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CASE REPORT

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A rare case report: Myopathy related to the interaction between azathioprine and infliximab in the treatment of ulcerative colitis and ankylosing spondylitis

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Key Clinical Message

Administering azathioprine or infliximab for UC and AS treatment carries a significant risk of adverse reactions. Here, we present the case diagnosed with UC and AS, who received treatment with azathioprine and infliximab for 10 months, and subsequently developed drug-induced myopathy affecting the right vastus medialis muscle.

Abstract

Drug-induced myopathy is an uncommon form of muscle injury that can arise in patients without preexisting muscle conditions when exposed to therapeutic doses of certain medications. Administering azathioprine or infliximab for ulcerative colitis (UC) and ankylosing spondylitis (AS) treatment carries a significant risk of adverse reactions, including drug-induced myopathy and increased susceptibility to opportunistic infections. However, occurrences of myopathy induced by the combination of azathioprine and infliximab are rarely reported in clinical practice. Here, we present the case of a 37-year-old male patient diagnosed with UC and AS, who received treatment with azathioprine and infliximab for 10 months. Despite the resolution of symptoms and improvement in intestinal mucosal inflammation observed via endoscopy, the patient subsequently developed drug-induced myopathy affecting the right vastus medialis muscle.

KEYWORDS

ankylosing spondylitis, azathioprine, case report, drug-induced myopathy, infliximab, ulcerative colitis

1 | BACKGROUND

Immune dysfunction serves as a significant causal factor in the onset of both ulcerative colitis (UC) and ankylosing spondylitis (AS).[1,2] To address this dysfunction in UC or AS patients, azathioprine and infliximab, commonly used immunomodulatory drugs, are employed.[3,4] However, the utilization of these drugs entails a considerable risk of adverse reactions (ADRs), which include drug-induced myopathy and increased susceptibility to opportunistic

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infections.[5] Specifically, drug-induced myopathy refers to the less frequent occurrence of muscle injury, characterized by manifestations such as muscle weakness, elevated creatine kinase (CK), or myoglobinuria, in patients lacking preexisting muscle disease following exposure to therapeutic doses of certain medications.[5,6]

While earlier studies have indicated an association between myopathy and azathioprine, the incidence of myopathy induced by conventional doses of azathioprine is notably low in clinical practice. Moreover, myopathy symptoms tend to diminish significantly upon discontinuation of azathioprine treatment in clinical settings.[7] However, it remains unreported whether the concurrent use of medications can heighten azathioprine-associated myopathy. Herein, we present a case involving a 30-year-old male patient diagnosed with UC and AS, who was treated with azathioprine and infliximab, and subsequently exhibited azathioprine-induced myopathy.

2 | CASE HISTORY

A 37-year-old male patient presented to our hospital with exacerbated bloody stool and diarrhea persisting for 10 days. He had previously been diagnosed with AS and was receiving regular enalapril treatment. Three years after his admission, the patient received a diagnosis of UC at another medical facility. During treatment with mesalazine (1 g qid po) combined with adalimumab (40 mg q2w h), his condition remained stable.

In February 2021, the patient experienced worsened symptoms, including abdominal pain, diarrhea, mucus-relieving bloody stool, difficulty in flexion and extension due to ankylosis of the spine, back muscle pain, and discomfort. Laboratory tests revealed an elevated C-reactive protein (CRP) level of 117.78 mg/L and an increased erythrocyte sedimentation rate (ESR) of 63 mm/h. All other laboratory values were within the normal range. Colonoscopy results showed extensive colitis, characterized by wide mucosal defects and spontaneous bleeding throughout the colon. Histopathological examination revealed increased inflammatory cell infiltration, cryptitis, and crypt abscesses in the colonic mucosa. Following treatment with mesalazine, nutritional support, and other interventions, symptoms significantly improved, and colonic mucosal ulcers decreased, as observed in colonoscopy (Figure 1A). However, the patient's conditions of both UC and AS remained inadequately controlled.

