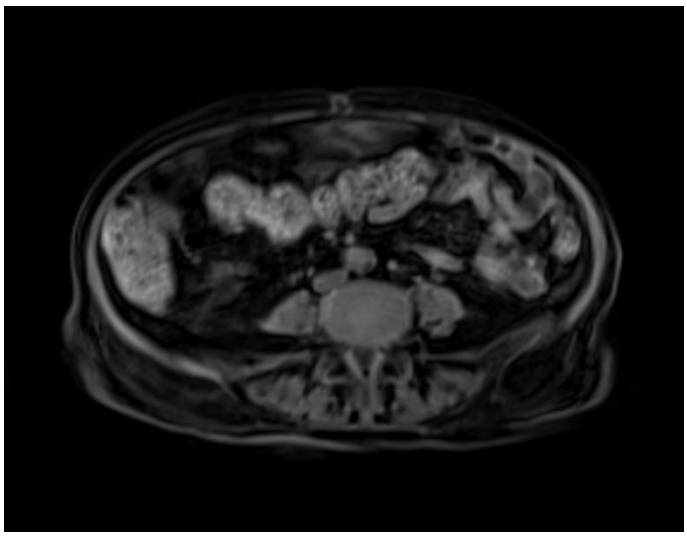

Figure 1 MRE showing a clump of thickened and enhanced bowel loops at the right iliac fossa following gadolinium administration, approximately 17-20cm from ileocaecal valve. The loop of bowel appears to be adhered to the right anterior abdominal wall. Few deep ulcers are noted.

Unfortunately, she was deteriorating after day 3 of admission, as evidence by fever, feeling shortness of breath and lethargic. Clinical examination revealed pallor of conjunctiva and bibasilar coarse crepitation with poor air entry. There was no evidence of overt gastrointestinal bleeding or purpuric rashes. Blood investigations showed severe bicytopenia of hemoglobin 3.7g/dL and platelet 12 x 10^9/L. Inflammatory markers were raised with white cell count 12 x 10^9/L and C-reactive protein 8.4mg/dL. Liver function test was normal except for mild hyperbilirubinemia of 33.2umol/L and hypoalbuminemia of 27g/L. Renal profile showed mild renal impairment with urea 10mmol/L and creatinine 141umol/L. Lactate dehydrogenase was 1089 U/L with international normalized ratio of 1.4. Due to abnormal full blood count result, her azathioprine was with held, and she was treated with packed red blood cells transfusion together with intravenous ceftriaxone for suspected lower respiratory tract infection.

She remained febrile and dependent on blood transfusion. Subsequent full blood picture demonstrated features of micro-angiopathic hemolytic anemia with thrombocytopenia in keeping with TTP (Figure 2a). Hence, plasma exchange was initiated, where she received total of 11 cycles of plasma exchanges with escalation of antibiotic to meropenem. Despite that, in view of lack of clinical and biochemical improvement, cyclosporine A 50mg twice daily and intravenous methylprednisolone 500mg once a day were also instituted.

Eventually, bone marrow aspiration and trephine biopsy was performed. Despite no blast cell was seen in the peripheral blood smear, surprisingly marrow aspirate showed 24% of blast cells (Figure 2b) which was consistent with refractory anemia with excess of blast (RAEB). This was rapidly progressed to AML that was confirmed by cytogenetic and flow cytometry studies. She was initially planned for chemotherapy, however, in view of her extremely ill condition, family members have opted for best supportive care. She succumbed to her illness at her pleasant home.

