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Renal Dysfunction in a Patient With Crohn's Disease During Ustekinumab Treatment: A Case Report and Review of the Literature

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ABSTRACT

Ustekinumab is a first-line drug for Crohn's disease. However, little is known about its potential adverse effects on renal function. We present the case of a 42-year-old man with Crohn's disease who developed chronic renal dysfunction during ustekinumab treatment, which resolved after discontinuing ustekinumab. The findings underscore the importance of close monitoring of renal function in patients receiving ustekinumab, particularly those with preexisting kidney disease or risk factors for renal dysfunction.

Introduction

Ustekinumab, a humanized monoclonal antibody to the p40 subunit of interleukin-12 and interleukin-23, plays a critical role in inhibiting the immune effect of these cytokines, which are known to induce and maintain inflammation and fibrosis in the bowel. In fact, ustekinumab has become the first-line drug for Crohn's disease (CD) owing to its high efficacy rates in inducing and maintaining clinical remission, as well as its favorable safety profile.[1,2]

In this case report, we present the case of a young man with CD who developed acute renal dysfunction during the course of ustekinumab treatment. We observed it as an unusual adverse event of ustekinumab, particularly considering only 2 other cases of ustekinumab-related renal dysfunction have been reported in the literature, both with more severe manifestations than that in our patient. In one case, a 24-year-old man with CD experienced acute renal dysfunction after a single dose of ustekinumab intravenous injection (260 mg) followed by subcutaneous administration (90 mg) 2 months later, which was diagnosed as immunoglobulin A nephropathy based on renal pathologic examination.[3] In another case, a 51-year-old man with psoriasis developed proteinuria after receiving a total dose of 585 mg of ustekinumab over 2 years, which was confirmed by renal pathologic examination as nephrotic syndrome.[4] In all 3 cases, including our patient, the renal dysfunction improved progressively after discontinuing ustekinumab, providing good evidence of drug-induced renal adverse effects.

In light of the 3 cases presented, it is apparent that the renal dysfunction symptoms induced by ustekinumab can vary considerably. Although ustekinumab is generally tolerable and effective in the treatment of CD and other diseases, it may have potential adverse effects on renal function and the consequence could be irreversible and progressive once severe renal functional loss occurs, which can lead to dialysis or death. Furthermore, the management of patients with inflammatory bowel disease (IBD) and kidney failure is very complex. Therefore, clinicians should monitor renal function closely in patients receiving ustekinumab, particularly those with preexisting kidney disease or risk factors for renal dysfunction.

Case Description

The patient we present is a 42-year-old man who was diagnosed with ileocolonic CD, classified as A2L3B2P according to the Montreal classification, with moderate disease activity. He had a history of more than 16 years of abdominal pain since 2006, and in May 2015, he started experiencing hematochezia with no obvious predisposing causes. He was then diagnosed at other hospitals with CD primarily and underwent partial colectomy, ileocecal resection, and partial resection of the ileum. He had received

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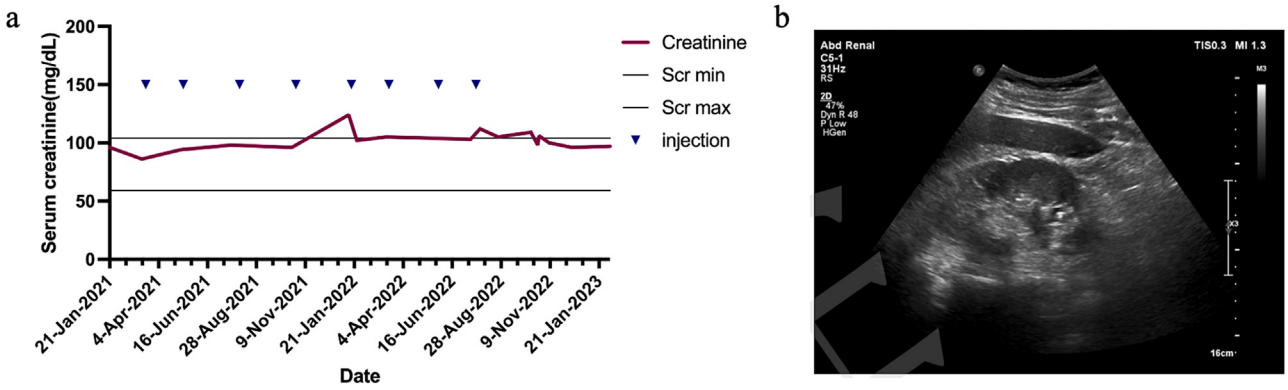

Figure 1. Renal dysfunction details. (A) Time course of serum creatinine (Scr) level of the patient. (B) Right kidney stone found via ultrasound examination.

mesalazine therapy and 14-day budesonide therapy since diagnosis, but his symptoms did not improve. Then he underwent primary anastomosis and partial ileal resection and subsequently has taken mesalazine therapy (1 g TID) ever since.

