CASE REPORT

Side effects from azathioprine in a patient with thiopurine S-methyl transferase deficiency

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Summary
Azathioprine is an immunosuppressant and cytotoxic pro-drug which acts to impair purine synthesis. Side effects including nausea, rash, hepatotoxicity and bone marrow suppression frequently limit its use. Thiopurine S-methyl transferase (TPMT) is an important enzyme which metabolises thiopurines such as azathioprine to inactive metabolites. TPMT activity varies greatly between individuals, and has a trimodal distribution. Individuals may be homozygous for the highly active wild type allele, heterozygous with a low activity variant allele, or be homozygous for the low activity variant. Reduced TPMT activity conveys a greater risk of drug related side effects from thiopurines.

We report a case in which azathioprine used to treat non specific interstitial pneumonia resulted in marked pancytopaenia. Azathioprine treatment had been commenced without first checking the TPMT status. The subsequent discovery of TPMT deficiency in this patient explained the development of complications. Limited therapeutic options led to the patient being treated with an extremely low azathioprine dose regime. The drug was tolerated without further toxicity.

This case highlights the benefits of screening the TPMT activity of all patients where azathioprine treatment is being considered. It also gives further evidence that TPMT deficient individuals are able to tolerate a very low dose azathioprine regime without side effects.

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Statement of clinical relevance/originality
This case report relates to the development of side effects following the use of azathioprine in a Thiopurine S-methyl transferase (TPMT) deficient individual. This is a topic of...
much interest currently as there is no consensus as to whether routine testing of TPMT is appropriate prior to commencing azathioprine therapy. This report speaks to that debate by highlighting the complications which can develop in TPMT deficient individuals. In addition this case adds to the very small number of reports in the literature where low dose azathioprine has been used in TPMT deficient individuals without the development of toxicity.

Case report

A 68-year old Caucasian woman presented with a three week history of progressive shortness of breath on exertion, a dry cough and general malaise. She was a non-smoker with no relevant previous medical or family history of respiratory disease. Positive findings from clinical examination included basal inspiratory crepitations in both lung fields.

Bilateral reticular–nodular shadowing was seen on the chest radiograph. High resolution computed tomography of the thorax demonstrated a fine reticular pattern with subpleural and basal predominance. Areas of ground glass shadowing and traction bronchiectasis were also noted (Fig. 1.) Full lung function tests showed a restrictive defect with a severe impairment in gas transfer (Table 1). Bronchoscopy and lavage was performed, but no atypical cells were seen or infectious agents cultured. Lavage fluid comprised 53% polymorphs, 24% lymphocytes, 21% macrophages, 2% eosinophils. Rheumatoid factor was positive by latex testing, but Rose Waaler titre was negative. Antinuclear antibodies, extractable nuclear antibodies, anti-dsDNA, anti-centromere, ANCA, antilglomerular basement antibody, and angiotensin converting enzyme levels were within normal limits. Avian precipitins were negative (budgerigar, chicken, pigeon) and protein electrophoresis did not demonstrate paraprotein banding. There was a polyclonal rise in IgM.

The patient was too unwell for an open lung biopsy, and a diagnosis of non-specific interstitial pneumonia (NSIP) was made on the basis of her clinical, lung function, laboratory, and radiological findings.

Prednisolone 30 mg once daily was commenced with azathioprine 50 mg twice daily, increased to three times a day after seven days, leading to significant clinical improvement. Repeat lung function showed improvement from baseline (Table 1).

The clinical improvement in the patient’s condition was maintained over the following month, however blood tests taken at the end of this period indicated the development of pancytopaenia (WCC fall from 11.1 to 2.9 \times 10^9/l, Hb fall from 12.9 to 8.7 g/dl.) Treatment with azathioprine was stopped, after which the blood indices normalised. Lung function continued to improve over the following five months on monotherapy with prednisolone (Table 1), however the gradual development of Cushingoid facies and body habitus emphasised the need for a steroid sparing agent.

| Table 1 | Serial lung function results showing marked improvement with therapy FVC Forced vital capacity, FEV1 Forced expiratory volume in one second, DLCO Diffusion capacity of the lung for carbon monoxide, % Pred Percentage predicted. |
|---------|-------------------------|---------|---------|---------|---------|---------|---------|---------|
| Length of time treated | Baseline | One month | Two months | Five months | Nine months | One year | Two years |
| FVC | 1.48 | 1.73 | 1.7 | 1.82 | 2.00 | 1.92 | 2.11 |
| % Pred | 62 | 72 | 71 | 81 | 89 | 85 | 95 |
| FEV1 | 1.23 | 1.54 | 1.58 | 1.67 | 1.76 | 1.66 | 1.82 |
| % Pred | 62 | 78 | 80 | 91 | 95 | 89 | 99 |
| DLCO | 0.93 | 1.51 | 1.71 | 2.27 | 2.89 | 3.07 | 3.22 |
| % Pred | 13 | 21 | 24 | 34 | 43 | 46 | 48 |