Eight months later, the patient returned to our hospital with more severe symptoms. Laboratory results showed an elevated ESR of 40 mm/h, and a positive antinuclear antibody test. Colonoscopy and histopathology revealed extensive mucosal defects and spontaneous bleeding in the sigmoid colon and rectum (Figure 1B). Consequently, infliximab (300 mg ivd) was added, aiming to address both UC and AS. After three infliximab treatments (300 mg ivd), symptoms such as abdominal pain, diarrhea, and bloody stool improved, along with normalization of ESR and CRP levels. However, colonoscopy indicated slight left hemi-colonic colitis (Mayo score of 3), with improved colonic mucosal inflammation (Figure 1C). Additionally, the patient continued to experience difficulty in flexion and extension due to ankylosis of the spine, as well as persistent back muscle pain and discomfort, which showed no significant relief.

3 | METHODS

Laboratory analyses indicated an increased fecal calcitonin concentration of 475.37 μg/g. The trough concentration of infliximab measured 2.15 μg/mL, with a negative infliximab antibody test result. Genetic testing for commonly used immunosuppressant genes revealed CC genotypes for the azathioprine TPMT gene detection sites (rs1800462, rs1800460, and rs1800584), CC genotype for ITPA gene rs1127354, AA genotype for rs7270101, and CC genotype for NUDT15 gene rs116855232. Consequently, in order to adequately control the patients' condition, azathioprine (50 mg qd) was incorporated into the treatment regimen for the patients with UC and AS because of its low drug resistance. Furthermore, due to the absence of serum antibodies and the lower trough concentration of infliximab, the infliximab dose was adjusted to 400 mg.

4 | RESULTS

After 10 months, the patient returned to our hospital with sudden soreness on the inside of his right thigh, without any clear cause. Clinical symptoms and the findings from colonoscopy and histopathology indicated a stable condition (Figure 1D). However, noticeable muscle soreness was present in the right thigh, without any restriction in spinal movement or discomfort. Laboratory tests showed elevated creatine kinase (CK) levels of 1247 U/L, with creatine kinase isoenzymes (CK-MB) increased to 27.9 U/L. All other laboratory values remained within normal ranges. Electromyographic investigation revealed a myopathic pattern in the right medial vastus muscles, without any signs of neuropathic changes. Suspecting myogenic damage induced by azathioprine, immediate discontinuation of azathioprine was initiated. Nonetheless, infliximab (400 mg ivd) was administered over the following 3 days.

Subsequent laboratory tests revealed serum CK levels of 473 U/L, with an increased CK-MB level of 16.1 U/L.

