ELSEVIER

Acute Allograft Renal Failure With Marked Hyperuricemia Developing During Mizoribine Administration: A Case Report With Review of the Literature

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ABSTRACT

Mizoribine (MZ) is a potent immunosuppressant used in conjunction with other immunosuppressants to prevent and treat allograft rejection after organ transplantation. Although hyperuricemia is the most common side effect of MZ, there are no case reports of acute allograft renal failure associated with MZ. This report describes a patient who developed acute allograft renal failure and hyperuricemia during MZ treatment. Accordingly, MZ treatment was terminated, hemodialysis was initiated, and allopurinol was administered. Hemodialysis was necessary only once. The patient's condition improved with these treatments, and renal function recovered. Care should be taken during treatment with MZ to avoid latent renal dysfunction. Monitoring of serum uric acid levels was necessary. Moreover, it may be necessary to consider discontinuation of MZ and initiation of hemodialysis in cases of transient renal dysfunction. No prisoners were used and no organs from prisoners were used in the study.

MIZORIBINE (MZ) is a water-soluble antimetabolite that selectively inhibits lymphocyte proliferation via inhibition of inosine monophosphate dehydrogenase, similar to mycophenolate mofetil (MMF).[1–3] MZ is a potent immunosuppressant, often used in conjunction with other immunosuppressants, to prevent and treat allograft rejection after organ transplantation.[2,4–6] Formation of uric acid (UA) has been shown to be increased, as a result of inhibited purine synthesis by MZ, and is thought to be the mechanism of hyperuricemia for MZ. We report herein a case with the development of acute allograft renal failure during treatment with MZ. No prisoners were used and no organs from prisoners were used in the study.

CASE REPORT

A 29-year-old man with chronic glomerulonephritis underwent kidney transplantation, with a kidney donated from his mother, on June 10, 2008. Acute rejection was not observed. Immunosuppressive therapy comprised cyclosporine A (CsA), MZ, and prednisone until readmission on October 28, 2008. After transplantation, his serum creatinine (SCr) levels decreased to 105 to 140 μmol/L and nearly stabilized. On October 28, 2008, the patient underwent examination because of progressive weakness and decreased appetite. The laboratory evaluation revealed elevated SCr (877.0 μmol/L) and UA (1077.0 μmol/L) levels. He was admitted to Beijing Friendship Hospital. Upon admission, immunosuppressive therapy included CsA (200 mg/d; trough level, 181.76 ng/mL), MZ (300 mg/d), and prednisone (15 mg/d). Physical examination results were entirely unremarkable. Urine volume was 4300 mL/d. Laboratory data were as follows: hemoglobin, 136 g/L; hematocrit, 38.7%; white blood cell count, 4.04×10^9/L; platelet count, 163×10^9/L, sodium, 139.9 mmol/L; potassium, 6.16 mmol/L; chloride, 102 mmol/L; carbon dioxide, 10.2 mmol/L; blood urea nitrogen (BUN), 61.65 mmol/L; SCr, 877.0 μmol/L; alkaline phosphatase, 47 IU/L; magnesium, 1.06 mmol/L; glucose, 5.63 mmol/L; calcium, 2.00 mmol/L; phosphorus, 3.67 mmol/L; glutamic pyruvic transaminase, 10 IU/L; UA 1077.0 μmol/L; and albumin, 27.7 g/L. Urinalysis revealed a specific gravity of 1.025 and pH 6.0. Urinary protein was (−) and occult blood was (2+). Neither casts nor UA crystals were observed in the urinary sediment. Renal ultrasound on October 28, 2008, revealed a kidney size of 12.0×6.4 cm, a cortical thickness of 0.9 cm, echogenicity of renal parenchyma increased, normal blood flow distribution and a resistance index (RI) of the interlobar artery of 0.66 (Fig 1A).

After admission, MZ therapy was discontinued and the immunosuppressive regimen was adjusted to CsA (200 mg/d), MMF (1500 mg/d), and prednisone (15 mg/d). Because of allograft failure, the patient was placed on 3 hours of hemodialysis on October 28, 2008. Intravenous 5% sodium bicarbonate (250 mL/d

