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CASE REPORT

Bone marrow inhibition induced by azathioprine in a patient without mutation in the thiopurine S-methyltransferase pathogenic site: A case report

Xiao-Shuang Zhou, Yuan-Yue Lu, Yan-Fang Gao, Wen Shao, Jia Yao

ORCID number: Xiao-Shuang Zhou 0000-0003-2210-7717; Yuan-Yue Lu 0000-0001-6222-5924; Yan-Fang Gao 0000-0003-1585-5565; Wen Shao 0000-0002-2922-4118; Jia Yao 0000-0003-0307-6118.

Author contributions: Zhou XS and Lu YY reviewed the literature and contributed to manuscript drafting; Gao YF and Shao W collected the data and participated in manuscript drafting; Yao J was responsible for the revision of the manuscript for important intellectual content; all authors issued final approval for the version to be submitted.

Informed consent statement: The procedure performed in the study was in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from the patient included in the study.

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Xiao-Shuang Zhou, College of Biomedical Engineering, Taiyuan University of Technology, Taiyuan 030012, Shanxi Province, China

Xiao-Shuang Zhou, Yuan-Yue Lu, Yan-Fang Gao, Department of Nephrology, The Affiliated People's Hospital of Shanxi Medical University, Taiyuan 030032, Shanxi Province, China

Wen Shao, Jia Yao, Department of Gastroenterology, Shanxi Bethune Hospital, Taiyuan 030012, Shanxi Province, China

Corresponding author: Jia Yao, MD, Doctor, Department of Gastroenterology, Shanxi Bethune Hospital, No. 99 Longcheng Street, Xiaodian District, Taiyuan 030012, Shanxi Province, China. 18535118814@163.com

Abstract

BACKGROUND

Azathioprine (AZA) and its close analog 6-mercaptopurine are thiopurines widely used in the treatment of patients with cancer, organ transplantation, and autoimmune or inflammatory diseases, including systemic lupus erythematosus. Bone marrow inhibition is a common side effect of AZA, and severe bone marrow inhibition is related to decreased thiopurine S-methyltransferase (*TPMT*) activity.

CASE SUMMARY

We herein report a patient with proliferative lupus nephritis who was using AZA for maintenance therapy, had no common *TPMT* pathogenic site mutations, and exhibited severe bone marrow inhibition on the 15th day after oral administration.

CONCLUSION

This report alerts physicians to the fact that even though the *TPMT* gene has no common pathogenic site mutation, severe myelosuppression may also occur.

Key Words: Azathioprine; Thiopurine S-methyltransferase; Bone marrow inhibition; Lupus nephritis; Case report

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Core Tip: Thiopurine S-methyltransferase (*TPMT*) gene polymorphism testing alone cannot fully predict the occurrence of azathioprine (AZA) adverse reactions such as bone marrow inhibition and alopecia. According to the literature mentioned above, nucleoside diphosphate-linked moiety X motif 15 (*NUDT 15*) and inosine triphosphate pyrophosphatase (*ITPA*) gene polymorphism tests should also be performed to predict the occurrence of AZA adverse reactions and further guide initial medication. On the other hand, AZA should be used with caution, and whole blood examination and liver and kidney function should be closely monitored during the entire treatment with AZA regardless of the status of *TPMT*, *NUDT 15*, and *ITPA* single nucleotide polymorphisms.

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INTRODUCTION

Azathioprine (AZA) and its close analog 6-mercaptopurine (6-MP) are thiopurines widely used in the treatment of patients with autoimmune inner-ear disease[1], inflammatory bowel disease[2], hematological malignancies[3], rheumatoid arthritis [4], autoimmune bullous diseases[5], and systemic lupus erythematosus[6]. Adverse reactions to AZA are mainly reflected as bone marrow inhibition, hepatic function lesions, and rash. Severe bone marrow inhibition is relevant to the patient's thiopurine S-methyltransferase (TPMT) activity and the pathogenic mutation of *TPMT*[7]. A case of severe bone marrow suppression in a patient with lupus nephritis induced by AZA but without a common *TPMT* pathogenic site mutation is reported in this paper.

CASE PRESENTATION

Chief complaints

The patient, a 22-year-old woman of Chinese Han ethnicity, was admitted for severe edema of the facial region and two lower limbs over 3 mo.

