Case Report

Azathioprine Induced Acute Interstitial Nephritis as the Cause of Rapidly Progressive Renal Failure in a Patient with Wegener's Granulomatosis

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ABSTRACT. Wegener's granulomatosis (WG) is a primary systemic vasculitis involving predominantly the upper and lower respiratory tracts and the kidneys. Few diseases can cause deterioration of renal function and progression to renal failure as rapidly as WG. We describe a woman with WG who developed rapid progression to renal failure within 10 days of starting azathioprine prescribed as maintenance therapy for vasculitis. Her renal biopsy showed acute tubulointerstitial nephritis and no active glomerulonephritis. This case illustrates the importance of the history and urine sediment in differentiating drug hypersensitivity from rapidly progressive glomerulonephritis in patients with WG. (J Rheumatol 2006;33:185–7)

Key Indexing Terms:
WEGENER'S GRANULOMATOSIS
INTERSTITIAL NEPHRITIS
AZATHIOPRINE
VASCULITIS

Wegener's granulomatosis (WG) is a clinicopathologic syndrome of unknown etiology characterized by the triad of necrotizing granulomas and vasculitis of the upper and lower respiratory tract and pauciimmune necrotizing crescentic glomerulonephritis[1]. Cytoplasmic staining of antineutrophil cytoplasmic antibodies (cANCA) with specificity against proteinase-3 (PR-3) is present in about 80%–90% of patients with active disease[1]. Patients with severe life-threatening WG are typically treated with a combination of high doses of corticosteroids and cyclophosphamide (CYC) for periods of 3 to 6 months. Once remission has been induced, lower doses of corticosteroids and less toxic alternatives to CYC, including azathioprine (AZA), methotrexate (MTX), or trimethoprim/sulfamethoxazole (T/S) are usually employed to maintain remission[1].

We describe a woman with diffuse WG who presented with rapidly progressive renal failure within 10 days of starting maintenance therapy with AZA.

CASE REPORT

A 47-year-old woman was diagnosed with diffuse WG in January 2003 when she presented with arthritis, positive cANCA/PR-3 (> 500 AAU/ml; normal < 20 U/ml), hematuria, and renal insufficiency. Her creatinine rose from 45 to 157 mmol/l over a period of 14 days and a renal biopsy was performed. The renal biopsy showed pauciimmune necrotizing crescentic glomerulonephritis (Figure 1A) with patchy mild interstitial fibrosis and tubular atrophy, and mild arteriolar sclerosis. During her hospital stay she was treated with intravenous methylprednisolone (750 mg daily for 3 days) and then maintained taking prednisone and CYC (100 mg PO daily) for 6 months. By June 2003, the prednisone had been tapered to 10 mg/day and CYC was replaced with AZA 100 mg/day.

Her creatinine at that time was 119 μmol/l. Other medications included ramipril 5 mg/day, omeprazole 20 mg/day, trimethoprim 160 mg/sulfamethoxazole 800 mg three times a week, and zopiclone 7.5 mg at bedtime. Ten days later, she presented to the emergency room with a 4 day history of fever, low back pain radiating to the abdomen, nausea, vomiting, and oliguria. She denied symptoms of nasal obstruction, crusting, epistaxis, sinusitis, cough, hemoptysis, or chest pain. Her temperature was 38.4°C, pulse 105/min, respiratory rate 20/min, and blood pressure 115/70. There was no rash or lymphadenopathy. The otolaryngologic examination was normal and her chest was clear to auscultation. Cardiovascular examination was normal with no bruits or murmurs. The abdomen was soft but diffusely tender, and she also had bilateral lower paraspinal tenderness. She had no peripheral edema and a normal musculoskeletal examination.

Hemoglobin was 110 g/l, white blood cell count 20.1×10^6/l, platelets 195×10^6/l, and the erythrocyte sedimentation rate was 54 mm/h. The creatinine was 459 μmol/l and the cANCA/PR-3 was 60 AAU/ml. Urine cultures were negative. All other laboratory findings were within normal limits. The urinalysis showed 5–10 red cells/high power with no white cells, red cell or white cell casts, and no eosinophils. A computer tomography scan of the abdomen showed bilateral enlarged kidneys with perinephric stranding and small bilateral pleural effusions. A renal ultrasound showed patent renal arteries and veins with no evidence of thrombosis. Acute interstitial nephritis secondary to AZA was suspected and the drug was discontinued. She was also given 1 g methylprednisolone intravenously for 3 consecutive days followed by a maintenance dose of prednisone 60 mg daily by mouth in divided doses. The day after admission her creatinine rose to 684 mmol/l and she required hemodialysis on Day 2 and Day 5. A renal biopsy was performed on Day 4 (Figure 1B). It showed mostly normal glomeruli with occasional fibrous crescents. The glomeruli showed no