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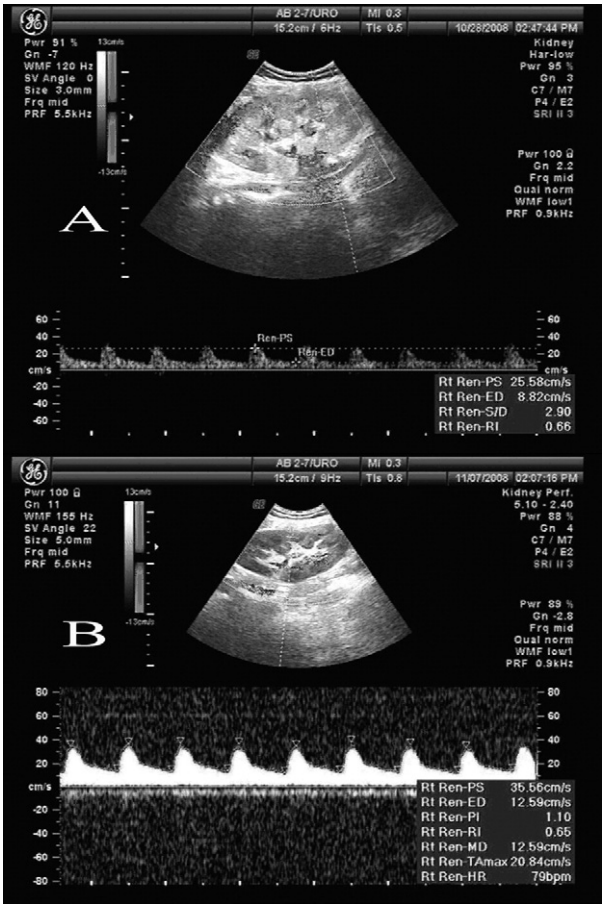

Fig 1. **(A)** Sonogram of acute urate nephropathy reveals graft enlargement and increased echogenicity of renal parenchyma. **(B)** After treatment, graft presents normal on ultrasonography.

for 5 days) and oral allopurinol (0.2 g/d for 10 days) treatments were initiated. Within the next few days, his SCr and UA levels slowly decreased. The patient was discharged 13 days after admission with SCr levels of 148.8 μmol/L and UA levels of 247.1 μmol/L. Renal biopsy was not performed during admission.

After recovering from acute renal failure, renal ultrasound findings revealed a 11.4 $\times$ 5.0 cm kidney with a cortical thickness of 0.7 cm; the echogenicity of the renal parenchyma was normal, blood flow distribution was normal, and RI of interlobar artery was 0.65 (Fig 1B).

At the 2-month follow-up, the SCr level was 141.0 μmol/L and the UA, 431.0 μmol/L. Urinalysis revealed a specific gravity of 1.025 and a pH of 5.50. Immunosuppressive therapy included CsA (200 mg/d; trough level, 254.09 ng/mL), MMF (1500 mg/d), and prednisone (10 mg/d). After follow-up, CsA was reduced to 175 mg/d, oral allopurinol to 0.1 g/d, and oral sodium bicarbonate to 1000 mg, 3 times per day.

At the 4-month follow-up, laboratory data were as follows: hemoglobin, 150 g/L; hematocrit, 47.0%; white blood cell count, 11.48 $\times$ 10^9/L; platelet count, 256 $\times$ 10^9/L; sodium, 138.4 mmol/L; potassium, 4.39 mmol/L; chloride, 100 mmol/L; carbon dioxide, 20.9 mmol/L; BUN, 12.39 mmol/L; SCr 153.0 μmol/L; alkaline phosphatase, 80 IU/L; magnesium, 0.60 mmol/L; glucose, 4.88 mmol/L; calcium, 2.54 mol/L; phosphorus, 1.23 mmol/L; glutamic pyruvic transaminase, 46 IU/L; UA, 438.0 μmol/L; and albumin, 46.0 g/L. Urinalysis revealed a specific gravity of 1.025 and a pH of 6.50. Urinary protein was (−) and occult blood was (−). Neither casts nor UA crystals were observed in the urinary sediment. Immunosuppressive therapy included CsA (175 mg/d; trough level, 184.13 ng/mL), MMF (1500 mg/d), and prednisone (10 mg/d). After follow-up, CsA was reduced to 150 mg/d, oral allopurinol to 0.1 g/d, and oral sodium bicarbonate to 1000 mg 3 times per day.

DISCUSSION

Hyperuricemia is a common complication in organ transplant recipients, although the precise incidence remains unclear. It has been reported that hyperuricemia occurs in 5%–84% of recipients of solid organ transplants.[7,8] In a study of 307 patients,[9] there was an association between hyperuricemia and kidney transplantation; 144 patients (47%) presented with hyperuricemia at 6 months after kidney transplantation.