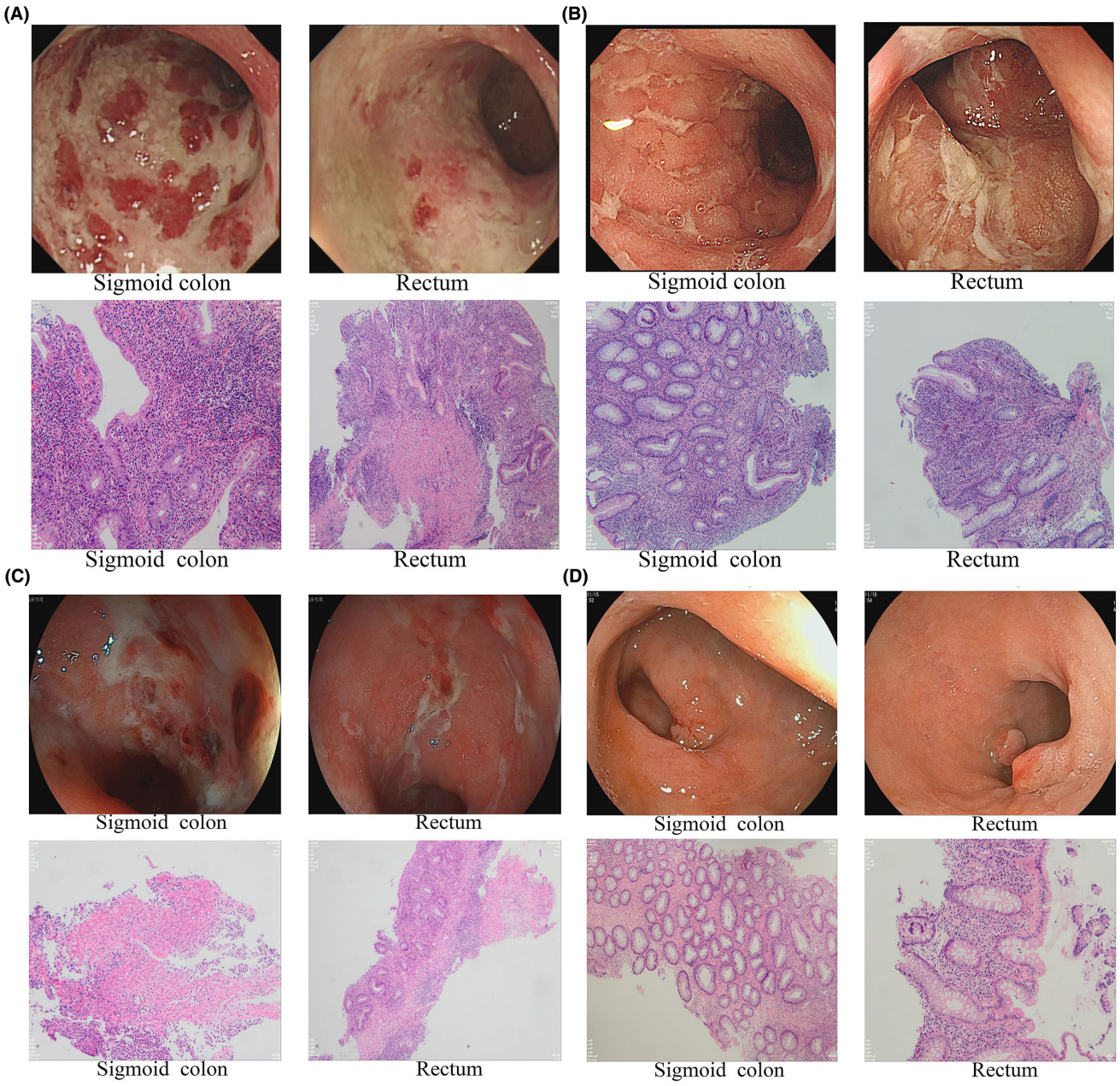

FIGURE 1 The colonoscopy and histopathological examination in colitis. (A) Colonoscopy and histopathology conducted in February, 3 years ago; (B) Colonoscopy and histopathology conducted in September, 3 years ago (H&E, 200×); (C) Colonoscopy and histopathology conducted in January, 2 years ago; (D) Colonoscopy and histopathology conducted in November, 2 years ago (H&E, 200×).

Upon reexamination, colonoscopy and histopathology showed significant improvement in colonic mucosal inflammation, with an endoscopic Mayo score of 1. Half a month later, serum CK and CK-MB levels returned to normal, coinciding with relief from symptoms of pain and discomfort in the right thigh. To date, the patient continues to receive treatment with infliximab, and the condition of the patient with UC and AS remains stable. Particularly noteworthy is the absence of recurrent muscle pain during follow-up.

5 | DISCUSSION

Drug-induced myopathy is characterized by acute symptoms such as myogenic damage, muscle pain, and elevated CK levels in patients without preexisting muscle conditions, who have been exposed to therapeutic doses of certain drugs.[6,8] The diverse causes of drug-induced myopathy lead to clinical or biochemical signs of muscle involvement, typically improving upon discontinuation of the suspected drug; thus, confirming the diagnosis of

drug-induced myopathy. However, despite understanding the causative factors, predicting the occurrence of drug-induced myopathy in clinical practice remains challenging.

