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Case Report

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Azathioprine-Induced Severe Bone Marrow Suppression

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ABSTRACT

Aplastic anemia is characterized by bone marrow failure and pancytopenia. It could be due to autoimmune disorders, radiation, drugs, or chemicals. Drugs that mostly cause aplastic anemia include chloramphenicol, non-steroidal anti-inflammatory drugs, antiepileptic drugs, gold salts, and antithyroid drugs. Clinical sign and symptoms often result from pancytopenia that includes signs of anemia and bleeding. In some patients, fever and sepsis are seen that are due to neutropenia. Azathioprine is a purine antimetabolite, an immunosuppressive drug that causes myelosuppression and pancytopenia, especially in patients who have some degrees of TPMT (Thiopurine Methyltransferase) activity. We present a patient who admitted to our hospital with fever and pancytopenia and a history of recent azathioprine treatment. Because of delay in the recovery of pancytopenia, she was suspected of aplastic anemia, and bone marrow aspiration and biopsy were done for her.

Introduction

Myelosuppression refers to pancytopenia in the presence of bone marrow failure. It could be due to autoimmune disorders, radiation, drugs, or chemicals. Drugs that mostly cause aplastic anemia include chloramphenicol, non-steroidal anti-inflammatory drugs, antiepileptic drugs, gold salts, and antithyroid drugs [1]. Clinical sign and symptoms often result from pancytopenia that includes the signs of anemia and bleeding. In some patients, fever and sepsis are seen due to neutropenia [2].

Azathioprine is a purine antimetabolite, an immunosuppressive drug that causes myelosuppression and

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pancytopenia by dose-dependent effect or idiosyncratic mechanism, especially in patients who have degrees of TPMT (thiopurine methyltransferase) deficiency [3]. Here we present a patient who suffers from azathioprine cytotoxic effects.

Case Presentation

A 33-year-old woman, a known case of Rheumatoid Arthritis (RA), referred to our hospital with a history of progressive fatigue and recently easy bruising. The patient was diagnosed as RA since 13 years ago, which was controlled by low dose prednisolone (5 mg/d), methotrexate (10 mg/wk), sulfasalazine and hydroxychloroquine. She stopped using methotrexate about 8 months ago, but by arthritis flare up, she started using azathioprine (150 mg/d) since the last 35 days and continued up to 10 days ago.

She was also complaining of progressive hair loss, few oral erosions, and frequent mucosal bleeding in the recent month. She did not note any exposure to chemical agents. She also had no history of recent fever or weight loss. In physical examination, she was a young oriented woman, with normal vital signs. She was pale, and patchy ecchymotic lesions could be seen on her skin. Severe hair loss was also apparent (Figure 1). Her other examination results were normal.

Her complete blood count were WBC=800/mm^3, Hb=8 g/dL, MCV=90 fL, Platelet=10000/mm^3. Other data are presented in Table 1. Abdominal ultrasound revealed no organomegaly and lymphadenopathy. Bone marrow aspiration and biopsy were performed due to severe and prolonged pancytopenia after drug secession. As shown in Figure 2, there was severe hypoplastic marrow. Maturation arrest was seen in myeloid series without any evidence of blasts or dysplastic cell.

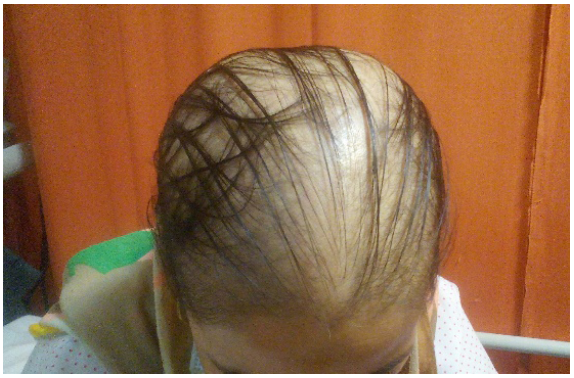

Figure 1. Severe hair loss

The patient was supported by packed cell and platelet transfusion. Three weeks after stopping azathioprine use, her WBC count started to increase; two days later her hemoglobin value increased and her platelet count was returned to normal after 4 weeks of drug secession.

Discussion

Pancytopenia has a wide differential diagnosis, such as congenital and acquired bone marrow suppression; infection; cytotoxic therapies, including chemotherapy and radiotherapy; bone marrow space occupying lesions; nutritional deficiency; destruction or sequestration. The workup of newly-onset pancytopenia must include a precise clinical examination and taking medication, recreational drug, and environmental exposure history [4, 5]. The cutoff reference ranges of pancytopenia include hemoglobin level <12 g/dL for non-pregnant

Table 1. Laboratory data

Laboratory Tests	Units
Reticulocyte count	0.8
LDH	276 U/L
AST	25 U/L
ALT	30 U/L
ALK.P	210 U/L
INR	1.01
PT	12.6 s
PTT	29 s

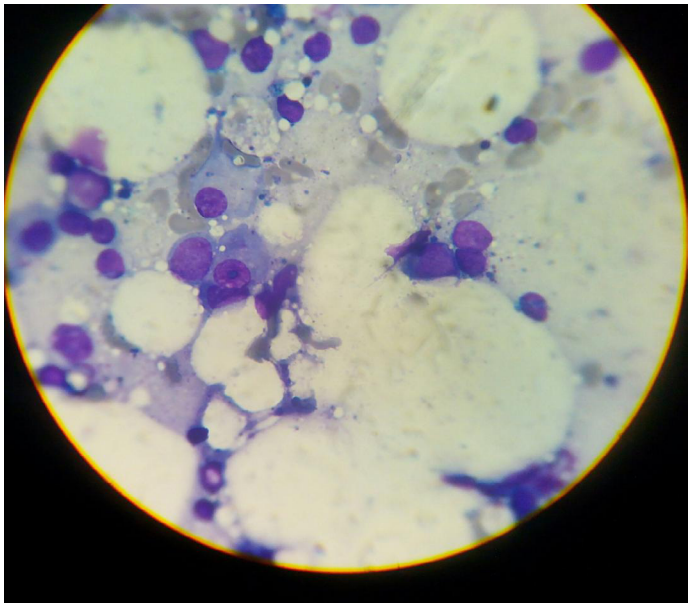

Figure 2. Severe hypoplastic bone marrow

women and <13 g/dL for men, absolute neutrophil count <1800/µL, and platelet count <150000/µL [6].

