CASE REPORT

Azathioprine hypersensitivity presenting as septic shock with encephalopathy

Antonia James,¹ Jelena Blagojevic,¹ Stuart W Benham,² Richard Cornall,^{1,3}
John Frater^{1,3,4}

¹Oxford University Hospitals Trust, Oxford, UK

²Nuffield Department of Anaesthetics, John Radcliffe Hospital, Oxford, UK

³Nuffield Department of Clinical Medicine, Oxford, UK

⁴Oxford NIHR Biomedical Research Centre, Oxford, UK

Correspondence to

Dr John Frater,
john.frater@ndm.ox.ac.uk

AJ and JB contributed equally to this manuscript and are joint first authors.

SUMMARY

We present a case of azathioprine hypersensitivity presenting as septic shock with associated encephalopathy. The patient was presented with rapid onset of fever, hypotension, confusion and a rapidly declining conscious level. He was admitted to the intensive care unit where he received numerous invasive investigations and treatments with broad-spectrum antibiotics, antivirals and antifungals. All microbial cultures were negative. The patient—consistent with azathioprine hypersensitivity—made a spontaneous recovery after 7 days. The case shows that a time line of drug initiation is a key part of the medical history and consideration of azathioprine hypersensitivity could avoid unnecessary interventions and excessive antimicrobial use.

BACKGROUND

Azathioprine is a widely used immunosuppressant introduced into clinical practice in the 1960s for kidney transplant recipients.¹ Its use is now widespread as a steroid sparing agent in multiple autoimmune conditions. Although azathioprine toxicity is well recognised, the syndrome of azathioprine hypersensitivity is less well known, but can mimic a number of life-threatening conditions presenting to both primary and secondary care physicians.² Here, we present a case of azathioprine hypersensitivity presenting to acute medical admissions and manifesting as septic shock.

CASE PRESENTATION

First admission

A 73-year-old man was presented following a fall from his bed at home. The medical history revealed worsening fatigue, an altered sleep pattern, intermittent confusion and fevers over the preceding 48 h. He had presented 3 months prior to this admission with acute renal failure, resulting in a diagnosis of antineutrophil cytoplasmic antibody and antimyeloperoxidase positive proliferative glomerulonephritis. Other medical history of note included non-insulin-dependent type 2 diabetes, hypertension, cerebrovascular accident (left internal capsule and full recovery) and a total hip replacement.

Following the diagnosis of glomerulonephritis, the patient had been started with cyclophosphamide (150/100 mg alternate days) with prednisolone (60 mg once daily) and cotrimoxazole prophylaxis. According to local protocol, his immunosuppression was changed to azathioprine

(125 mg once daily) after 3 months of cyclophosphamide. On admission his dose of prednisolone was 15 mg once daily and he had been taking azathioprine for 8 days. His drugs at the time of admission were: azathioprine 125 mg once daily, lisinopril 1.25 mg once daily, prednisolone 15 mg once daily, cotrimoxazole 480 mg once daily, gliclazide 40 mg twice daily, folic acid 5 mg twice daily, hydroxocobalamin 1000 µg/3 monthly and ranitidine 150 mg twice daily. His social and family histories were unremarkable.

On examination the patient had a Glasgow Coma Score (GCS) 8/15, fever 40.6°C, oxygen saturation 96% on room air, heart rate 130 beats/min and blood pressure 109/66. Examination was normal except for a previously documented pansystolic murmur. Initial investigations revealed haemoglobin 10.4 g/dl, white blood cell count $5.94 \times 10^9/l$ (neutrophils $5.23 \times 10^9/l$), platelets $76 \times 10^9/l$, C reactive protein 125 g/l with normal electrolytes, creatine 148 µmol/l (baseline value), normal clotting and liver function. Urine dipstick was negative for leucocytes and nitrites, but revealed 3+ proteinuria and 3+ haematuria. Venous blood gas analysis showed a pH of 7.44 and lactate of 2.2 mmol/l.