He was admitted to our hospital in January 2021, and his diagnosis of CD was confirmed by dye colonoscopy and intestinal ultrasonography. The patient then accepted the first course of ustekinumab treatment (390 mg IV) on March 16, 2021, and his symptoms improved. He received the second to eighth doses of ustekinumab (90 mg SC) from May 2021 to July 2022 (every 8 weeks), with no other adverse event noted except high blood creatinine concentration and a low ustekinumab blood concentration of 2.0 μg/mL (reference level, >2.2 μg/mL) measured on September 9, 2022, before the ninth dose of ustekinumab.

The patient initially reported high blood creatinine concentration (112 μmol/L) between the fourth and fifth courses of treatment in November 2021, which was left untreated. Before the fifth course of ustekinumab treatment on January 13, 2022, we observed that the patient's blood creatinine level was 124 μmol/L (reference range, 59–104 μmol/L), and his estimated glomerular filtration rate was 64.6 mL/min/1.73 m^2.

Our analysis of the patient's creatinine levels (Figure 1 A) indicated that during the fifth and eighth courses of ustekinumab treatment, his mean creatinine level exceeded the maximum threshold of 104 μmol/L and reached 108.6 μmol/L. To identify causes, a thorough evaluation was conducted in July 2022 (see Supplementary Table 1), including laboratory tests such as urinalyses and ultrasound examinations, which revealed no significant abnormalities except for a right kidney stone (Figure 1 B). Physical examination revealed no abnormalities in the abdominal signs, skin, joints, and ocular and neurologic findings. The patient had no history of kidney disease.

The laboratory tests, which were carried out on March 14, 2022, and September 9, 2022, revealed negative antibody titers, and the blood concentration of ustekinumab was measured as 3.0 μg/mL and 2.0 μg/mL (reference level, >2.2 μg/mL), respectively. The dye colonoscopy on September 16, 2022, showed that clinical symptoms had partially improved; however, the endoscopic evaluation still revealed stenosis at the ileocecal anastomosis site, with scattered circumferential ulcers covered with white plaques (Rutgeerts score is 4). Consequently, evidenced by low blood concentration and lack of submucosal healing, the ustekinumab treatment failed to achieve satisfactory results. In addition, considering the potential renal side effects of ustekinumab, we discontinued ustekinumab therapy and switched to infliximab treatment on October 26, 2022, with a single intravenous infusion of 400 mg, and monitored kidney function via laboratory testing more regularly. Subsequently, the patient achieved stable levels of creatinine and his renal function improved completely before the second treatment with infliximab.

Discussion

High rates of induction and sustained remission have been reported with ustekinumab in patients with moderate-to-severe CD,[5,6] making it a strong recommendation for patients with an inadequate response to conventional therapy (such as steroids and/or thiopurines) and/or anti–tumor necrosis factor therapy.[6] Multiple clinical trials have reported that the rates of adverse events associated with ustekinumab are similar to those of placebos,[5,7–9] with common adverse effects such as abdominal pain, nausea, nasopharyngitis, arthralgia, cough, pyrexia, fatigue, and infection, among others.[5,7,8] Infusion reactions were uncommon, mild, and occurred at similar rates.[5] However, renal impairment-related symptoms, with the exception of urinary tract infections, have been less frequently reported. A case report has even suggested that ustekinumab may be a viable alternative for patients with psoriasis and renal failure.[10]

In this case, the patient's medical history revealed no hypertension, diabetes, or prior drug allergies, and no family history of kidney disease. Nonetheless, a slow but persistent increase in creatinine level was observed during the patient's fifth to eighth treatments with ustekinumab.

To identify causes, a thorough evaluation was conducted. Renal dysfunction can arise from 3 main causes: prerenal, renal, and postrenal dysfunction.

