

World Journal of *Clinical Cases*

World J Clin Cases 2021 June 16; 9(17): 4116-4459



EDITORIAL

- 4116 Is it time to put traditional cold therapy in rehabilitation of soft-tissue injuries out to pasture?
Wang ZR, Ni GX

MINIREVIEWS

- 4123 Health-related quality of life after gastric cancer treatment in Brazil: Narrative review and reflections
Pinheiro RN, Mucci S, Zanatto RM, Picanço Junior OM, Oliveira AF, Lopes Filho GJ
- 4133 Nonalcoholic fatty liver disease and COVID-19: An epidemic that begets pandemic
Ahmed M, Ahmed MH

ORIGINAL ARTICLE**Retrospective Study**

- 4143 Why *MUC16* mutations lead to a better prognosis: A study based on The Cancer Genome Atlas gastric cancer cohort
Huang YJ, Cao ZF, Wang J, Yang J, Wei YJ, Tang YC, Cheng YX, Zhou J, Zhang ZX
- 4159 Design and development of a new type of phimosis dilatation retractor for children
Yue YW, Chen YW, Deng LP, Zhu HL, Feng JH
- 4166 Primary needle-knife fistulotomy for preventing post-endoscopic retrograde cholangiopancreatography pancreatitis: Importance of the endoscopist's expertise level
Han SY, Baek DH, Kim DU, Park CJ, Park YJ, Lee MW, Song GA

Observational Study

- 4178 Patients with functional bowel disorder have disaccharidase deficiency: A single-center study from Russia
Dbar S, Akhmadullina O, Sabelnikova E, Belostotskiy N, Parfenov A, Bykova S, Bakharev S, Baulo E, Babanova A, Indeykina L, Kuzmina T, Kosacheva T, Spasenov A, Makarova A
- 4188 Self-perceived burden and influencing factors in patients with cervical cancer administered with radiotherapy
Luo T, Xie RZ, Huang YX, Gong XH, Qin HY, Wu YX

SYSTEMATIC REVIEWS

- 4199 COVID-19 in gastroenterology and hepatology: Lessons learned and questions to be answered
Liu S, Tang MM, Du J, Gong ZC, Sun SS

META-ANALYSIS

- 4210 Efficacy of topical *vs* intravenous tranexamic acid in reducing blood loss and promoting wound healing in bone surgery: A systematic review and meta-analysis

Xu JW, Qiang H, Li TL, Wang Y, Wei XX, Li F

CASE REPORT

- 4221 *Ex vivo* liver resection followed by autotransplantation in radical resection of gastric cancer liver metastases: A case report

Wang H, Zhang CC, Ou YJ, Zhang LD

- 4230 Bone marrow inhibition induced by azathioprine in a patient without mutation in the thiopurine S-methyltransferase pathogenic site: A case report

Zhou XS, Lu YY, Gao YF, Shao W, Yao J

- 4238 Eosinophilic gastroenteritis with abdominal pain and ascites: A case report

Tian XQ, Chen X, Chen SL

- 4244 Tunica vaginalis testis metastasis as the first clinical manifestation of pancreatic adenocarcinoma: A case report

Zhang YR, Ma DK, Gao BS, An W, Guo KM

- 4253 "AFGP" bundles for an extremely preterm infant who underwent difficult removal of a peripherally inserted central catheter: A case report

Chen Q, Hu YL, Su SY, Huang X, Li YX

- 4262 Dynamic magnetic resonance imaging features of cavernous hemangioma in the manubrium: A case report

Lin TT, Hsu HH, Lee SC, Peng YJ, Ko KH

- 4268 Diagnosis and treatment of pediatric anaplastic lymphoma kinase-positive large B-cell lymphoma: A case report

Zhang M, Jin L, Duan YL, Yang J, Huang S, Jin M, Zhu GH, Gao C, Liu Y, Zhang N, Zhou CJ, Gao ZF, Zheng QL, Chen D, Zhang YH

- 4279 Stevens-Johnson syndrome and concurrent hand foot syndrome during treatment with capecitabine: A case report

Ahn HR, Lee SK, Youn HJ, Yun SK, Lee IJ

- 4285 Rosai-Dorfman disease with lung involvement in a 10-year-old patient: A case report

Wu GJ, Li BB, Zhu RL, Yang CJ, Chen WY

- 4294 Acute myocardial infarction in twin pregnancy after assisted reproduction: A case report

