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Case Report

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Reversible azathioprine-induced myelodysplastic syndrome

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Abstract

Myelodysplastic Syndrome (MDS) is an irreversible hematopoietic stem cell disorder. Azathioprine can rarely induce MDS, which portends poor prognosis and short survival. We report a unique case of azathioprine induced MDS that was completely reversed with discontinuation of azathioprine. A 59-year-old woman with history of neuromyelitis optica treated with azathioprine for 2 years presented with low grade fever and fatigue. Complete Blood Count (CBC) showed white blood count of 1,000/µl, absolute neutrophil count of 300/µl, hemoglobin of 8.1 g/dl, Mean Corpuscular Volume (MCV) of 109 fl and platelet count of 109,000/µl. The patient had normal CBC 7 months prior to presentation but a gradual rise of MCV could be traced for more than 13 months. Bone marrow biopsy revealed dysplastic erythrocytogenesis and leukogenesis. Azathioprine was discontinued with subsequent normalization of CBC and MCV. Repeat bone marrow biopsy performed 3 months later revealed disappearance of all dysplastic changes. The patient remains with normal CBC 5 years after initial presentation. We document a case of azathioprine induced MDS with subsequent reversal by discontinuation of azathioprine with long survival exceeding 5 years. Progressive macrocytosis typically precedes cytopenias and may serve as an early marker of developing MDS, which should prompt discontinuation of azathioprine.

Introduction

Myelodysplastic Syndrome (MDS) is an irreversible clonal hematopoietic stem cell disorder characterized by ineffective hematopoiesis, which results in cytopenias and their related complications such transfusion dependency, recurrent infections, and bleeding. MDS can also progress to Acute Myeloid Leukemia (AML), with variable transformation risk based on bone marrow blast count, cytogenetic findings and the number of cell lines involved [1]. MDS could arise de-novo or after treatment with chemotherapy or radiotherapy. Therapy-related MDS (t-MDS) is typically associated with prior use of alkylating agents and topoisomerase II inhibitors with an overall poor prognosis and high risk for AML transformation [2-5]. Azathioprine, a thiopurine is an alkylating agent that inhibits purine synthesis and results in immunosuppression. It has been successfully used for treatment of rheumatologic diseases, inflammatory bowel diseases, autoimmune hepatitis and to prevent rejection after solid organ transplantation [6]. The association between azathioprine use and development of t-MDS is rarely reported in the medical literature [7-11]. While typically irreversible, we present a unique case of t-MDS induced by azathioprine that was successfully reversed with discontinuation of azathioprine.

Case presentation

59-year-old woman with history of neuromyelitis optica well-controlled for 2 years with azathioprine 1 mg/kg twice a day presented to the hospital with generalized fatigue and low-grade fever for a few weeks. Apart from azathioprine, the patient was not receiving any other immunosuppressants. She denies alcohol use or starting any new medication. She has

history of chronic hepatitis C for many years but without cirrhosis or splenomegaly. Clinical examination was unremarkable except for blindness. Complete Blood Count (CBC) revealed White Blood Cells (WBC) of 1,000/µl, absolute neutrophil count of 300/µl, hemoglobin of 8.1 g/dl, Mean Corpuscular Volume (MCV) of 109 fl and platelet count of 109,000/µl. Seven months prior to presentation, WBC was 5,000/µl, hemoglobin was 13.9 g/dl, MCV was 105.7 fl and platelet count was 280,000/µl. MCV values were 100.2 and 91.8 approximately 13 and 17 months prior to presentation, respectively (Figure 1). Vitamin B12 and folic acid were normal. Viral testing was negative for human immunodeficiency virus, Epstein-Barr virus, and parvovirus. Peripheral blood smear showed reduction of all blood cells with frequent pseudo-Pelger-Huet cells (Figure 2), concerning for underlying MDS. Bone marrow aspiration and biopsy revealed hypocellular marrow (10-15%) with 2% blasts, dysplastic erythrocytogenesis (nuclear budding, irregular contours, and satellitosis) and dysplastic leukogenesis (nuclear hyposegementation) (Figure 3). Cytogenetic testing noted normal female karyotype. The patient was diagnosed with low-risk t-MDS (intermediate-1 by international prognostic scoring system and low risk by the revised international prognostic scoring system). Azathioprine was discontinued and pancytopenia and macrocytosis gradually resolved. Repeat bone marrow aspiration and biopsy performed 3 months after discontinuation of azathioprine revealed normal cellularity at 30% with disappearance of all dysplastic changes (Figure 3). Azathioprine was replaced by mycophenolate mofetil for treatment of neuromyelitis optica with good neurologic control. The patient remains asymptomatic with normal CBC 5 years after initial diagnosis.