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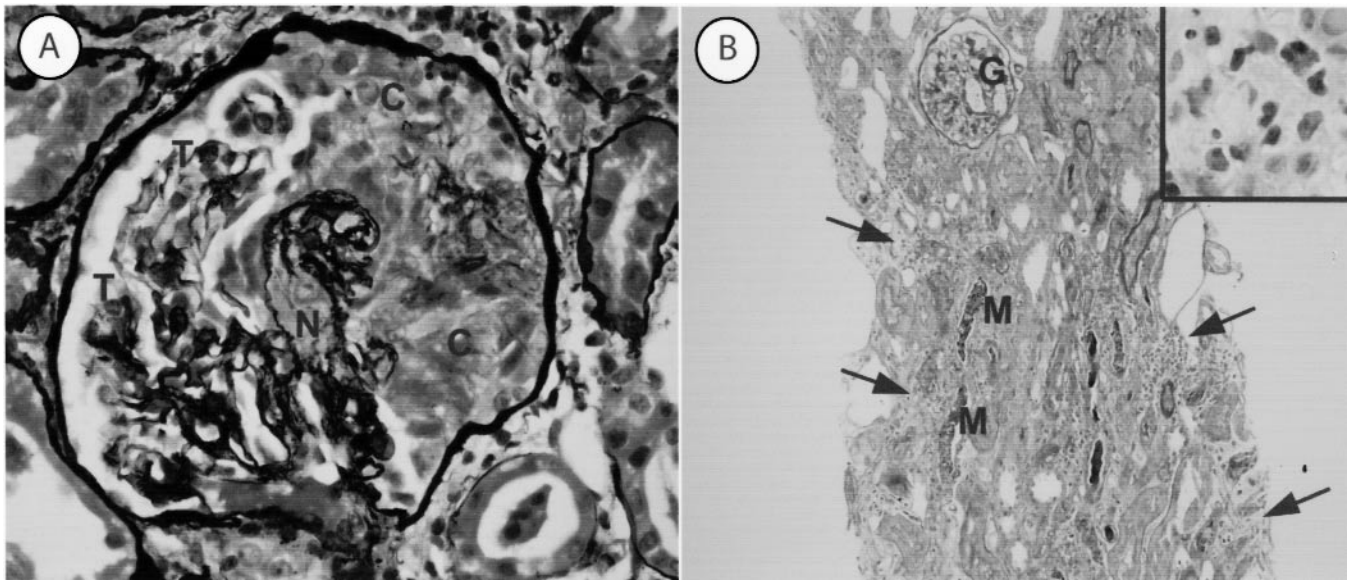

Figure 1. Renal biopsy findings. A. The patient's initial biopsy shows necrotizing crescentic glomerulonephritis. There is a large cellular crescent (C). The glomerular tuft shows segmental necrosis (N) and uninvolved tuft (T) shows no endocapillary hypercellularity and an unremarkable mesangium (Jones stain, original magnification ×400). B. The subsequent renal biopsy shows a normal glomerulus (G) with no cellular crescents, vasculitis, or granulomas. There is mixed interstitial inflammation (arrows) consisting of mononuclear cells, neutrophils, and eosinophils (inset). Tubular microabscesses (M) containing neutrophils and eosinophils are present (periodic acid Schiff stain, original magnification ×50; inset H&E stain, original magnification ×600).

necrosis, endocapillary hypercellularity, or any cellular or fibrocellular crescents. The biopsy was diagnostic of acute interstitial nephritis and showed a diffuse cortical interstitial inflammatory infiltrate of lymphocytes, monocytes, occasional plasma cells, and numerous eosinophils. There were several foci of tubulitis and some tubules contained intraluminal eosinophils. White blood cell tubular microabscesses (white cell casts) consisting of neutrophils and eosinophils were present.

Diffuse moderate interstitial fibrosis and tubular atrophy were present. There was mild arteriolar hyalinosis and no vasculitis. There were no granulomas. Immunofluorescence was negative for IgG, IgM, IgA, C3, C4, kappa and lambda light chains, and fibrin.

Electron microscopy revealed normal glomerular basement membrane thickness, intact foot processes, and no immune deposits or necrosis.

By Day 6 post-admission her renal function began improving and at one month post-admission her serum creatinine was 116 μmol/l. She was maintained taking MTX 15 mg per day and prednisone therapy was tapered off 2 months after discharge. She continued to have reasonable renal function and 16 months later had a creatinine of 104 μmol/l with no clinical evidence of recurrent interstitial nephritis or vasculitis.

DISCUSSION

Acute interstitial nephritis is most commonly associated with exposure to drugs, in particular antibiotics. Other etiologies include infections and autoimmune disorders. Less than 10% of cases are idiopathic[2].

Azathioprine is a purine antagonist commonly used in solid organ transplant and in the treatment of chronic inflammatory diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus, vasculitis, chronic hepatitis, and inflammatory bowel diseases. It is a biologically inactive prodrug until converted to 6-mercaptopurine *in vivo*, where it is then further metabolized to 6-thioguanine nucleotides[3]. It gets taken up into nucleic acids, resulting in nucleic acid malfunction, chromosomal breakage, and inhibition of protein synthesis and mitosis[3]. AZA is inactivated by xanthine oxidase and thiopurine methyltransferase (TPMT). A number of side effects have been described with AZA, including marrow suppression, infection, gastrointestinal disturbance, infertility, and hepatic dysfunction[4].