Dai NN, Zhou R, Zhuo YL, Sun L, Xiao MY, Wu SJ, Yu HX, Li QY

- 4303 Complete recovery of herpes zoster radiculopathy based on electrodiagnostic study: A case report

Kim HS, Jung JW, Jung YJ, Ro YS, Park SB, Lee KH

- 4310** Acute liver failure with thrombotic microangiopathy due to sodium valproate toxicity: A case report
Mei X, Wu HC, Ruan M, Cai LR
- 4318** Lateral epicondyle osteotomy approach for coronal shear fractures of the distal humerus: Report of three cases and review of the literature
Li J, Martin VT, Su ZW, Li DT, Zhai QY, Yu B
- 4327** Pancreatic neuroendocrine carcinoma in a pregnant woman: A case report and review of the literature
Gao LP, Kong GX, Wang X, Ma HM, Ding FF, Li TD
- 4336** Primary primitive neuroectodermal tumor in the pericardium—a focus on imaging findings: A case report
Xu SM, Bai J, Cai JH
- 4342** Minimally invasive surgery for glycogen storage disease combined with inflammatory bowel disease: A case report
Wan J, Zhang ZC, Yang MQ, Sun XM, Yin L, Chen CQ
- 4348** Coronary sinus endocarditis in a hemodialysis patient: A case report and review of literature
Hwang HJ, Kang SW
- 4357** *Clostridium perfringens* bloodstream infection secondary to acute pancreatitis: A case report
Li M, Li N
- 4365** Kidney re-transplantation after living donor graft nephrectomy due to *de novo* chromophobe renal cell carcinoma: A case report
Wang H, Song WL, Cai WJ, Feng G, Fu YX
- 4373** Pelvic lipomatosis with cystitis glandularis managed with cyclooxygenase-2 inhibitor: A case report
Mo LC, Piao SZ, Zheng HH, Hong T, Feng Q, Ke M
- 4381** Prone position combined with high-flow nasal oxygen could benefit spontaneously breathing, severe COVID-19 patients: A case report
Xu DW, Li GL, Zhang JH, He F
- 4388** Primary intratracheal schwannoma misdiagnosed as severe asthma in an adolescent: A case report
Huang HR, Li PQ, Wan YX
- 4395** Prenatal diagnosis of cor triatriatum sinister associated with early pericardial effusion: A case report
Cánovas E, Cazorla E, Alonzo MC, Jara R, Álvarez L, Beric D
- 4400** Pulmonary alveolar proteinosis complicated with tuberculosis: A case report
Bai H, Meng ZR, Ying BW, Chen XR
- 4408** Surgical treatment of four segment lumbar spondylolysis: A case report
Li DM, Peng BG

- 4415** Efficacy of artificial liver support system in severe immune-associated hepatitis caused by camrelizumab: A case report and review of the literature
Tan YW, Chen L, Zhou XB
- 4423** Anti-Yo antibody-positive paraneoplastic cerebellar degeneration in a patient with possible cholangiocarcinoma: A case report and review of the literature
Lou Y, Xu SH, Zhang SR, Shu QF, Liu XL
- 4433** Intraneural ganglion cyst of the lumbosacral plexus mimicking L5 radiculopathy: A case report
Lee JG, Peo H, Cho JH, Kim DH
- 4441** Effectiveness of patient education focusing on circadian pain rhythms: A case report and review of literature
Tanaka Y, Sato G, Imai R, Osumi M, Shigetoh H, Fujii R, Morioka S
- 4453** Schwannoma mimicking pancreatic carcinoma: A case report
Kimura K, Adachi E, Toyohara A, Omori S, Ezaki K, Ihara R, Higashi T, Ohgaki K, Ito S, Maehara SI, Nakamura T, Fushimi F, Maehara Y

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The primary aim of *World Journal of Clinical Cases (WJCC, World J Clin Cases)* is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

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INDEXING/ABSTRACTING

The *WJCC* is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2020 Edition of Journal Citation Reports® cites the 2019 impact factor (IF) for *WJCC* as 1.013; IF without journal self cites: 0.991; Ranking: 120 among 165 journals in medicine, general and internal; and Quartile category: Q3. The *WJCC*'s CiteScore for 2019 is 0.3 and Scopus CiteScore rank 2019: General Medicine is 394/529.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Jia-Hui Li; Production Department Director: Yu-Jie Ma; Editorial Office Director: Jin-Lai Wang.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

EDITORS-IN-CHIEF

Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

June 16, 2021

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

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

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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.