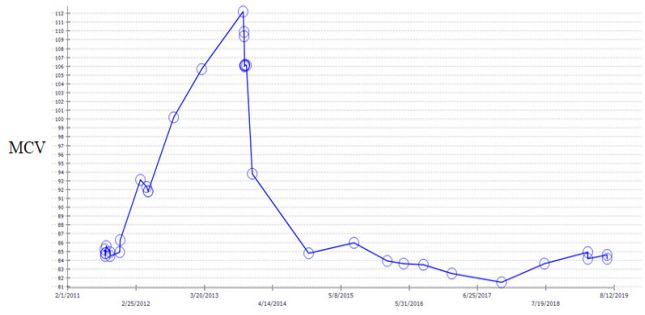

Figure 1: Trend of mean corpuscular volume over time.

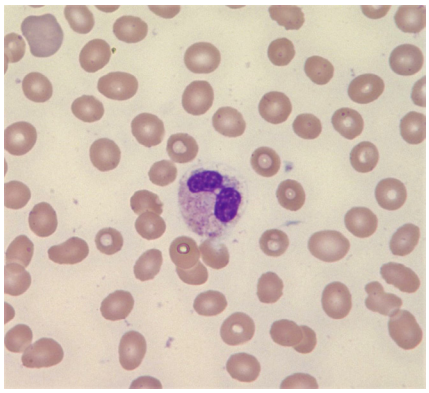

Figure 2: Peripheral blood smear shows pelgeroid morphology.

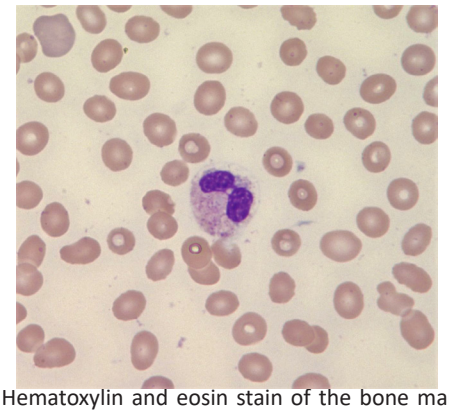

Figure 3: Hematoxylin and eosin stain of the bone marrow aspirate shows dysplastic features including erythroid satelitosis **(A)**, dysplastic erythroid precursors with nuclear budding **(A & B)**, hypogranulated myeloid precursors **(C)** and bilobed erythroid precursors **(D)**.

Discussion

MDS is a hematopoietic stem cell disorder that leads to ineffective hematopoiesis with variable degrees of cytopenias and significant risk of progression to AML [1]. Several scoring systems were developed and revised to predict this risk, which in turn remarkably impact therapeutic decisions [12,13]. t-MDS is a well-described entity with considerably high risk of progression to AML with alkylating agents and topoisomerase II inhibitors are most common offenders [3,4].

Azathioprine is a purine inhibitor that was first introduced in the 1960s after it was found to prolong survival of kidney allograft recipients [14]. It is also successful in treating multiple autoimmune conditions such as rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, and neuromyelitis optica. Azathioprine can induce immunosuppression and cytopenias, which are often reversed with azathioprine withdrawal. Non-specific bone marrow dysplasia, particularly in the erythroid lineage is also commonly seen in patients with autoimmune diseases which makes it difficult to distinguish it from true MDS [15]. The diagnosis of MDS is primarily based on morphological evidence of dysplasia with flow cytometry and cytogenetic testing are usually complementary [16]. Our patient met the 2018 World Health Organization criteria for MDS. In addition, the extensive degree of bone marrow dysplasia, the associated severe cytopenias and resolution of bone marrow findings after discontinuation of the drug are all consistent with t-MDS.