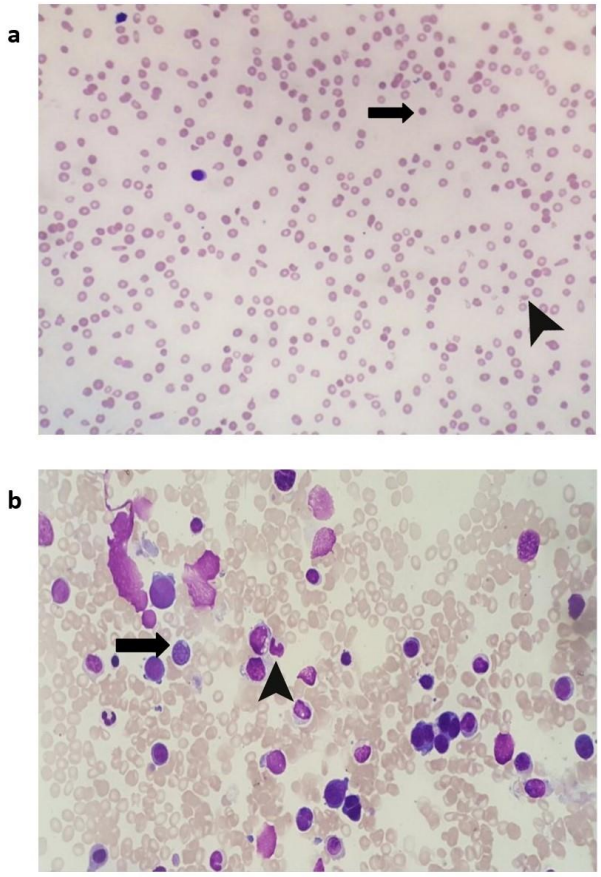

Figure 2 Full blood picture showing (a) presence of spherocyte (arrow) and fragmented cell (arrowhead) with the background of anemia & thrombocytopenia and (b) blast cell (arrow) with binucleated red blood cell (arrowhead).

3. DISCUSSION

The etiology of TTP is largely unknown, but a few triggers have been associated with it such as bacterial infection, autoimmune diseases, and pregnancy. A few case reports (Almogy et al., 2001; Schleinitz et al., 2003) on the occurrence of TTP in long-standing inflammatory bowel disease (IBD) have been published while one recent case report has reported TTP as the first presentation of CD (Unverdi et al., 2011). Drug-induced TTP is a well-known phenomenon and example of the culprits includes quinine, ticlopidine and chemotherapy agents.

While thiopurines (azathioprine and mercaptopurine) are not known to cause TTP, they have been associated with an increased risk of lymphoproliferative disorders, non-melanoma skin cancers, and to a lesser extent, myeloid neoplasms, namely AML and MDS. Greenstein et al., (1985) found that the incidence of myeloid neoplasms in IBD patients treated with thiopurines was 10 per 100,000 person-years as compared to general population of 3.7 per 100,000 person-years. Recently, one case of AML has been described in CD patient, following 9-year history of azathioprine therapy (Fahimi et al., 2015). The exact role of thiopurines in the development of myeloid neoplasms is not well understood but could be attributed to the chronic inflammatory process, thiopurines' intrinsic toxicity and its immunosuppressive effects.

In our case, the precipitating events that lead to AML could be multifactorial such as infection, presence of autoimmune disease, and possibly the azathioprine therapy. It worth noted that previous studies have proposed an increased risk of AML with thiopurines after a cumulative dose of 600g and longer treatment duration of more than 5 years (Knipp et al., 2005). It is not possible to fully establish the causal link between azathioprine and occurrence of AML in our patient since she had only been on azathioprine for 2 years with a relatively low cumulative dose. Having said that, there were other studies that showed the AML risk continue to be high in a subgroup of patients even with low cumulative dose of azathioprine (Bo et al., 1999). This might be due to low individual thiopurine methyltransferase (TPMT) activity that cause increase in sensitivity to azathioprine, which eventually leads to higher risk of myelotoxicity and AML.

However, in Asian patients with Crohn's disease, mutation of nudix hydrolase 15 (NUDT15) gene is actually play a greater role than mutation of TPMT in inducing myelotoxicity, as described in many of previous studies (Zhang et al., 2018). Unfortunately, we did not perform genetic testing of TPMT or NUDT15 in this patient, due to unavailability of these tests in our country.

4. CONCLUSION

In conclusion, our case demonstrated a rare occurrence of AML in elderly patient with CD. To complicate the case, patient initially developed a clinical picture of TTP, in which somehow masking and delayed the diagnostic workup for AML. Treating physician need to recognize any potential hematological issues early in patient with IBD. Early referral to hematologist with timely investigations such as bone marrow biopsy is paramount. Although incidence of AML associated with thiopurines is very low - therefore the benefit of treatment usually outweighs the risk; the risk should be enclosed to the patients as part of the informed consent prior to initiation of thiopurines therapy, especially in elderly patient.

Authors' contribution

Involved in clinical care of the case: SAW, KNMN, WZ, NRT, RARA
Drafting the manuscript: SAW, KNMN
Revising the manuscript: KNMN, RARA
All authors critically appraised the manuscript and approved the final version.

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Conflict of interest

All authors declared that there is no conflict of interests.

Informed consent

Appropriate consent was taken from the patient's family prior to manuscript production.

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Conflict of interest

The authors declare no conflict of interest.

Data and materials availability

All data associated with this study are present in the paper.

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