In this scenario, infliximab was administered alone for 8 months to manage active UC and AS in the patient. However, due to the suboptimal trough concentration of infliximab (300 mg/d), limited improvement was observed in spinal ankylosis and colonic inflammatory lesions. Importantly, there was no evidence of myogenic impairment, suggesting that infliximab was not the cause of myopathy. Consequently, the patient's treatment plan was adjusted, with an increased dosage of infliximab (400 mg/d) along with azathioprine (50 mg/d).

Following a 10-month treatment period with infliximab and azathioprine, the patient developed symptoms indicative of myopathy, including soreness and muscle discomfort in the right thigh, electromyographic evidence of myogenic damage in the right medial vastus muscle, and elevated CK and CK-MB levels. Discontinuation of azathioprine for 3 days resulted in a gradual normalization of serum CK levels and a significant reduction in clinical symptoms. After ruling out potential factors such as infection, fatigue, trauma, and electrolyte disturbance, it was concluded that myopathy was likely induced by the administration of infliximab and azathioprine.

Azathioprine, a widely used immunosuppressant, is employed in managing acute UC and AS. Numerous studies have shown that azathioprine is significantly more effective than placebo in maintaining remission of UC for patients who cannot tolerate 5-aminosalicylic acid treatment and for those who require repeated steroid use.[9,10] It is also commonly used to sustain remission of AS.[11] In vivo, azathioprine is converted into 6-mercaptopurine (6-MP), which then inhibits the synthesis of 6-mercaptopurine nucleotides (6-TGNs). During this metabolic process, several genes that encode metabolic enzymes are essential. Notably, gene polymorphisms in TPMT and NUDT15 have been recognized as key factors that influence both the effectiveness and the occurrence of ADRs. Prior research has established a strong link between NUDT15 gene polymorphism and azathioprine-induced leukopenia.[12] Furthermore, ADRs associated with azathioprine have been connected to TPMT allele variations, leading to a sixfold increase in the incidence of ADRs in patients with genetic variations compared to those with standard genotypes.[13] Additionally, the modulation of TPMT expression in individuals with Crohn's disease has been suggested to potentially decrease the incidence of leukopenia, while reduced TPMT gene activity may lead to hepatotoxicity.[14] Despite these findings, the presence of allele variations in TPMT and NUDT15 genes did not show an increased susceptibility to adverse drug reactions. However, ethnic and individual differences in response to azathioprine were noted. Considering the potential immunogenic properties of azathioprine in patients with autoimmune disorders is crucial.

In addition, infliximab, a recombinant anti-TNF-α human monoclonal antibody, has been shown to be effective in treating UC and AS, with a minimal association with immunologically mediated myopathy.[15,16] Recent studies have suggested a possible relationship between elevated anti-infliximab antibodies and the onset of infliximab-induced myopathy.[17,18] However, in the case under review, the absence of anti-infliximab antibodies indicates that myopathy may not be directly linked to their presence. Furthermore, previous research has shown that the combined administration of infliximab and azathioprine may reduce the formation of anti-infliximab antibodies, improve therapeutic outcomes, and possibly aggravate autoimmune rheumatic diseases.[19] Therefore, it is hypothesized that the simultaneous administration of high doses of azathioprine and infliximab may significantly contribute to the development of myopathy.

6 | CONCLUSION

The concurrent use of azathioprine and infliximab in patients with UC and AS carries a potential risk for myopathy, which may be attributed to their interaction. It is essential to maintain vigilance and monitor for myopathy associated with the simultaneous administration of azathioprine and infliximab.

AUTHOR CONTRIBUTIONS

Lingyu Fu: Conceptualization; data curation; investigation; writing – original draft. **Shiying Wang:** Conceptualization; data curation; investigation; writing – original draft. **Yingyan Wang:** Data curation; methodology; supervision; writing – review and editing. **Haiyan Zhang:** Conceptualization; formal analysis; investigation; supervision; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflict of interest.

DATA AVAILABILITY STATEMENT

Data can be obtained from the corresponding author upon request.

ETHICS STATEMENT

Ethical Approval was obtained by the ethical review committee of the Second Affiliated Hospital of Guangzhou University of Chinese Medicine under ID G2023-12.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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