Further investigation with ECG, chest x-ray and a CT scan of the head did not reveal a focus of infection. The patient was treated empirically with intravenous gentamicin, ceftriaxone and steroids for sepsis with underlying immunosuppression. Azathioprine was stopped. He continued to spike fevers of $>39^\circ\text{C}$ over the following 24 h with intermittent episodes of fluid-responsive hypotension. The patient made a gradual improvement and the fever settled over the next 48 h, and he was discharged home with a 7-day course of coamoxiclav and with his azathioprine restarted on discharge.

Second admission

The morning after discharge the patient woke up feeling well and took his regular medications. Three hours later his wife found him sitting on the edge of his bed, faecally incontinent, confused, with rigours and had fever. He was re-admitted to hospital directly.

The patient presented with new confusion (abbreviated mental test score of 1/10), GCS 14/15, fever 39.2°C, oxygen saturations 94% on room air and blood pressure 98/56 mm Hg. His azathioprine was stopped again on admission. Preliminary investigations revealed few significant changes from the first admission (haemoglobin 10.4 g/dl, white blood cell count $3.45 \times 10^9/l$, neutrophils $3.38 \times 10^9/l$,

To cite: James A, Blagojevic J, Benham SW, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2012-008340

platelets $120 \times 10^9/l$, C reactive protein 49.4 g/l, alkaline phosphatase enzyme had raised to 497 U/l with normal electrolytes and clotting screen). Urine analysis again was negative for leucocytes and nitrite, with proteinuria and microscopic haematuria.

The patient was treated again for sepsis assumed secondary to immunosuppression with intravenous ceftriaxone, gentamicin, hydrocortisone and fluid resuscitation. Three hours after his presentation the patient became drowsier and his blood pressure dropped to 76/43 (pulse 115 beats/min, regular rhythm). He was admitted to the adult intensive care unit for inotropic support with a GCS 14/15 and self-ventilating. Antibiotics were broadened to piperacillin-tazobactam, and aciclovir plus fluconazole were added. A bedside echocardiogram showed no evidence of endocarditis. Further blood cultures and cerebrospinal fluid (CSF) were taken including viral PCR, plus viral serology. Within 24 h his GCS dropped to 6/15 without a clear precipitating event, requiring intubation. His noradrenaline requirements increased from $0.047 \mu\text{g/kg/min}$ to a peak of $0.163 \mu\text{g/kg/min}$ (after 48 h), his steroid dose was increased to hydrocortisone 30 mg three times a day and phenytoin was added to cover non-convulsive status epilepticus. A CT scan of the head/chest/abdomen/pelvis with contrast showed an unchanged left thalamic internal capsule infarct and generalised free fluid around the liver and gallbladder, but no septic focus around the prosthetic hip joint was observed.

Investigations in adult intensive care unit revealed urine, no significant growth $\times 2$ (microscopy, occasional casts); blood cultures, no growth $\times 6$; CSF, acellular and no growth. Viral serology: Epstein-Barr virus nuclear antigen IgG (–), Epstein-Barr virus viral capsid Antigen IgM (–), *Cytomegalovirus* IgG (+), *Cytomegalovirus* IgM (–), hepatitis B surface antigen (–), hepatitis C antibody (–) and HIV (–). His immunological investigations showed perinuclear antineutrophil cytoplasmic antibody 80 units, antimyeloperoxidase 29.2 units, with normal serum electrophoresis.

The patient developed myoclonus in the upper limbs with an upgoing plantar reflex on the left at the point when carbamazepine was initiated. An EEG showed diffuse encephalopathy with focal changes in the posterior parts of the right hemisphere but no features of non-convulsive status epilepticus were observed. An MRI scan of the brain excluded small vessel cerebral vasculitis.