Conflict-of-interest statement: There are no conflicts of interest or commercial interests to declare.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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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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Manuscript source: Unsolicited manuscript

Specialty type: Medicine, research and experimental

Country/Territory of origin: China

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: December 10, 2020

Peer-review started: December 10, 2020

First decision: January 7, 2021

Revised: January 20, 2021

Accepted: March 24, 2021

Article in press: March 24, 2021

Published online: June 16, 2021

P-Reviewer: Innocenti T

S-Editor: Fan JR

L-Editor: Wang TQ

P-Editor: Li JH



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.

Citation: Zhou XS, Lu YY, Gao YF, Shao W, Yao J. Bone marrow inhibition induced by azathioprine in a patient without mutation in the thiopurine S-methyltransferase pathogenic site: A case report. *World J Clin Cases* 2021; 9(17): 4230-4237

URL: <https://www.wjgnet.com/2307-8960/full/v9/i17/4230.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v9.i17.4230>

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

$\mu\text{mol/L}$. Routine blood test results were as follows: Hemoglobin 92 g/L, white blood cells $4.8 \times 10^9/\text{L}$, blood platelets $218 \times 10^9/\text{L}$, 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 $\mu\text{mol/L}$, 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 °C occurred on the 15th day. The patient came to the hospital for the second time. Physical examination revealed the following: Body temperature, 39.4 °C; 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 $1.25 \times 10^9/\text{L}$, blood platelet count $13 \times 10^9/\text{L}$, lymphocyte ratio 95.7%, neutrophil ratio 1.6%, and neutrophil count $0.01 \times 10^9/\text{L}$ (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 abnormality 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