Evaluation of pancytopenia starts with detailed history taking including precise drug history and physical examination. Initial laboratory evaluation includes Complete Blood Count (CBC); examination of the Peripheral Blood Smear (PBS); electrolytes, renal and liver function tests. Bone marrow aspiration and biopsy is a handy test in detecting the underlying cause of pancytopenia, especially in hematologic disorders [7, 4].

Diagnostic considerations in hyperproliferative pancytopenia include aplastic anemia, vitamin or mineral deficiencies like folate, B12, or copper, ineffective hematopoiesis like myelodysplastic syndromes, bone marrow infiltration like myelofibrosis, metastatic cancer, storage diseases, hematologic malignancies like hairy cell leukemia, T cell large granular lymphocytic leukemia, and cytotoxic medications [8-12].

Several drugs can cause pancytopenia like non-steroidal anti-inflammatory drugs, antithyroid drugs, antibiotics, antiepileptic drugs, diuretics, immunosuppressant agents such as azathioprine, antipsychotic agents, etc. Many drugs can cause bone marrow aplasia with generally predictable extension and duration. Blood counts may reach to the lowest point 7 to 10 days after drug administration and recovers within 2 to 4 weeks. Our patient started using azathioprine about 5 weeks ago and did not check any blood count. Her full recovery time was 5 weeks after drug cessation [13].

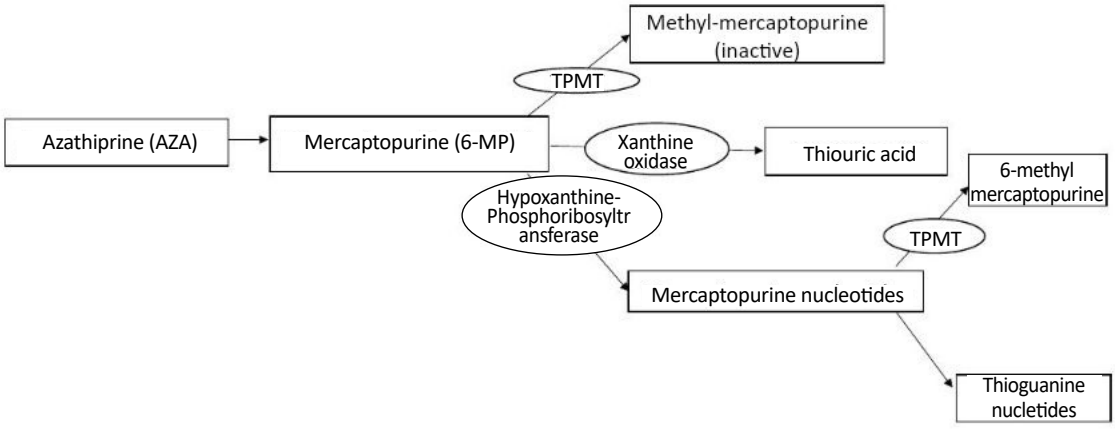

Figure 3. Effect of azathioprine in purine metabolism (TPMT action)

The bone marrow in our patient was profoundly hypocellular with a decrease in all elements, especially myeloid, erythroid, and megakaryocyte cells. The marrow space contains fat cells and marrow stroma with patchy normal lymphoid infiltration, which is seen in bone marrow failures with different causes like drug toxicity and aplastic anemia typically.

Azathioprine (1-methyl-4-nitro-5-imidazolyl derivative of thioguanine) is a purine-mimic antimetabolite immunosuppressive agent that acts as an antagonist of purine metabolism. It causes inhibition of DNA, RNA, and protein synthesis [14]. The two important enzymes responsible for the metabolism of this drug are Thiopurine s-Methyltransferase (TPMT) and hypoxanthine phosphoribosyltransferase (Figure 3) [15].

The most common side effects of azathioprine include gastrointestinal intolerance, bone marrow suppression, and infection [16]. Patients with TPMT allele homozygous for low activity are incredibly susceptible to acute myelotoxicity with thiopurine drugs [17]. The current guidelines for azathioprine administration are weekly monitoring patient's blood count in the first 2 months to prevent dose-dependent myelosuppression.

TPMT testing is not routinely performed before azathioprine initiation in our country; although some clinicians in the other places use it. It may be a reasonable approach to increase azathioprine dose gradually by close CBC monitoring, instead of TPMT test in the Middle East countries. In our patient, the TPMT test was not performed, although the azathioprine starting dose was 150 mg/d which was high with regard to her body weight.

It is more probable that pancytopenia in our patent was due to azathioprine dose-dependent effect, as she had severe hair loss accordingly. But because of the lack of TPMT test, we cannot rule out idiosyncratic effects due to TPMT deficiency. We suggest her not to use azathioprine after that. In conclusion, the indications for treatment with azathioprine should be reviewed and its safety monitoring should reassessed [18].

Ethical Considerations

Compliance with ethical guidelines

All of the authors conduct themselves in accordance with professional ethics.

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Conflict of interest

The authors declared no conflict of interest.

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