After 4 days of deterioration, he spontaneously began to improve. After 3 days his inotropes and sedation were stopped and he was extubated. All the antibiotics, antifungals and antivirals were stopped on day 7. The patient was sat out in a chair 7 days after presentation to acute medicine with resolution of his major symptoms, except for some mild residual confusion, peripheral oedema secondary to fluid overload and deterioration of his renal function (creatinine $395 \mu\text{mol/l}$).

From the adult intensive care unit, the patient was transferred to renal specialist care and was discharged home 19 days after his initial presentation having made a full recovery. His azathioprine was stopped and his immunosuppression was changed to mycophenolate mofetil (500 mg twice daily) and prednisolone (15 mg once daily).

OUTCOME AND FOLLOW-UP

The patient almost made a complete recovery over 3 days, culminating on day 7 of admission. He was discharged home on day 19, having fully recovered. His azathioprine has been changed to mycophenolate, and he has had no subsequent episodes. He has been told never to take azathioprine again. His notes have been clearly marked with a warning of azathioprine hypersensitivity, to ensure he does not receive the same medication once again.

DISCUSSION

Azathioprine is a purine analogue immunosuppressant, first synthesised in 1957,³ which interferes with DNA synthesis, reduces lymphoid cell proliferation and cellular immunity. It has been used clinically in the 1960s to protect against rejection following kidney transplantation,¹ and is now widely used in multiple medical specialities, and as such is frequently encountered as part of a patient's medication on the acute medical take.

Adverse reactions to azathioprine are documented in up to 28% of patients, and can be divided into 'toxicity' and 'hypersensitivity', the former being much more widely acknowledged.^{2–4} Toxicity is related to the six-mercaptopurine (6-MP) moiety of azathioprine and its metabolites, and typically presents with nausea, myelotoxicity and hepatotoxicity. Toxicity can be screened for (and the azathioprine dose was adjusted) using assays for thiopurine methyltransferase (TPMT) activity, although normal TPMT activity can be associated with toxicity and therefore TPMT screening should not replace blood count monitoring.^{5–6}

The azathioprine hypersensitivity reaction has a different clinical presentation and likely mechanism. It is rare—there are only 71 reported cases with azathioprine hypersensitivity in the medical literature, although this underestimates the true number of cases,^{2–7–10} even though the actual incidence is likely to be significantly less than 1%. Presentation is frequently with a rash such as Sweet's syndrome, erythema nodosum or small vessel vasculitis, but importantly around half of the reported cases (35/71, 49.3%) did not present with a skin manifestation.

The timing of the presentation with azathioprine hypersensitivity is the key to the diagnosis, as is the case with a number of severe idiosyncratic drug reactions, such as DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms).¹¹ Typically, a patient presenting with azathioprine hypersensitivity will have started the drug in the preceding 4 weeks and symptoms will resolve spontaneously within 7 days of drug cessation,² as our case demonstrates. On rechallenge, often within hours of taking a single tablet, as we describe, presentation is more pronounced and rapid,¹² and frequently culminates in admission to an intensive care unit.²

The case we present demonstrates the rapid and severe onset of symptoms on rechallenge with azathioprine in a patient with undiagnosed hypersensitivity. The presence of fever with profound circulatory collapse resulting in admission to the adult intensive care unit is indistinguishable from severe sepsis. A further aspect to this case was the sudden neurological decline associated with EEG findings compatible with encephalopathy, which have not been reported previously in the context of azathioprine hypersensitivity. Despite multiple microbiological and virological investigations, the patient remained culture negative throughout both admissions, and the rapid, spontaneous recovery within 7 days was consistent with a severe hypersensitivity reaction.

The mechanism behind the reaction remains unclear and appears to be independent of TPMT activity, age or sex. There is no screening test available, and the diagnosis is clinical. Although the mechanism has not been fully defined, an allergic response—likely to be type I hypersensitivity—to the imidazole side chain (which is not present on 6-MP) has been proposed as a possible mechanism.¹³ Further challenge may then result in a massive cytokine and histamine release with circulatory collapse.