History of present illness

The patient developed edema of the facial region and two lower limbs 3 mo ago without obvious cause. Her symptoms were mild in the morning and severe in the afternoon. At the same time, she experienced migratory pain of the small joints, which improved after movement, as well as decreased urinary volume, weakness, and poor appetite.

History of past illness

The patient had a free previous medical history.

Physical examination

The patient's temperature was 36.6 °C, heart rate was 78 bpm, respiratory rate was 20 breaths per minute, blood pressure was 122/80 mmHg, and oxygen saturation in room air was 98%. The patient was conscious and she complied with the physician's physical examination. Her heart, lungs, and abdomen examinations showed no significant abnormalities, no percussion pain in her kidney area, and severe pitting edema in both lower extremities.

Laboratory examinations

Routine urine examination revealed the following: Proteinuria +++, hematuria ++; phase of urinary red blood cells: Deformed erythrocytosis 70%, urine protein quantitation 4.2 g/24 h; urea nitrogen 15.7 mmol/L, and serum creatinine 141.4

μmol/L. Routine blood test results were as follows: Hemoglobin 92 g/L, white blood cells 4.8 × 10^9/L, blood platelets 218 × 10^9/L, antinuclear antibody 1:3200, cytoplasmic granules 1:1000, ds-DNA antibody > 1:3200, C3 0.56 g/L, and C4 0.22 g/L.

Further diagnostic work-up

Pathological results showed 35 glomeruli in the punctured renal tissue, including one with global sclerosis, two with ischemic sclerosis, and the remaining glomeruli with diffuse proliferation of mesangial cells and endothelial cells, accompanied by segmental dual-track formation of a thickened basement membrane, segmental Meyer's loop, leukocyte infiltration, and segmental microthrombus formation. Fuchsinophilic protein deposition can be found at the mesangial region and subepithelial region, including fibrin crescent formation of one cell. The kidney tubular epithelium exhibited granular and vacuolar degeneration, as well as multifocal atrophy. The renal interstitium showed multishaped lymphocyte and monocyte infiltration, together with mild thickening of the arteriole wall. Paraffin immunofluorescence revealed: Immunoglobulin (Ig) G (++), IgA (++), IgM (++), C3 (+), fall risk assessment (+), C1q (++), and granular deposition along the mesangial region and capillary wall. Combined with clinical findings, this condition was considered diffuse proliferative lupus nephritis, with IV-G (A), AI = 11, and CI = 5. AI was scored as follows: Cellular proliferation (2 points), leukocyte infiltration (1 point), nuclear fragmentation/fibrinoid necrosis (2 points), cell crescent (0 points), Meyer's loop/thrombus (2 points), and interstitial monocyte infiltration (2 points). CI was scored as follows: Sclerosis (2 points), fibrin crescent (0 points), tubular atrophy (2 points), and interstitial fibrosis (2 points) (Figure 1).

TPMT genotyping testing (four single nucleotide polymorphisms, single base extension method)

After consideration of the renal puncture results, oral administration of prednisone was begun at 50 mg/d, and meanwhile, cyclophosphamide was applied through intravenous injection at a dosage of 1.0 g monthly, which lasted for a consecutive 6 mo and was stopped after an accumulative use of 6 g. The serum creatinine fluctuated within an approximate range of 120-160 μmol/L, and blood albumin fluctuated from approximately 29-35 g/L. Then, the patient began to take AZA 50 mg/d as maintenance treatment but experienced extensive alopecia and shedding of pubic hair on the 13th day after oral administration. Pharyngalgia appeared on the 14th day, and fever with a body temperature up to 42 ℃ occurred on the 15th day. The patient came to the hospital for the second time. Physical examination revealed the following: Body temperature, 39.4 ℃; pulse, 92 times/min; breath rate, 22 times/min; blood pressure, 182/100 mmHg. The patient exhibited clear consciousness and emotional distress; she presented scattered chromatosis on her skin, and a rash was found on the inner surface of the bilateral thighs. Pharyngeal congestion was noted, and the breath sounds of the two lungs were clear. The heart rate was 92 times/min. The abdomen was flat, soft, and free from tenderness or rebound tenderness, and there was no liver or spleen involvement. Routine blood work showed the following: Hemoglobin 72 g/L, white blood cell count 1.25 × 10^9/L, blood platelet count 13 × 10^9/L, lymphocyte ratio 95.7%, neutrophil ratio 1.6%, and neutrophil count 0.01 × 10^9/L (Figure 2). The results of the bone marrow biopsy were as follows: Myelodysplasia low in the myelogram and focal hyperplasia in bone marrow tissue with active hyperplasia in some areas (Figure 3). Routine urinalysis results were as follows: Protein (+), occult blood 2+, and Epstein-Barr virus (EBV) positivity (3.58 × 10^4). *TPMT* genotyping testing (four single nucleotide polymorphisms, single base extension method) revealed the following: *TPMT 3C* gene polymorphism (719A>G) (this site is the most common gene mutation site in Asians) test result: A/A; *TPMT 3B* gene polymorphism (460G>A) test result: G/G; *TPMT 2* gene polymorphism (238G>C) test result: G/G; no abnormity was found in any of the above results.

