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Exceptional Case

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Azathioprine hypersensitivity syndrome in anti-myeloperoxidase anti-neutrophil cytoplasmic antibody-associated vasculitis

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ABSTRACT

Two patients with anti-neutrophil cytoplasmic antibody–associated vasculitis (AAV) and rapid onset of high fever, tachycardia and systemic hypotension accompanied by elevated laboratory markers of infection were diagnosed with azathioprine hypersensitivity syndrome only after repeat exposure. Azathioprine hypersensitivity can closely mimic sepsis and/or vasculitis activity and should be considered in AAV, a condition with frequent use of this drug. We discuss the pitfalls in diagnosis and the possible pathophysiologic background.

Keywords: ANCA vasculitis, azathioprine, fever, relapse, sepsis

BACKGROUND

Infectious complications of immunosuppressive therapy and vasculitis activity are the main causes of death in patients early after diagnosis of anti-neutrophil cytoplasmic antibody–associated vasculitis (AAV) [1]. Azathioprine is part of the standard maintenance regimen in this condition [2]. We here report two cases where azathioprine hypersensivity syndrome closely mimicked complications of vasculitis leading to intensive care unit (ICU) admissions and significant disease burden.

Case 1

A 64-year-old man with acute renal failure and known chronic kidney disease (CKD) after partial nephrectomy for renal cell cancer, arterial hypertension, aortic aneurysm and plaque psoriasis was diagnosed with renal anti-myeloperoxidase AAV [Figure 1A, initial Birmingham Vasculitis Activity Score (BVAS) 14]. Therapy with intravenous cyclophosphamide (cumulative dose 6.2 g) stabilized the glomerular filtration rate (GFR) (Figure 1B). His course was complicated by a spinal fracture sustained when jumping from a burning building, necessitating insertion of foreign materials for stabilization. Two weeks after he was started on azathioprine maintenance therapy, he presented in the emergency room (ER) with diarrhoea. He admitted to not regularly taking either azathioprine or corticosteroid. On examination, he was incompletely oriented to time and situation and febrile (38.4°C), with blood pressure of 90/50 mmHg, heart rate 193/min and arrhythmic. A papular, indolent rash was noted on all limbs. Physical examination of the lungs and spinal column

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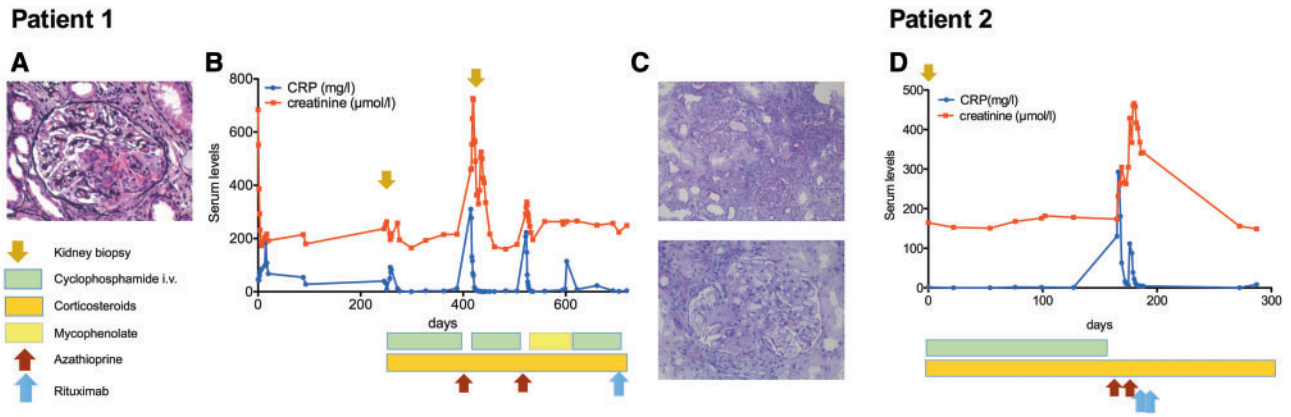