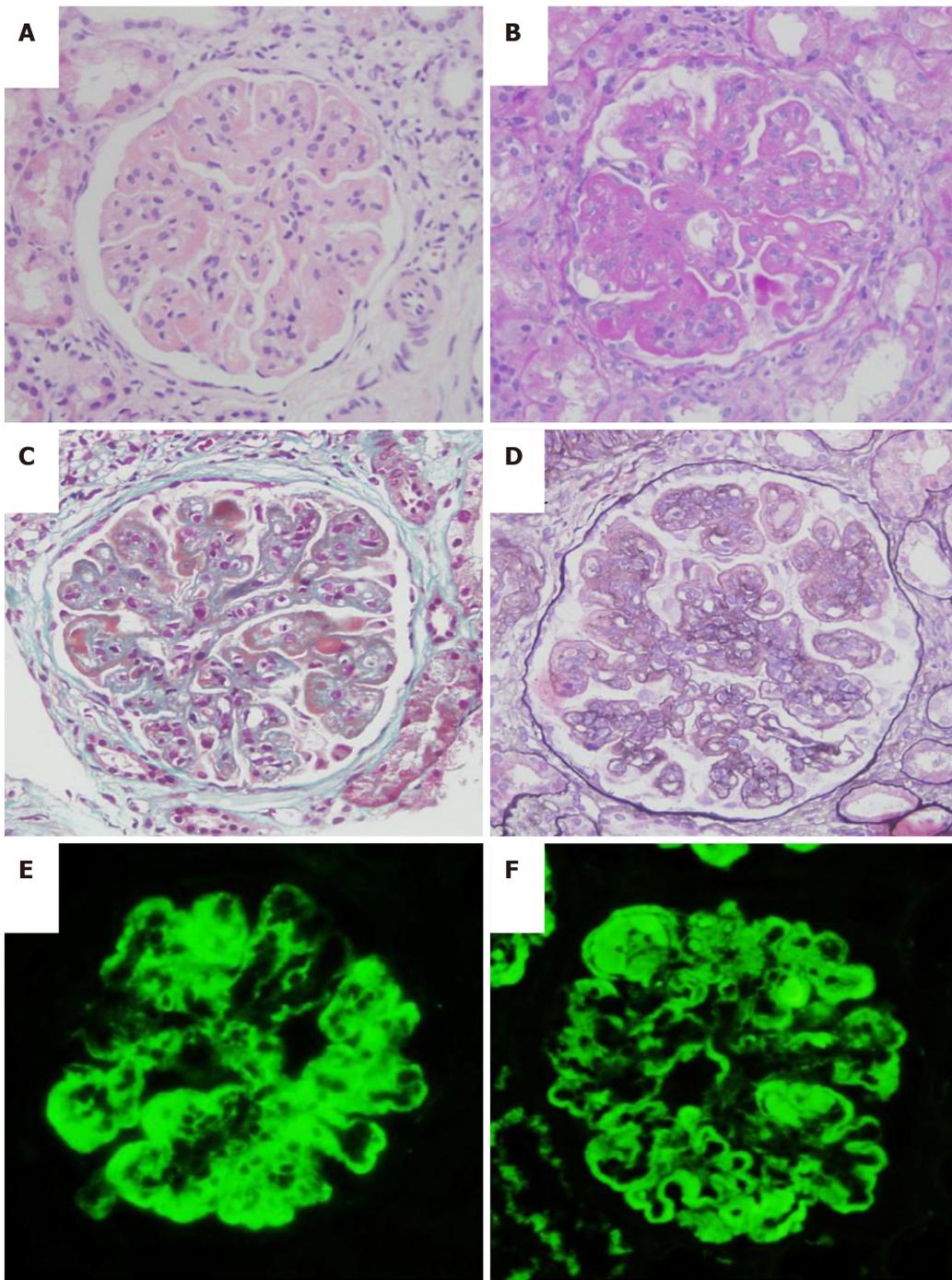


Figure 1 Biopsy pathology. A: Thickened basement membrane (hematoxylin-eosin staining, $\times 400$); B: Proliferation of mesangial cells and endothelial cells (periodic acid-Schiff stain, $\times 400$); C: Segmental wire loop (Masson, $\times 400$); D: Segmental dual track formation (periodic acid-silver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

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.