In summary, we present an example of severe azathioprine hypersensitivity following drug rechallenge presenting as septic shock with encephalopathy and requiring admission to the adult intensive care unit. Not only should a full drug history be taken

at the time of admission, but a time line of drug initiation should be considered particularly for those drugs associated with severe side effects. In this case the patient received a number of antibiotics, antivirals and antifungal agents as well as numerous investigations and interventions, which in retrospect may not have impacted the outcome. In the acute situation and in a patient likely with immunocompromise, empiric management of septic shock needs to be considered and implemented, although consideration of such hypersensitivity reactions as a differential may help prevent unnecessary escalation and interventions, especially in the presence of persistently negative microbiological investigations.

Learning points

- ▶ Azathioprine hypersensitivity is rarer than toxicity and is not excluded by thiopurine methyltransferase assay.
- ▶ Azathioprine can mimic multiple conditions including severe sepsis.
- ▶ Azathioprine hypersensitivity can present without a skin rash.
- ▶ If suspected, azathioprine should be withdrawn completely as rechallenge could be fatal.
- ▶ All drug allergies should be clearly documented in the patient's notes for the attention of clinical staff, particularly nurses administering medicines.

Acknowledgements JF is funded by the Oxford NIHR BRC and the Oxford Martin School.

Contributors AJ, JB, SWB, RC and JF jointly prepared and wrote the manuscript.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Murray JE, Merrill JP, Harrison JH, *et al.* Prolonged survival of human-kidney homografts by immunosuppressive drug therapy. *N Engl J Med* 1963;268:1315–23.
- 2 Bidingier JJ, Sky K, Battafarano DF, *et al.* The cutaneous and systemic manifestations of azathioprine hypersensitivity syndrome. *J Am Acad Dermatol* 2011;65:184–91.
- 3 Elion GB, Callahan SW, Hitchings GH, *et al.* The metabolism of 2-amino-6-[(1-methyl-4-nitro-5-imidazolyl)thio]purine (B.W. 57-323) in man. *Cancer Chemother Rep* 1960;8:47–52.
- 4 Ansari A, Hassan C, Duley J, *et al.* Thiopurine methyltransferase activity and the use of azathioprine in inflammatory bowel disease. *Aliment Pharmacol Ther* 2002;16:1743–50.
- 5 Holme SA, Duley JA, Sanderson J, *et al.* Erythrocyte thiopurine methyl transferase assessment prior to azathioprine use in the UK. *QJM* 2002;95:439–44.
- 6 Lennard L. TPMT in the treatment of Crohn's disease with azathioprine. *Gut* 2002;51:143–6.
- 7 Hurtado-Garcia R, Escibano-Stablé JC, Pascual JC, *et al.* Neutrophilic dermatosis caused by azathioprine hypersensitivity. *Int J Dermatol* 2012;51:1522–5.
- 8 Turow A, Yong TY, Fok JS, *et al.* Azathioprine hypersensitivity presenting as cardiogenic shock and Sweet's syndrome in a patient with microscopic polyangiitis. *Intern Med* 2012;51:1889–92.
- 9 Kim MJ, Jang KT, Choe YH. Azathioprine hypersensitivity presenting as sweet syndrome in a child with ulcerative colitis. *Indian Pediatr* 2011;48:969–71.
- 10 Grassia R, Paolo Coppeta G, Staiano T. Severe muscular weakness as an isolated symptom of azathioprine hypersensitivity. *Inflamm Bowel Dis* 2011;17:E61.
- 11 Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug Rash with Eosinophilia and Systemic Symptoms: DRESS). *Semin Cutan Med Surg* 1996;15:250–7.
- 12 Knowles S, Shear NH. Azathioprine hypersensitivity reactions: caution upon rechallenge. *Muscle Nerve* 1997;20:1467–8.
- 13 Davis M, Eddleston AL, Williams R. Hypersensitivity and jaundice due to azathioprine. *Postgrad Med J* 1980;56:274–5.

Copyright 2013 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow