CASE REPORT

Thiopurine-induced Myelosuppression with Severe Sepsis in a Patient with Crohn's Disease: A Case Report

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Abstract

Thiopurines by their glucocorticoid-sparing property help in maintaining remission for patients with inflammatory bowel disease (IBD), when glucocorticoids are reduced and withdrawn. However, due to bone marrow suppression, it cannot be used in various conditions where it is indicated.

A 17-year-old patient presented with pancytopenia with neutropenic sepsis and alopecia after 3 weeks of starting azathioprine for her underlying Crohn's disease. Thiopurine S-methyltransferase (TPMT;*2, *3A, *3C) analysis resulted in a wild-type genotype, whereas homozygous Nudix hydrolase 15 (NUDT 15 C415T) variant was positive. Azathioprine was stopped immediately, and she was started on broad-spectrum antibiotics that led to some clinical improvements initially, but later on, the patient developed intestinal obstruction along with postoperative complications leading to death.

In this report, we highlight a case of serious hematological toxicity associated with azathioprine use in a patient with Crohn's disease with homozygous NUDT 15 variant, thus favoring the implementation of a pharmacogenomic approach before starting azathioprine, particularly in the Asian population.

Keywords: Azathioprine toxicity, Crohn's disease, Nudix hydrolase 15, Thiopurine S-methyltransferase.

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Introduction

Inflammatory bowel disease (IBD) is a chronic, progressive, immune-mediated disease, occurring in the presence of genetic and environmental risk factors, and consists of ulcerative colitis and Crohn's disease. In about 60% of IBD patients, azathioprine or 6-mercaptopurine (6-MP) is used to induce and maintain clinical remission. After absorption, azathioprine (85–90%) is rapidly converted to 6-MP by a nonenzymatic reaction. Three enzymes, namely, xanthine oxidase (XO), hypoxanthine-guanine phosphoribosyl transferase (HGPRT), and thiopurine S-methyltransferase (TPMT), compete to metabolize 6-MP. 6-MP is either metabolized by XO to 6-thiouric acid or by TPMT to 6-methyl mercaptopurine (6-MeMP) or by HGPRT to thioinosine monophosphate (TIMP), which is then metabolized to 6-thioguanine (6-TG). 6-TG is associated with both clinical benefits and bone marrow suppression, whereas 6-MeMP is related to liver toxicity.[1,2]

Nudix hydrolase 15 (NUDT 15), a member of pyrophospho-hydrolases, acts on nucleoside diphosphates. It catalyzes the active metabolites of azathioprine, like thioguanosine triphosphates (TGTP) and deoxy-thioguanosine triphosphates (TdGTP), tothioguanosine monophosphates (TGMP) and deoxy-thioguanosine monophosphates (TdGMP). Thus, it prevents the addition of TGTP and TdGTP into deoxyribonucleic acid (DNA-TG), thus reducing the cytotoxic effects of azathioprine. When the expression of NUDT 15 is downregulated, TGTP level increases significantly with an increased TGTP-to-TGMP ratio. Consequently, DNA-TG also increases in NUDT 15 knockdown cells. Thus, it provides a clear biological role of NUDT 15 variant in thiopurine host toxicity.[3,4] In this case report, we want to highlight the importance of pharmacogenomics in clinical practice before considering the azathioprine use.

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Case Presentation

A 17-year-old female patient presented to us with pain in the abdomen for the past 10 months, acute exacerbation for 1 month, and on-and-off episodes of low-grade fever, loose stools, and vomiting for 5 days. Based on colonoscopy findings and histopathological assessments, she was diagnosed with Crohn's disease around 3 weeks later. She was put on azathioprine 50 mg (1 mg/kg) once daily, along with prednisolone (30 mg) and mesalamine (2400 mg). Then, azathioprine was increased to 100 mg (2 mg/kg) after 7 days of initial presentation. Her baseline investigations before starting azathioprine were hemoglobin (Hb) of 9.2 g/dL, total leukocyte count (TLC) of 9100/µL, absolute neutrophil count (ANC) of 5200/µL,

Table 1: Detailed investigation chart

Parameters	*March 4, 2018*	*March 26, 2018*	*March 30, 2018*	*April 9, 2018*
Azathioprine dose	50 mg started	100 mg (for 14 days, since March 12, 2018) Azathioprine stopped since March 26, 2018		
Hemoglobin (g/dL)	9.2	6.6	7.2	8.8
Total leukocyte count (×10^3/mL)	9,100	900	300	3,200
Absolute neutrophil count (×10^3/mL)	5,200	180	60	1,800
Platelet count	5,64,000	1,44,000	3,000	98,000
Bilirubin (mg/dL)	0.8	1.0	0.8	1.1
AST (U/L)	28	32	45	36
ALT (U/L)	22	20	36	28
ALP (IU/L)	148	202	196	158
Protein (g/dL)	6.1	5.9	5.6	6.2
Albumin (g/dL)	3.2	3.0	3.0	3.1
LDH (U/L)	320	430		
CRP (mg/L)	4.64	140		78
ESR (mm/1st hour)	48	102		
Vitamin B12 (ng/mL)		436		
Folate (ng/mL)		12		
Blood culture		3 Culture: no growth	MDR *Escherichia coli*	
Urine culture		No growth		
6-Thioguanine (pmol/8 × 10^8 RBCs)		554		
Bone marrow biopsy	Hypocellular bone marrow with reduction in all cell lines.			

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LDH: lactate dehydrogenase

platelet count of 5,64,000/µL, elevated erythrocyte sedimentation rate of 48 mm/1st hour, and C-reactive protein (CRP) of 4.64 mg/L, with normal liver chemistries (Table 1).

With not much relief in her abdominal complaints, she presented to our center after 3 weeks, with high-grade fever and an increase in pain in the abdomen associated with vomiting. On investigation, she was found to have pancytopenia (normocytic, normochromic anemia with Hb of 6.6 g/dL, TLC of 900/µL with an ANC of 180/µL, and platelet count of 1,44,000/µL) with elevated inflammatory markers (CRP, 140 mg/L). Vitamin B12 and folate levels were within the normal range. During her hospital stay, the patient started having excessive hair loss as well. The patient was started on broad-spectrum antibiotics (febrile neutropenia regimen) along with Filgrastim (G-CSF analog) at 5 µg/kg/day, which was increased to 10 µg/kg/day, but the patient had gradually falling Hb, TLC, and platelet counts. The least TLC noted was 300/µL with ANC of 60/µL and the lowest platelet count being 3000/µL. Bone marrow aspiration with biopsy was done, which showed hypoplastic marrow. Despite broad-spectrum antibiotics, cefepime, and linezolid along with antifungals, the patient continued to have fever with three sterile blood culture reports. In course of her hospital stay, the patient also developed closed-loop intestinal obstruction of proximal ileum with hemorrhage within the bowel wall due to severe thrombocytopenia. Multiple transfusions in the form of red blood cell concentrate and single-donor apheresis platelet were given and managed conservatively. Finally, blood culture was repeated, which grew *Escherichia coli,* which was resistant to multiple drugs but sensitive to Tigecycline and Amikacin. The patient was then started on the same antibiotic, which led to a response in fever after 7 days along with improvement in her cell counts. Genetic analysis for TPMT activity was done, which showed normal TPMT (wild-type) genotype. NUDT 15 variant analysis showed a homozygous NUDT 15 C415T type. After a long hospital stay of 2 months with all supportive treatments, the patient developed intestinal obstruction (stricturing type of Crohn's disease) and was referred for surgery. On the third postoperative day, the patient developed anastomotic site leak with wound infection and sepsis, leading to clinical deterioration and later on the death of the patient.

Discussion

Azathioprine or 6-MP is an immunosuppressive drug of thiopurine class, effective in the treatment of IBD. Around 10% of patients with IBD develop adverse events related to treatment. Myelosuppression is the most potentially serious adverse event related to azathioprine use. Though many cases of azathioprine-induced hematological side effects are being reported in the literature, our case remains the first of its kind to report such severe myelosuppression with sepsis.

Previous studies have shown that in large series of 739 patients, azathioprine (2 mg/kg/day) led to bone marrow toxicity in 5% of population when used for around 12.5 months, and the duration ranged from 2 weeks to 11 years during the treatment.[5] Moreover, it has been suggested that Asian patients have a low tolerance to full doses of azathioprine and suffer more adverse events.[6-10] However, all of these studies were based on the evaluation of TPMT genotype and phenotype. Presently, the American Gastroenterological Association (AGA) suggests routine testing of TPMT (enzymatic activity or genotype) to decide the dosing of azathioprine. But no such recommendation exists for NUDT 15.[11]

Yang et al. in their study have found that the NUDT15 variant (Arg139Cys) was strongly linked with thiopurine-induced early leukopenia in patients with Crohn's disease on thiopurines.[12]

Moreover, the sensitivity and specificity of the NUDT15 variant for thiopurine-induced early leukopenia were found to be 89.4 and 93.2%, respectively. A further study from India has found that NUDT15 (C415T) risk allele frequency was 10.7%, with the frequency of wild, heterozygous, and mutant genotypes being 80.6, 17.5, and 1.9%, respectively. Among patients with thiopurine-induced toxicity, 10% of patients developed myelotoxicity, and all patients were found to harbor NUDT 15 variant.[13]

A recent European study by Schaeffeler et al. has shown that severe hematotoxicity in patients on thiopurines has been associated with genetic polymorphism in both TPMT and NUDT 15. Thirty-one percent of their patient cohort had TPMT variant with NUDT 15 variant seen in 13, and 6% had both TPMT and NUDT 15 variant.[14] Similarly, Walker et al. in their casecontrol study on thiopurines in patients with IBD in European ancestry have found that NUDT 15 variant was independently associated with azathioprine-induced bone marrow suppression irrespective of TPMT genotype and thiopurine dose.[15] Similarly, other studies have also demonstrated an increased risk of thiopurine-induced leukopenia with NUDT15 R139C.[16-18]

In patients with previous bone marrow suppression, genetic evaluation is of interest as this can predict the future occurrence of a new hematologic accident. Though the presence of heterozygous state or lack of mutation could allow restarting of the drug at a lower dose with careful step-up, the presence of nonfunctional homozygous mutations should lead to complete avoidance of azathioprine or 6-MP. Thus, before initiating thiopurines, screening patients with TPMT mutation remains justifiable for Caucasians, but for Asians, preemptive NUDT 15 variant analysis remains more important in order to prevent future life-threatening complications like myelosuppression.

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