Prerenal dysfunction can result from renal vessel occlusions or drug-induced renal vasoconstriction (calcineurin inhibitor, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, and NSAIDs) and cardiovascular disease, such as cardiorenal syndrome. It may also result from blood volume depletion secondary to gastrointestinal complications (ie, bleeding, vomiting, or diarrhea) or generalized vasodilation resulting from sepsis. Considering that this patient has no pertinent medical history symptoms, no abnormal findings were observed on the renal artery and vein ultrasound results and complete blood count, so the possibilities of renal vessel stenosis and thrombotic microangiopathy were ruled out. Furthermore, throughout treatment with ustekinumab and infliximab, the patient continued to have regular soft bowel movements with no change in stool consistency, passing yellow, pasty, or soft stools 3 to 4 times daily. This indicates that the patient did not experience watery diarrhea and dehydration, and the likelihood of prerenal dysfunction is low.

Also, in this case, although a stone was discovered in his right kidney, no evidence of postrenal obstruction was identified upon

performing bilateral renal, ureteral, and bladder ultrasound examination, thus deeming postrenal dysfunction unlikely.

Renal dysfunction was further analyzed through laboratory tests involving antineutrophilic cytoplasmic antibody, antinuclear antibody, anti–glomerular basement membrane antibody, serum protein electrophoresis, and urinalyses alongside other indicators of primary renal disorders. All test results were negative, no hematuria or proteinuria was found, and the patient did not exhibit oliguria, which excludes glomerular and renal tubular diseases. The patient also lacks secondary risk factors, such as hypertension, diabetes, or prior drug allergies, despite exhibiting signs of mild obesity (body mass index of 25.43 kg/m^2). In addition, through detailed history taking, we excluded other possibilities such as diet, exercise, and other medications (including traditional Chinese herbs).

We believe that the patient's renal insufficiency may have been caused by acute interstitial nephritis after conducting a comprehensive analysis. Furthermore, based on the gradual increase in creatinine levels observed during treatment with ustekinumab and the subsequent return to normal levels after its discontinuation, we suspect that ustekinumab treatment could be a contributing factor to the renal dysfunction experienced by the patient. To determine the likelihood of this being associated with ustekinumab, the Naranjo Adverse Drug Reaction Probability Scale was used,[11] indicating a probable adverse drug reaction with 7 points.

After determining that ustekinumab was responsible for the renal dysfunction and observing an unexpected lack of therapeutic effect on IBD, we decided to switch from ustekinumab to infliximab and closely monitor kidney parameters during follow-up therapy. The discontinuation of ustekinumab was mandatory because of the potential severity of renal involvement, and switching to a different class of biologic treatment was a reasonable option. This decision to use infliximab was based on overall clinical judgment and the need for effective IBD management and was made jointly by the patient and clinicians.

The mechanisms underlying ustekinumab-induced renal disorders have not yet been fully identified.[12] Notably, renal disorders associated with IBD, including nephrolithiasis, entero-vesical fistulae, urinary tract malignancy, renal amyloidosis, tubulointerstitial disease, glomerulonephritis, and drug-related nephrotoxicity, are relatively underreported compared with other extraintestinal symptoms.[13] However, early studies have reported that renal disorders account for nearly 25% of patients with IBD, and nephrolithiasis (right kidney stone in this case), obstructive uropathy, and fistula formation between the bowel and urinary tract are the most common manifestations.[14] Long-term clinical studies of high quality are necessary to explore the relationship between IBD and renal disorders. Such studies would enable the implementation of preventive measures and the provision of appropriate therapy for patients at high risk of renal dysfunction.

Conclusions

In the case of a 42-year-old man with CD who developed acute renal dysfunction during ustekinumab treatment, the renal dysfunction resolved after discontinuing ustekinumab. Close monitoring of renal function in patients receiving ustekinumab is important, particularly in those with preexisting kidney disease or risk factors for renal dysfunction.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Yuge Wei: Project administration, Writing – original draft. **Gechong Ruan:** Conceptualization, Supervision, Writing – review & editing, Funding acquisition. **Yan Qin:** Conceptualization, Writing – review & editing. **Xiaoyin Bai:** Resources, Supervision, Writing – review & editing. **Hong Yang:** Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing.

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Ethics Statement

We conducted this study in compliance with the principles of the Declaration of Helsinki. The study has been approved by the Institutional Review Board of Peking Union Medical College Hospital (No. K2250). Written informed consent was obtained.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGPT3.5 to improve language and readability. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.curtheres.2024.100753.

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