MULTIDISCIPLINARY EXPERT CONSULTATION

Hematology expert opinion

Combined with the patient's medical history, laboratory tests, and examination results, it has been established that the patient has severe bone marrow suppression. The patient had no bone marrow suppression before the medication. She appeared after the medication. Considering the possibility of bone marrow suppression caused by the

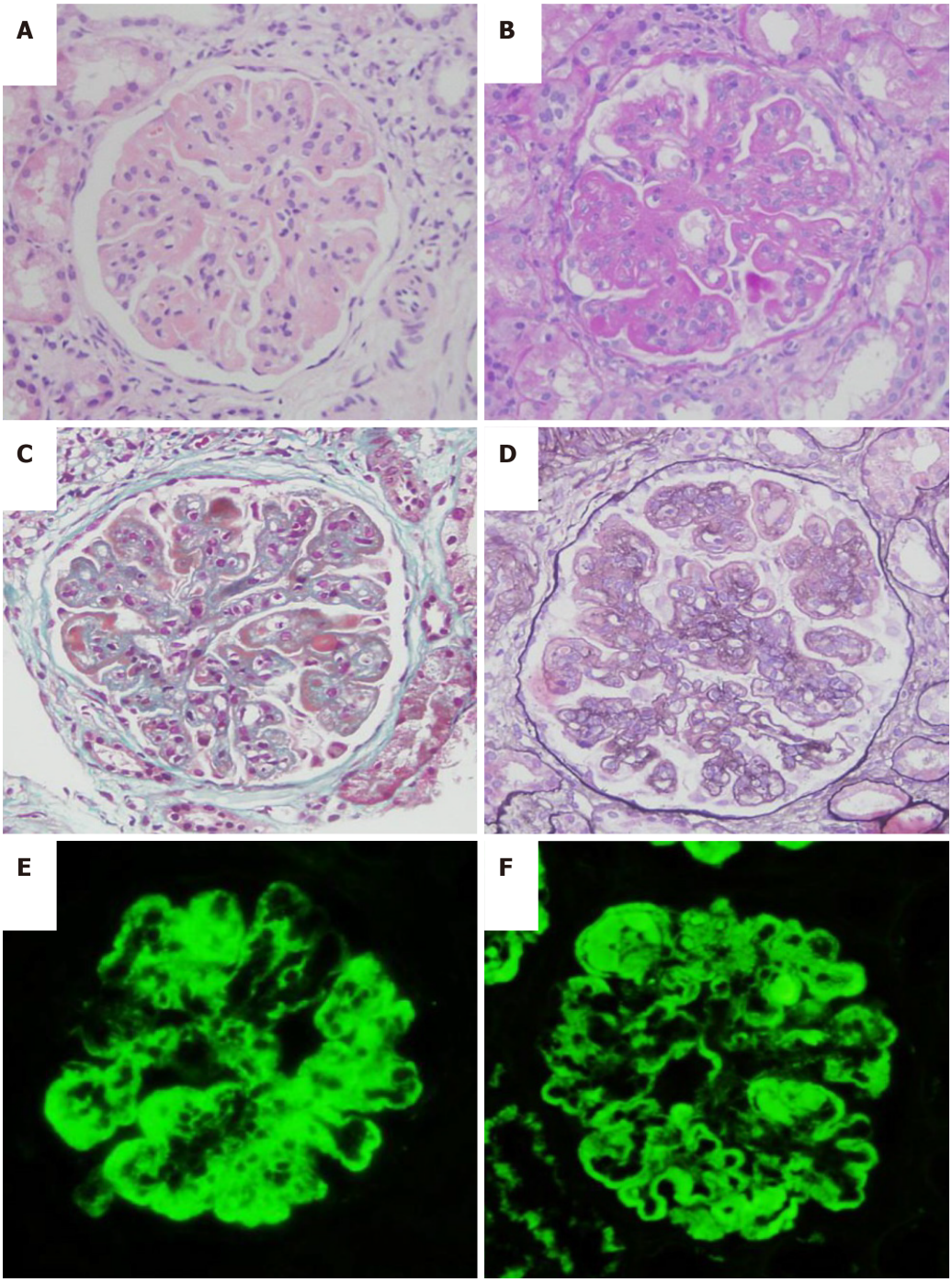

Figure 1 Biopsy pathology. A: Thickened basement membrane (hematoxylin-eosin staining, × 400); B: Proliferation of mesangial cells and endothelial cells (periodic acid–Schiff stain, × 400); C: Segmental wire loop (Masson, × 400); D: Segmental dual track formation (periodic acid-silver methenamine, × 400); E and F: Granular deposition along the mesangial region and capillary wall (immunofluorescence, × 400).

drug, it is recommended that the patient stops it in time.

Opinions of rheumatology experts

The patient currently has systemic lupus erythematosus and lupus nephritis, and suffers from EBV infection. It is recommended that the patient be given oral hormones to control systemic lupus erythematosus activities and receive antiviral treatment.

Nephrology expert opinion

The patient is currently suffering from chronic renal insufficiency, and nephrotic anemia should be corrected, avoiding the use of nephrotoxic drugs and delaying the progression of kidney disease. It is recommended that the patient be regularly checked and evaluated for renal function.