FIGURE 1: Clinical course and results of renal biopsy. **(A–C)** Patient 1 received a diagnosis of AAV from a renal biopsy showing necrotizing crescentic glomerulonephritis [(A) Jones haematoxylin and eosin stain, 60× original magnification] and was subsequently treated with cyclophosphamide boli (B). Repeat biopsy at the time of acute clinical presentation yielded persistent vasculitis activity and additionally aggressive tubulointerstitial disease [(C) periodic acid–Schiff stain, 40× and 60× original magnification]. Major elevations of creatinine and CRP were noted at the times of azathioprine exposure and clinical hypersensitivity. **(D)** Patient 2 similarly responded with CRP and creatinine elevations to azathioprine exposure.

was unremarkable; neither meningism nor focal neurological abnormalities were noted. Laboratory values showed an elevated relative neutrophil count (88.7%), C-reactive protein (CRP) and procalcitonin (204 µg/L). Serum creatinine had risen markedly (Figure 1B). The patient was admitted to the ICU for circulatory management and received antibiotic therapy with piperacillin/tazobactam and metronidazole for suspected enteral infection and sepsis plus high-dose steroids for a suspected relapse of vasculitis. He improved rapidly and was transferred to the general ward, where he underwent repeat renal biopsy 4 days later (Figure 1C). Active vasculitis and aggressive tubulointerstitial inflammation were seen. Cyclophosphamide was administered along with five courses of plasma exchange. Renal function improved while receiving monthly intravenous cyclophosphamide and de-escalation of therapy was planned. One day after taking the first dose of azathioprine he was found by his sister in a confused and dishevelled state and admitted to the ER for suspected intoxication. On examination, he was aphasic and disoriented without meningism. Atrial fibrillation with a heart rate up to 180/min was noted, his blood pressure was 147/100 mmHg and his temperature was mildly elevated at 37.8°C. Laboratory results showed no ethanol, elevated CRP, procalcitonin (31.5 µg/L) and an increase in creatinine (Figure 1B). Cerebral computed tomography, magnetic resosnance imaging and electroencephalography yielded no pathologic results. He was admitted to the stroke unit and treated with ampicillin/sulbactam for suspected infection. His rhythm spontaneously converted to normofrequent sinus rhythm and he regained the ability to speak and write over the ensuing 48 h. A diagnosis of azathioprine hypersensitivity syndrome was made. Maintenance immunosuppression was switched to mycophenolate, then rituximab, with limited success. He died 6 months later at home.

Case 2

A 49-year-old man diagnosed with rapid progressive glomerulonephritis due to anti-MPO AAV on kidney biopsy (initial BVAS 16) was started on azathioprine for maintenance therapy (100 mg/d) after six courses of intravenous cyclophosphamide (cumulative dose 7 g). His past medical history was significant for excessive leg swelling after insect stings. After 7 days, the patient presented with fever (40.7°C), tachycardia (105/min) and tachypnoea (24/min) in the ER. CRP and procalcitonin (3.6 µg/L) were significantly elevated. Acute renal failure was diagnosed (Figure 1D). Antibiotic treatment with piperacillin-tazobactam and moxifloxacin was started and azathioprine was held for a suspected bacterial infection. Chest X-ray, abdominal ultrasound and echocardiography showed no signs of infection. On Day 2 he developed generalized exanthema. Microbiological testing remained negative and he was discharged 1 week later.

Azathioprine was restarted on Day 17. Approximately 2 h later he was readmitted to the ER with nausea, thoracic wall exanthema, fever (39°C), hypotension (98/52 mmHg), tachycardia (99/min) and tachypnoea (19/min). He was in acute renal failure. CRP and procalcitonin (384 µg/L) were again markedly elevated. The patient was transferred to the ICU and received renal replacement therapy for hyperkalaemia. Microbiological testing was again negative. A diagnosis of azathioprine hypersensitivity was made. After a 5-month follow-up period, he is well with rituximab maintenance therapy and his renal function has returned to baseline (Figure 1D).

DISCUSSION

Idiosyncratic effects of azathioprine therapy occur independently of dose with an incidence of 1-6.5% [3]. Azathioprine hypersensitivity is independent of hepato- and myelotoxicity, which were absent in our patients and others (Supplementary data, Table S1). Diagnosis is by exclusion of other causes and improvement after drug withdrawal [4].