Figure 1  High resolution CT scans of the thorax before and after 18 months of treatment. A widespread reticular patterning, patchy ground glass opacification, and traction bronchiectasis are evident on the first scan. There has been almost complete resolution of these changes following steroid and immunosuppressive therapy.
Measurement of the patients whole blood Thiopurine S-methyl transferase (TPMT) activity was requested and found to be undetectable at <1 nmol 6-MTG/g Hb/hr. The deficient TPMT activity status of the patient was also confirmed by TPMT genotyping. The patient was found to be homozygous for the most common polymorphism associated with deficient TPMT enzyme activity in Caucasians, TPMT*3A, which is characterised by a double mutant allele (G to A transition at nucleotide 460 on exon 7, and A to G transition at nucleotide 719 on exon 10).2,3

A very low dose of azathioprine (5 mg OD) was restarted, and the steroid dose to be weaned. No significant side effects were suffered by the patient. Lung function continued to improve two years out from the initial presentation (Table 1), and a repeat HRCT showed almost complete resolution of the previously observed radiological abnormalities (Fig. 1).

Discussion

Azathioprine is a mercaptopurine derivative with both cytotoxic and immunosuppressive effects. Indications for its use are found across many medical specialties, and include rheumatoid arthritis, inflammatory bowel disease, vasculitis, chronic hepatitis, a number of dermatological conditions and the prevention of rejection of solid organ transplants.

The subject of this case report was diagnosed and treated for NSIP. Whilst many respiratory physicians use azathioprine in the management of interstitial lung disease there is limited evidence of its efficacy, even for idiopathic pulmonary fibrosis (IPF) which is the most common and well investigated of these conditions.4,5 Of the few good quality studies in this area, a randomised controlled trial comparing an azathioprine and prednisolone combination with prednisolone alone in 27 patients with IPF demonstrated a small but statistically significant improvement in survival for the combination therapy group when adjusted for age.6

Side effects are common with azathioprine and include nausea, vomiting, rash, hepatotoxicity, and myelosuppression. Severe toxicity has been recorded in 30% of patients treated with the drug.7,8 International guidelines recommend a cautious approach to azathioprine treatment, using small increments from a low initial dose.9 The relatively high starting dose in our patient may have contributed to the development of side effects.

The desire to identify patients at particular risk of drug related complications following the use of azathioprine led to the introduction of TPMT testing to the UK in the early 1990s. TPMT is one of the principal enzymes involved in the metabolism of thiopurines such as azathioprine to inactive metabolites There is a marked variation in the activity of TPMT between individuals, largely as a result of single nucleotide polymorphisms, many of which result in a loss of enzyme activity compared to the wild type. A trimodal distribution in enzyme activity has been described which corresponds to homozygosity for a highly active allele, heterozygosity with a low activity allele, and homozygosity for the low activity variant. Thus normal/high levels of activity are seen in approximately ninety percent of the population, whilst ten percent have low TPMT activity, and one in three hundred has severely deficient TPMT activity.10,11 Low levels of TPMT are strongly associated with marked toxicity secondary to azathioprine.12,13 However, individuals known to have low TPMT activity can subsequently have their azathioprine dose adjusted, allowing continuing treatment without acute dose limiting toxicity. Particular caution is necessary in treating individuals in the severely TPMT deficient group such as the subject of this case report, although successful use of very low doses of azathioprine has previously been described in both inflammatory bowel disease14,15 and acute lymphoblastic leukaemia.13,16,17 Conversely, patients with particularly high TPMT activity may require higher than usual azathioprine doses.

Current guidelines from different specialty professional bodies vary greatly in whether to recommend routine TPMT testing prior to the use of azathioprine.18–20 These differences reflect the lack of evidence at present as to whether routine pre-treatment TPMT testing will actually reduce the number of adverse reactions in practice.

This case highlights the problems that can develop when a patient with TPMT deficient status is treated with standard azathioprine doses, and the benefits which would be gained from TPMT testing. Checking TPMT status is becoming increasingly common practice and can both ensure that we do not normally use thiopurine drugs in deficient patients and also so that we can reduce the dose in heterozygote patients. We also give further evidence that it is possible to treat TPMT deficient patients using very low doses of azathioprine without side effects.

Patient details

The subject of this case report has read the final version of the manuscript, understands the implications of publication, and has given written consent.

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Contributors

DP, AF, and LF carried out the first drafting of the manuscript. JB and AHM were responsible for initiating and reviewing the report, and final drafting of the manuscript.

Conflict of interest statement

The authors have no conflict of financial or other interest to declare with regards to the contents of this case report.

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References