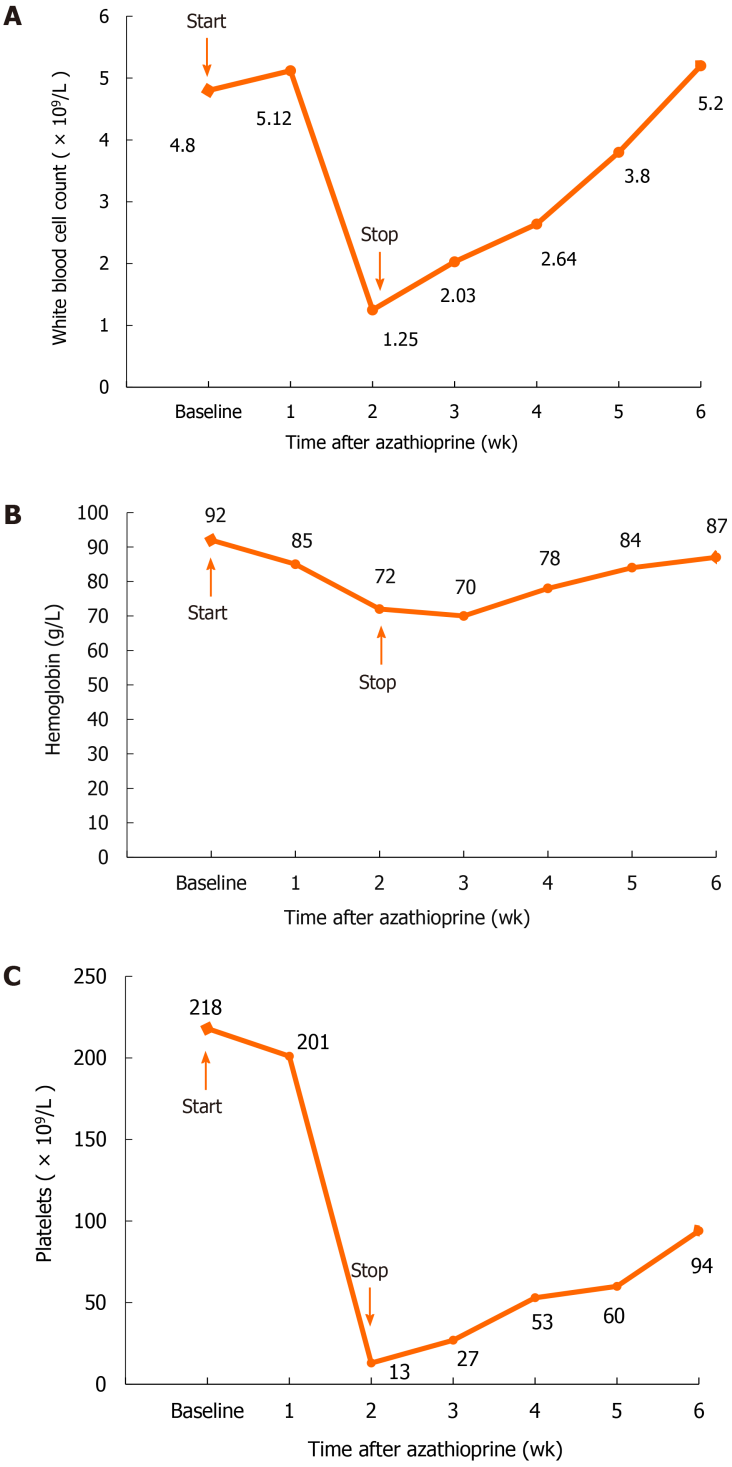

Figure 2 Routine blood work. The 'baseline' time point is the initiation of azathioprine therapy. Four weeks after azathioprine therapy was stopped, all values returned to their baseline levels. A: Changes in the white blood cell count. The increase in the white blood cell count after azathioprine therapy was stopped was caused by the injection of filgrastim; B: Changes in hemoglobin; C: Changes in the platelet count.

FINAL DIAGNOSIS

Systematic lupus erythematosus, lupus nephritis, chronic renal insufficiency, hypertension phase-3, drug-related bone marrow inhibition, granulocytopenia, and EBV infection.