UA may be involved in the development and progression of kidney diseases. Long-standing hyperuricemia has been associated with chronic tubulointerstitial disease, afferent arteriopathy, intrarenal vasoconstriction, and increased vascular resistance.[10] UA also contributes to acute renal damage. Although acute urate nephropathy is typically observed as a complication of the "tumor lysis syndrome," it has also been occasionally reported with rhabdomyolysis[11] and other conditions. In addition, UA may play a role in allograft renal dysfunction in patients after renal transplantation.[12]

Acute renal failure is associated with increased serum UA levels, as a result of both increased generation and decreased excretion. Although markedly elevated levels of UA are widely recognized to cause acute renal failure via supersaturation within the tubules, resulting in crystallization and intrarenal obstruction ("acute urate nephropathy"), there is a possibility that UA may affect renal outcomes at concentrations that do not lead to tubular obstruction. Indeed, recent studies have documented that acute renal failure is not simply mediated by tubular cell injury, but is frequently accompanied by renal vasoconstriction, microvascular injury, and a local inflammatory response.[13–16]

Animal models have demonstrated a key role of UA in acute renal failure; experimentally induced hyperuricemia has been shown to lead to marked uricosuria with intratubular crystal deposition, tubular obstruction, and a marked local inflammatory response.[17,18] Increased renal UA excretion results in supersaturation of urine, crystallization of urate, and obstruction of the tubular lumina, resulting in local granulomatous inflammation, which is associated with macrophage and T-cell infiltration.[17,19] Furthermore, UA can activate inflammatory cells, stimulate monocyte chemoattractants,[20] and induce pro-oxidative effects in vascular cells.[21] UA may also influence dendritic cell activation of injured cells.[21] Experimental hyperuricemia also causes profound renal vasoconstriction.[18,22]

Hyperuricemia is a common complication in renal transplant recipients; diuretic or cyclosporine treatment are associated with posttransplant hyperuricemia.[9] The similar effects of tacrolimus (Tac) remain debatable. Studies have shown that hyperuricemia is the most common adverse event with MZ (16%), although it is transient.[23]

Steady serum urate levels result from a balance between production and excretion. Hyperuricemia results when the formation is increased or difficulties in (mostly) renal excretion occur. Two thirds of urate excretion occurs in the kidney, and the gut excretes the remainder. In an estimated 85%–90% cases, gout results from poor renal disposal of urate.[24] However, MZ-induced hyperuricemia is primarily a result of increased UA production.

The clinical manifestations of MZ-induced acute allograft renal failure may be nonspecific. In the case presented here, increased SCr and UA levels were the primary clinical manifestation of acute allograft renal failure, with normal or increased urinary volume.

Because UA crystals and calculus cannot be detected by x-ray plates, the significance of x-ray examination remains limited. However, they do present with altered echogenicity in ultrasound examination. Therefore, ultrasonography may be helpful in the diagnosis of acute allograft renal failure caused by hyperuricemia. This patient exhibited increased renal parenchyma echogenicity in the renal ultrasound examination before treatment. After treatment, the renal parenchyma echogenicity recovered to normal.

Because routine renal biopsies do not provide reliable objective evidence for the clinical diagnosis of acute allograft renal failure caused by UA, as well as the absence of analogous experience, a renal biopsy was not performed in this case.

Prevention and treatment of acute hyperuricemia and renal failure are aimed at maintaining adequate hydration, reducing serum uric acid levels, and alkalinization of the urine (which promotes urate solubilization).[25,26] Therapy for reducing UA levels include recombinant uricase, xanthine oxidase inhibitor, and dialysis. A number of studies have reported the use of the UA-reducing drug, allopurinol, in acute renal failure models. Allopurinol is a xanthine oxidase inhibitor that blocks UA formation. Allopurinol should be used with caution, because it interacts with azathioprine, resulting in bone marrow suppression. Substitution of MMF for azathioprine avoids this interaction. In the present study, allopurinol was utilized to reduce serum UA levels; no side effects of allopurinol presented during treatment. Benzbromarone has been indicated in allopurinol-intolerant patients with renal failure, solid organ transplant, or tophaceous/polyarticular gout. Monitoring for hepatotoxicity is essential for patients taking benzbromarone.[27] Recently, the use of recombinant urate oxidase, or rasburicase, has been shown to be markedly effective at reducing UA, and seems to be superior to allopurinol for promoting diuresis and improving renal function in patients.[25] Dialysis reduces UA levels and rapidly improves patient conditions. In acute renal failure patients, dialysis is often necessary.

In conclusion, it is important to identify the risks for the development of acute urate allograft renal failure. Care should be taken regarding latent renal dysfunction during MZ treatment. In addition, serum UA monitoring was necessary. In the case of transient renal dysfunction, it may be necessary to consider the discontinuation of MZ and initiation of hemodialysis.

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