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Practice

Lesson of the Week

Life threatening myelotoxicity secondary to azathioprine in a patient with atopic eczema and normal thiopurine methyltransferase activity

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Anticipate myelotoxicity in patients treated with azathioprine and monitor levels closely, particularly when starting treatment

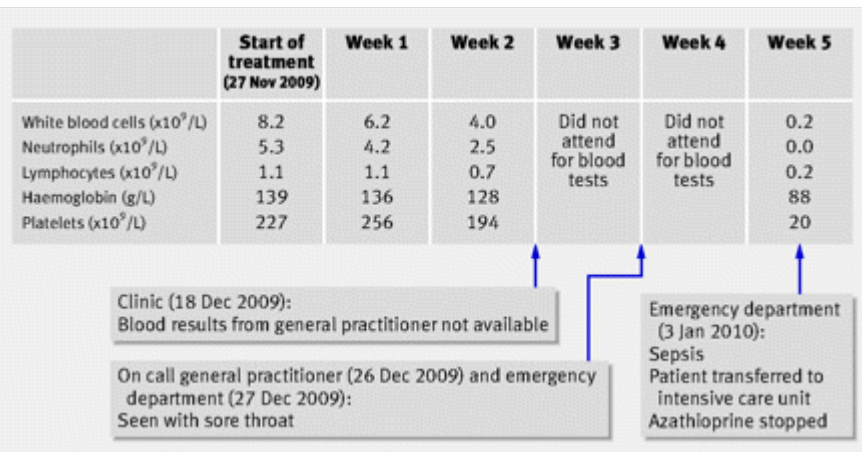
Azathioprine is an immunosuppressive agent belonging to a class of drugs known as thiopurines. Azathioprine was originally used to prevent rejection of transplant organs and is now widely used as a steroid sparing agent in the treatment of autoimmune and chronic inflammatory diseases. Use in atopic eczema has been supported by randomised controlled trials, with a reported improvement in disease activity of 37% after 12 weeks.¹ Treatment can be limited by adverse effects, leading to withdrawal in 10-28% of patients,² with the most serious complication, myelosuppression, occurring in 7% of cases.³ Thiopurine methyltransferase (TPMT) is a key enzyme in the metabolism of azathioprine, methylating azathioprine metabolites at the expense of formation of cytotoxic thioguanine nucleotides. TPMT deficiency is a well documented cause of azathioprine induced myelosuppression,⁴ and routine TPMT testing is established best practice for identifying patients at risk.⁵

We report a patient with normal TPMT activity who was prescribed azathioprine for severe atopic eczema and subsequently developed profound, life threatening myelotoxicity, which could potentially have been identified earlier.

Case report

A 24 year old Filipino man presented to the dermatology department with a lifelong history of generalised atopic eczema that was uncontrolled with superpotent topical corticosteroids. Infective exacerbations were frequent, with an overall adverse effect on his quality of life. He had a history of asthma, and his only medication was a salbutamol inhaler. After discussion with the patient, systemic treatment with azathioprine was agreed. Screening bloods were normal, with a TPMT activity of 37 pmol/h/mg Hb (normal range (26-50 pmol/h/mg Hb)). He was counselled on potential side effects and provided with an information leaflet. Azathioprine was started at a dose of 75 mg/day (1 mg/kg/day), and his general practitioner was asked to check his full blood count and arrange renal and liver function tests on a weekly basis for the first month.

The full blood count was in the normal range during the first two weeks; however, a retrospective analysis showed a drop of more than 50% in total white blood cell and neutrophil counts from the start of azathioprine to week 2 (figure 1). The patient was well when seen in clinic at week 2 and told the clinician that he had normal blood results, although these were not available for review. The patient forgot to attend for the monitoring blood tests at week 3 but presented that same week to the on-call general practitioner and then to the emergency department the following day with a severe sore throat. Both the general practitioner and the emergency doctors prescribed antibiotics but did not check his full blood count. He missed further blood tests at week 4 before presenting to the emergency department at week 5 with sepsis and a 10 day history of sore throat, fevers, rigors, and diarrhoea. The full blood count showed a severe pancytopenia (white cell count $0.2 \times 10^9/L$, neutrophils $0.0 \times 10^9/L$, lymphocytes $0.2 \times 10^9/L$, haemoglobin 88 g/L and platelets $20 \times 10^9/L$).