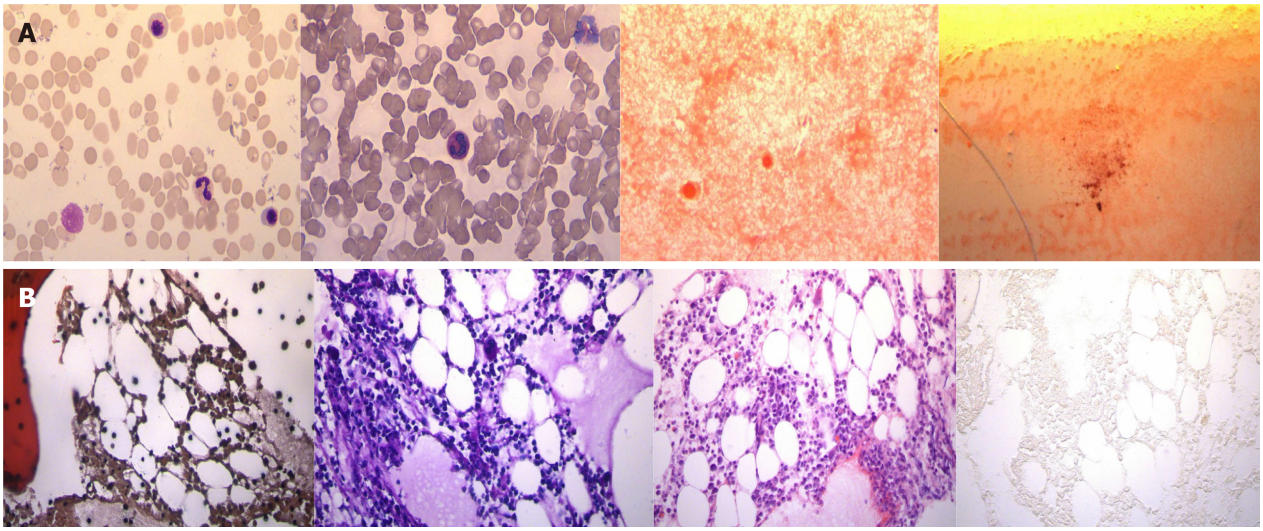

Figure 3 The results of the bone marrow biopsy. A: Results of bone marrow aspiration-myelogram. The myelogram showed low myelodysplasia (G = 52.0%, E = 25.0%, G/E = 2.1/1); cells in the lower and middle granulocyte stages were observed, with a low proportion of mesoblastic granulocytes and a high proportion of lobulated nuclei, with obvious abnormal morphology. Cells in the lower erythroid stage could be seen with a higher proportion of late immature red cells, smaller cell bodies, different sizes of mature red cells, and some hollow enlargement. No obvious abnormality was found in lymphocytes; only one naked nucleus was found in the whole sample, with few platelets and no parasites; B: Bone marrow biopsy showed focal hyperplasia in some areas (70%) and normal hyperplasia in some areas (40%). The proportion of granulocyte red staining was generally normal. Cells at various granulocyte stages were visible, mainly in the middle and late juvenile stage; there were many megakaryocytes, mainly with lobulated nuclei, and some megakaryocytes were less abundant. Reticular fiber staining: Mf0 grade iron staining: Negative.

TREATMENT

Although the patient had no common *TPMT* pathogenic site mutation, the relationship of severe bone marrow inhibition and alopecia with the use of AZA was recognized and the treatment stopped in a timely manner. Treatment with ganciclovir, meropenem, cystatin sodium, linezolid, and itraconazole was given, with transfusion of suspended red blood cells, plasma, and blood platelets, as well as injection of filgrastim, recombinant human interleukin-11, and erythropoietin. Moreover, the oral administration of prednisone at 10 mg/d was carried out to control systematic lupus erythematosus.

OUTCOME AND FOLLOW-UP

Three weeks later, the patient's body temperature decreased to normal, with routine blood parameters recovering to normal values, as well as blood creatine levels at 161 μmol/L. More than 2 mo after AZA was withdrawn, the patient's hair regrew. Serum creatinine was maintained at 160-190 μmol/L.

DISCUSSION

The enzyme activity of TPMT is key to the safe use of AZA, which strongly inactivates thiopurine metabolites (6-MP and 6-thiguanine nucleotide) to protect the body from thiopurine cytotoxicity[8]. *TPMT* allelic polymorphism testing shows that the 3/100-14/100 crowd is heterozygous, and its enzyme activity is 50% of that of the normal crowd, while the 1/3736-1/178 crowd is completely defective[9]. Hence, the United States Food and Drug Administration and World