Hypersensitivity reactions are rare. Typical manifestations include fever, arthralgia, myalgia, maculopapular rash or erythema nodosum, pneumonitis, and very rarely interstitial nephritis leading to renal insufficiency[5-7]. Hypersensitivity reactions to AZA appear within 7 days to many weeks of drug exposure. In a large series of 546 patients with RA treated with AZA, hypersensitivity reactions were not specifically noted[4]. However, in a similar smaller series of 25 patients, 12% noted hypersensitivity reactions[8]. In another study of 591 patients with inflammatory bowel disease (IBD) treated with AZA, 2.7% developed hypersensitivity reactions[8,9].

Three patients with vasculitis and hypersensitivity reaction to AZA have been described. A 29-year-old woman with myeloperoxidase-ANCA associated vasculitis and renal involvement was started on AZA after taking steroids and CYC for 4 months. Within 11 days she developed fever, nausea, vomiting, malaise, and myalgias, with an elevation of her C-reactive protein (14 mg/dl) with unchanged myeloperoxidase-ANCA values. The symptoms resolved with drug discontinuation, but recurred upon rechallenge with AZA[10]. A 58-year-old woman with WG developed general malaise, headache, fevers, a maculopapular rash, and a rise in creatinine within 20 days of initiating AZA for maintenance therapy. There was no demonstrable infective

foci and ANCA were negative; however, broad-spectrum antibiotics were started and AZA was discontinued. The fever and rash resolved. One month later AZA was restarted, with immediate reappearance of fever and malaise. Once AZA was discontinued again, the symptoms resolved within a few hours. After a second rechallenge, the appearance of identical complaints suggested a hypersensitivity reaction to AZA[10]. The third case was a 63-year-old man with focal segmental pauciimmune necrotizing glomerulonephritis and lung, peripheral nervous system, and joint involvement. His cANCA/PR-3 was 129 U/ml. Treatment to induce remission was started with CYC 2 mg/kg/day combined with prednisone 1 mg/kg. Maintenance therapy with AZA 150 mg/day and prednisone 2 mg/day was initiated. Within 10 days he developed fever (39.7°C) and his creatinine rose steadily to 459 μmol/l. The urine showed no active sediment and there was no rise in cANCA titer. There were no signs of WG activity in other organ systems. He underwent a kidney biopsy following a rechallenge with AZA months later that resulted in a recurrence of the same symptoms. The biopsy was consistent with interstitial nephritis, supporting the diagnosis of hypersensitivity reaction to AZA. His renal function returned to its former level of 141 μmol/l within 2 weeks of discontinuing AZA[11].

In patients with WG, rapid deterioration of renal function due to crescentic glomerulonephritis will almost always be associated with an active urine sediment, including hematuria, proteinuria, and red cell casts and a rise in ANCA titers. In contrast, in patients with renal deterioration due to acute interstitial nephritis, the urine sediment will be benign or it may show eosinophils or eosinophil casts.

Withdrawal of AZA is the single most important component of treatment. Some authors have advocated the use of steroids, i.e., prednisone 1–2 mg/kg/day for patients with severe renal dysfunction. If there is no improvement after 2–3 weeks of steroid therapy, the use of either CYC 2 mg/kg/day or mycophenolate mofetil may be considered[12]. To date there has been no evidence of irreversible renal failure when the drug was stopped.

Rechallenging a patient who developed a hypersensitivity reaction to AZA is dangerous and should not be attempted. However, Schmitt, *et al* found that using azathioprine's active metabolite, 6-mercaptopurine, may be a safe alternative[7].

Patients with TPMT mutations associated with low or intermediate TPMT activity may be at a higher risk of severe toxicity from AZA[13]. In a study of 67 patients with rheumatic disease treated with AZA, Black, *et al* used polymerase chain reaction based assays to detect mutations in TPMT. Six patients (9%) were found to be heterozygous for mutant TPMT alleles. Five of these 6 patients discontinued therapy within one month of starting treatment because of low leukocyte counts[13]. In the remaining patients, therapy was discontinued in 25 patients because of side effects (nausea, abnormal liver function tests, and low leukocyte counts), and in 18 patients because of lack of or loss of efficacy. A number of authors have suggested that testing TPMT status prior to starting AZA in patients with IBD may be a reliable and cost-effective way to predict life-threatening bone marrow toxicity[14]. However, in rheumatology practice there is little evidence that TPMT status testing would obviate the need for continuous hematological monitoring.

We have described a patient with WG who developed rapidly progressive renal failure within days of starting azathioprine as a remission maintenance agent. The temporal relationship between initiating treatment with AZA, the acute rise in creatinine, and development of symptoms in combination with a confirmatory renal biopsy allowed the diagnosis of acute interstitial nephritis. Clinicians caring for patients with WG should be aware of this rare complication, which is potentially reversible when recognized on time and managed appropriately.

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