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Downward trend in the patient's blood counts from the start of azathioprine treatment to his admission to hospital with sepsis

Azathioprine was stopped and he was admitted to the intensive care unit for fluid resuscitation, antibiotics, and blood transfusions. Bone marrow aspirate and trephine biopsy showed marked hypoplasia consistent with azathioprine toxicity. A septic screen identified *Escherichia coli* in the blood, and computed tomography, performed because of persistent fevers, showed features of typhilitis (inflammation of the caecum and a recognised complication of neutropenia). He was discharged after three weeks, with blood counts only returning to normal four months after admission. Our Purine Research Laboratory has since screened him for all known TPMT and inosine triphosphate pyrophosphatase mutations; none was identified.

Discussion

Azathioprine is a prodrug that is non-enzymatically converted to 6-mercaptopurine before being metabolised by three competitive enzymatic pathways. Whereas the TPMT and xanthine oxidase pathways result in inactive metabolites, hypoxanthine phosphoribosyltransferase leads to the formation of thioguanine nucleotides (the active metabolite). The relative activities of these three enzymes determine the number of thioguanine nucleotides produced, which are incorporated into lymphocyte DNA, resulting in cytotoxic and immunosuppressive effects.⁶ Although a genetic deficiency of xanthine oxidase is very rare, TPMT expression is under the control of a common genetic polymorphism.² Individuals with intermediate or absent TPMT activity (11% and 1 in 300 of the white population respectively)⁷ have an increased risk of developing myelosuppression,⁸ presumably owing to increased shunting of substrate towards the production of thioguanine nucleotides.

The importance of assessing TPMT status is to avoid azathioprine exposure in patients with complete TPMT deficiency and to identify those with intermediate activity who may require more cautious dosing. However, a normal TPMT status does not preclude the occurrence of myelosuppression. A study of 41 patients with Crohn's disease who developed myelosuppression with azathioprine found that only 27% had alleles associated with TPMT deficiency.⁹ Similarly, a systematic review of 492 cases of myelosuppression induced by thiopurines found that 69% had high or normal TPMT activity.⁸ This suggests the involvement of other factors, including intercurrent infection (such as parvovirus), drugs (such as allopurinol, a known xanthine oxidase inhibitor), and unknown gene mutations. Complete xanthine oxidase deficiency was excluded in our patient, as was reduced inosine triphosphate pyrophosphatase activity, which has been closely related to myelotoxicity induced by azathioprine in Japanese patients.¹⁰

Monitoring the full blood count is of paramount importance in patients taking azathioprine, especially during the first few weeks, when myelotoxicity is often reported, although occurrence can be at any time during treatment (reported range from 12 days to 27 years).³ Although informed patients should be responsible for attending for blood tests, the opportunity for checking our patient's full blood count was missed in the dermatology clinic at week 2 and in two healthcare settings when he presented with a sore throat (mentioned in the patient information leaflet). The pronounced downward trend in the white cell count after two weeks' treatment, even though it remained within the normal range, should also raise suspicion of possible myelotoxicity. Shared care arrangements and clear communication (for example, in correspondence) between secondary and primary care are vital in guiding drug monitoring. We present this case as a reminder that severe azathioprine myelotoxicity can occur in the context of normal TPMT activity and that earlier detection could have prevented this adverse event becoming life threatening.

Notes

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Footnotes

Contributors: JSW was involved in the care of the patient whose case is reported, reviewed the literature, and wrote the report; AM organised the TPMT and inosine triphosphate pyrophosphatase mutation analysis and reviewed the report; CHS reviewed the report and is the guarantor.

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