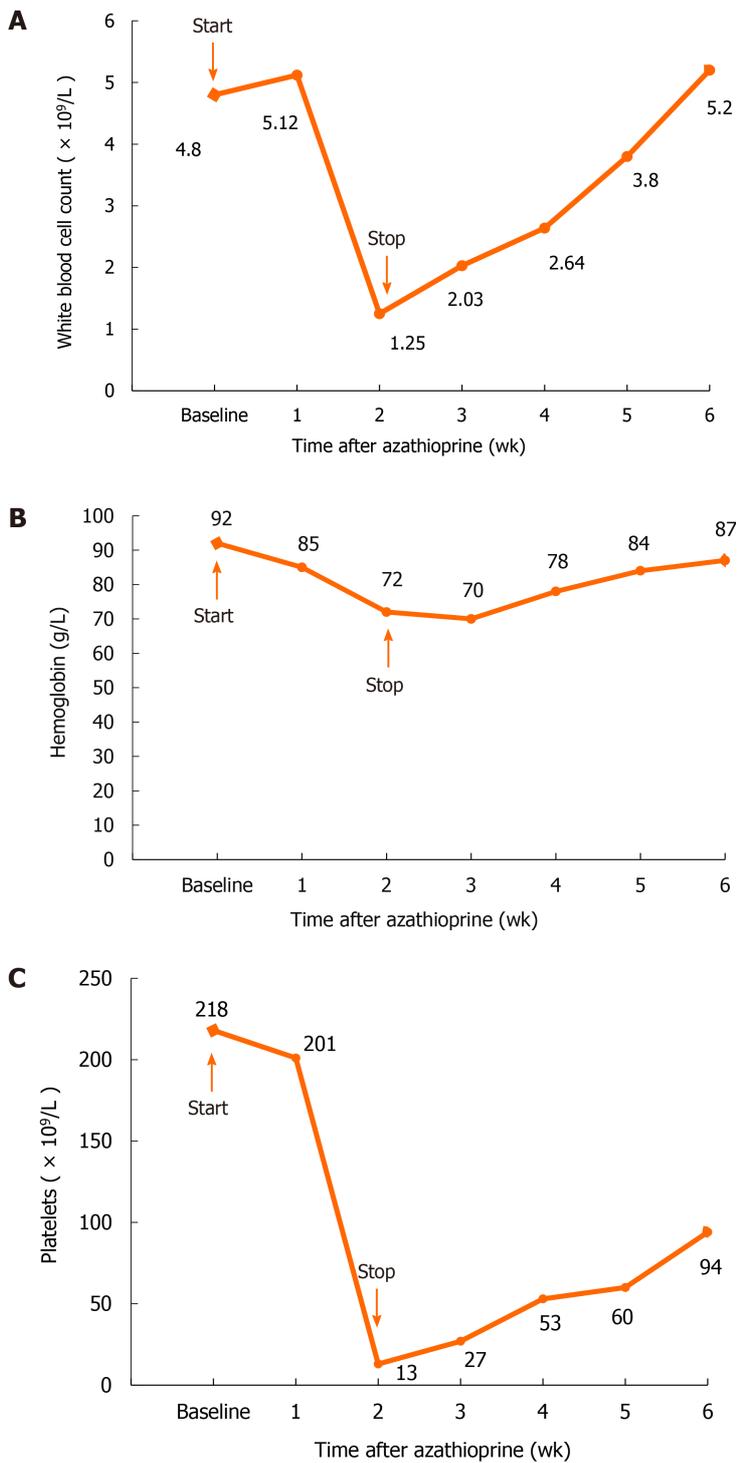


Figure 2 Routine blood work. The ‘baseline’ time point is the initiation of azathioprine therapy. Four weeks after azathioprine therapy was stopped, all values returned to their baseline levels. A: Changes in the white blood cell count. The increase in the white blood cell count after azathioprine therapy 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.

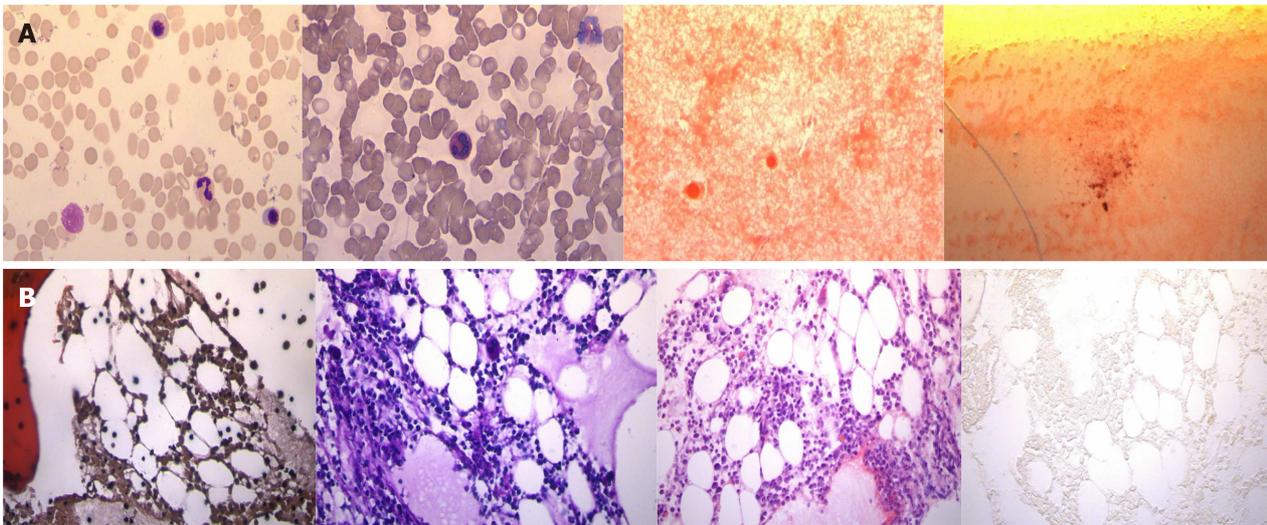


Figure 3 The results of the bone marrow biopsy. A: Results of bone marrow aspiration-myelogram. The myelogram showed low myelodysplasia (G = 52.0%, E = 25.0%, G/E = 2.1/1); cells in the lower and middle granulocyte stages were observed, with a low proportion of mesoblastic granulocytes and a high proportion 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 $\mu\text{mol/L}$. More than 2 mo after AZA was withdrawn, the patient's hair regrew. Serum creatinine was maintained at 160-190 $\mu\text{mol/L}$.

DISCUSSION

The enzyme activity of *TPMT* is key to the safe use of AZA, which strongly inactivates thiopurine metabolites (6-MP and 6-thioguanine 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 abnormality 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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