Azathioprine is initially metabolized into 6-mercaptopurine (6-MP) and methylnitroimidazole. The 6-MP is further metabolized by hypoxanthine phosphoribosyl transferase to 6-thioguanine nucleotides [5]. These nucleotides are responsible for drug action and the dose-dependent side effects. Further metabolism of 6-MP by thiopurine methyltransferase (TPMT) and xanthine oxidase (XO) results in inactive metabolites. Low TPMT activity or XO inhibition are associated with increased toxicity. TPMT polymorphisms can be determined prior to treatment. However, hypersensitivity has been linked to the imidazole side chain

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Table 1. Clinical constellations that may aid differential diagnosis of vasculitis activity, sepsis and azathioprine hypersensitivity

		Clinical signs					Laboratory values				Serum markers		
	Time of onset (typical)	Fever	Acute renal failure (histology)	Nausea and vomiting	Rash	Atrial fibrillation	Leucocytosis	Urinary sediment	Bacterial cultures	CRP	PCT	ANCA
Vasculitis activity	After reduction of immunosuppression	(↑)	Frequent (crescentic glomerulonephritis)	Rare	Common (petechial, vasculitic)	Rare	Rare, usually mild	Red cell casts, acanthocytes	–	↑	–	=/↑
Sepsis	During induction therapy	↑	Frequent (prerenal, acute tubular necrosis)	Infrequent	Infrequent	Rare	↑↑	Unspecific findings	Frequently +	↑↑	↑	=/↓
Azathioprine hypersensitivity	Days after start of azathioprine therapy, within hours after re-exposure	↑	Frequent (acute interstitial nephritis)	Common	Common (neutrophilic dermatitis)	Frequent	↑↑	Unspecific findings	–	↑↑	↑↑	=/↓

PCT, procalcitonin.

rather than TPMT, as 6-MP lacking the imidazole side chain has not yet not caused such reactions [5, 6].

Azathioprine hypersensitivity in AAV is frequently diagnosed only after re-exposure to the drug (Supplementary data, Table S1), also because of overlapping features with both active vasculitis and sepsis, two very common conditions during the first year after diagnosis of vasculitis [1]. Table 1 shows some characteristics that may aid in discriminating these entities. Features that favour hypersensitivity include onset within days of azathioprine administration, marked elevation of laboratory markers of sepsis in the absence of a clinical focus or positive bacterial cultures and stable or declining ANCA titres. However, there is no diagnostic test for azathioprine hypersensitivity. Even renal biopsy may not always determine the diagnosis and indeed, in our first patient, even suggested coexistence of vasculitis activity and hypersensitivity. However, increased awareness of this rare side effect of azathioprine may improve the care of patients with this condition.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Flossmann O, Berden A, de Groot K *et al*. Long-term patient survival in ANCA-associated vasculitis. *Ann Rheum Dis* 2011; 70: 488–494
2. Jennette JC, Nachman PH. ANCA glomerulonephritis and vasculitis. *Clin J Am Soc Nephrol* 2017; 12: 1680–1691
3. de Boer NK, van Bodegraven AA, Jharap B *et al*. Drug insight: pharmacology and toxicity of thiopurine therapy in patients with IBD. *Nat Clin Pract Gastroenterol Hepatol* 2007; 4: 686–694
4. Bidinger JJ, Sky K, Battafarano DF *et al*. The cutaneous and systemic manifestations of azathioprine hypersensitivity syndrome. *J Am Acad Dermatol* 2011; 65: 184–191
5. Liu Y-P, Xu H-Q, Li M *et al*. Association between thiopurine S-methyltransferase polymorphisms and azathioprine-induced adverse drug reactions in patients with autoimmune diseases: a meta-analysis. *PLoS One* 2015; 10: e0144234
6. Godeau B, Paul M, Autegarden JE *et al*. Hypersensitivity to azathioprine mimicking gastroenteritis. Absence of recurrence with 6-mercaptopurine. *Gastroenterol Clin Biol* 1995; 19: 117–119