Gastroenterology Organization recommend that *TPMT* levels be tested prior to treatment and hold that those with low TPMT enzyme activity (those with *TPMT* homozygotes) shall prevent the use of AZA and those with median or normal enzyme activity can be used to an appropriate extent with routine blood tests to avoid severe adverse reactions[10]. Among Chinese Han people, there may be those without TPMT activity or with homozygous *TPMT* gene mutations. The most common alleles are *TPMT**3C[11].

The patient in this paper experienced severe bone marrow inhibition, agranulocytosis, and alopecia 15 d after the use of AZA. The *TPMT* gene polymorphism test showed no abnormity in *TPMT* gene polymorphism. Possible reasons for this result are as follows: (1) Over 40 polymorphisms in *TPMT* have been documented to have an effect on the enzymatic activity of TPMT at present, and we did not test all the sites sufficiently; (2) In addition to TPMT, the activity of other enzymes, such as nucleoside diphosphate-linked moiety X motif 15 (NUDT 15) and inosine triphosphate pyrophosphatase (ITPA), also affects the metabolic process of AZA and is linked with the toxicity of AZA[12-15]. Unfortunately, in this case, the *NUDT 15* and *ITPA* gene polymorphisms were not detected, and we do not know if there is any abnormality of this gene in the patient; (3) There may be other factors related to the toxicity of AZA that have not yet been found or validated, such as fat mass and obesity-associated protein[16]; and (4) In addition, this patient did have hypoproteinemia and decreased renal function, which may cause an increase in plasma concentration and the occurrence of adverse reactions.

CONCLUSION

This case alerts us that even though the *TPMT* gene has no common pathogenic site mutation, severe myelosuppression may also occur. The adverse reactions of AZA are caused by polygenes and multiple factors. Only *TPMT* gene polymorphism testing cannot fully predict the occurrence of AZA adverse reactions such as bone marrow inhibition and alopecia. According to the literature mentioned above, *NUDT 15* and *ITPA* gene polymorphism tests should be performed as well to predict the occurrence of AZA adverse reactions and further guide initial medication. On the other hand, AZA should be used with caution, and whole blood examination and liver and kidney function should be closely monitored during the entire treatment of AZA regardless of the status of *TPMT*, *NUDT 15,* and *ITPA* single nucleotide polymorphisms.

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