There is sufficient evidence that implicates azathioprine in carcinogenesis. Two prospective epidemiological studies revealed increased risk of development of non-Hodgkin's lymphoma, squamous cell skin cancer, hepatobiliary cancers and mesenchymal tumors among kidney transplant patients receiving azathioprine, suggesting a possible association between exposure to azathioprine and development of cancer [17]. Patients with autoimmune conditions treated with azathioprine appear also to have an increased risk for malignancy such as non-Hodgkin's lymphoma [17-19]. There were conflicting reports on whether the increased risk for malignancy in patients with autoimmune disorders is related to exposure to azathioprine or due to the underlying disease itself. Autoimmune disorders are associated with continuous release of inflammatory cy-

tokines which chronically activates the myeloid hematopoietic progenitors, and may trigger development of malignancy, particularly myeloid neoplasm [9,20]. A large recent case-control study of more than 40,000 patients with primary autoimmune disorders showed 7-fold increase in the risk of developing myeloid neoplasm (AML or t-MDS) in those who were exposed to azathioprine compared to those who were not. Notably, most of the patients with t-MDS in this study had normal karyotying with various other cytogenetic abnormalities noted in the rest of the patients including −7/deletion (del)(7q), −5/del(5q), +8, del(20q) and complex abnormalities. It is noteworthy that not all MDS patients reported in this study received azathioprine, which makes it difficult to drive a conclusion about any association between certain cytogenetic abnormality and azathioprine exposure [9]. In a smaller study of 33 patients with azathioprine-induced MDS who had successful karyotypic analysis, 79% had monosomy 7, deletion of the long arm of chromosomes 7 and 5, and rearrangement of chromosome 11q23 [11]. In another study of 14 patients with azathioprine-induced myelodysplastic syndrome, there was a significant association with aberration of chromosome 7 [10]. While these abnormalities are similar to those frequently seen in MDS induced by chemotherapy, there are conflicting reports of effects about the incidence of chromosomal aberrations in the bone-marrow cells of patients treated with azathioprine [5,21].

Azathioprine is believed to exert its leukemogenesis effect though impairing DNA repair, which results in highly mutational DNA bases. Moreover, direct azathioprine-induced DNA damage is possible in patients with already impaired DNA repair mechanism, which may induce leukemogenesis [22-24]. In addition, azathioprine is metabolized by Thiopurine Methyltransferase (TPMT). This enzyme exhibits genetic polymorphism. Approximately 1 in 300 individuals have very low activity of this enzyme, and these individuals may be at an increased risk for development of t-MDS [7,25]. Several other factors were linked to higher risk for development of t-MDS among patients exposed to azathioprine with the dose and duration of exposure to azathioprine appear to be the most significant [8,9]. The median time from diagnosis to development of t-MDS/AML is reported to be 5 to 8 years with median cumulative dose of 89-260g [9,11,22]. Our patient developed t-MDS after only 2 years of exposure with cumulative dose of 73g, which is shorter duration and with lower cumulative dose than what is reported in the literature, which may explain its reversibility. Other contributing factors include preexisting dysfunctional immune response due to autoimmune diseases, chronic inflammatory state, chronic immune stimulation, and possible preexisting hematopoietic disorder [9,26].

Prognosis of patients with t-MDS is poor due to the irreversible nature of the disease and rapid progression to AML with an overall survival that is much shorter compared to de novo MDS (16 vs 34 months) with shorter duration to transformation to AML (7.9 vs 13 months) [27]. The overall survival in patients with azathioprine-induced MDS is reported to be approximately 9 months [10]. To our knowledge, there is only one other reported case of reversible azathioprine-induced t-MDS. It occurred in a young renal transplant recipient that presented with refractory anemia and found to have monosomy 7, which was reversed by drug withdrawal with normalization of hematological and karyotypic parameters. However, the authors reported a very short follow-up of 5 months [28]. Our patient t-MDS was also reversed with discontinuation of the azathioprine with continued complete remission at 5 years. This is potentially explained by early diagnosis of t-MDS before clonal cytogenetic abnormities occur.

The progressive macrocytosis which preceded cytopenias by more than 1 year in our patient is noteworthy. Since macrocytosis is commonly associated with MDS, it presents an attractive early surrogate of developing t-MDS, that can prompt discontinuation of the offending agent.

Conclusion

t-MDS is rare complication of azathioprine therapy with poor prognosis. However, early diagnosis and prompt discontinuation of azathioprine may potentially halt and even reverse the disease process. The presence of progressive macrocytosis may serve as an early indicator of evolving t-MDS. Patients on azathioprine therapy who develop macrocytosis should be investigated for MDS manifestations and should have the drug discontinued.

Declarations

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