CASE REPORT

Azathioprine Hypersensitivity Presenting as Cardiogenic Shock and Sweet’s Syndrome in a Patient with Microscopic Polyangiitis

Arthur Turow¹, Tuck Y Yong¹, Jie Shen Fok¹ and Jordan YZ Li²,³

Abstract

Azathioprine hypersensitivity is a clinical syndrome which may manifest from isolated fever and rash to multi-organ failure. This rare condition is usually self-limiting following the discontinuation of azathioprine. Therefore, it is important to maintain a high index of clinical suspicion for hypersensitivity reactions with azathioprine therapy. We report a case of azathioprine hypersensitivity in a 69-year-old woman who developed cardiogenic shock and Sweet’s syndrome following the initiation of azathioprine for her underlying autoantibodies to neutrophil cytoplasmic antigens (ANCA) associated microscopic polyangiitis.

Key words: azathioprine, cardiogenic shock, congestive heart failure, hypersensitivity, microscopic polyangiitis, Sweet’s syndrome

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Introduction

Azathioprine, a steroid-sparing immunosuppressant, is used in a wide range of conditions such as inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus, solid organ transplantation and vasculitis. Azathioprine is widely used as a maintenance therapy in vasculitis associated with autoantibodies to neutrophil cytoplasmic antigens (ANCA) after a trial demonstrated that azathioprine is as effective as cyclophosphamide in the prevention of relapse and has fewer adverse-effects (1). The side effects of azathioprine are well-documented and include dose-dependent myelosuppression and hepatotoxicity as well as a dose-independent hypersensitivity syndrome ranging from isolated fever, rash to multi-organ failure, which is relatively less frequent (2, 3). We report a case of azathioprine-induced cardiogenic shock with concurrent Sweet’s syndrome (neutrophilic dermatosis) following the initiation of this drug in a woman with p-ANCA associated microscopic polyangiitis (MPA).

Case Report

A 69-year-old woman with stage 3 chronic kidney disease secondary to biopsy-proven p-ANCA associated MPA presented with a 3-day history of acute breathlessness, malaise and watery bloody diarrhoea. Her other medical problems include hypertension, anaemia of chronic disease and recurrent deep vein thromboses for which she was taking warfarin. She had no known history of congestive cardiac failure. MPA was diagnosed 6 months prior to the index admission. She was initially treated with a course of cyclophosphamide and prednisolone. Azathioprine (75 mg daily) was commenced 11 days prior to presentation to replace cyclophosphamide as part of her maintenance immunosuppressive therapy. Her other medications included perindopril, pantoprazole, risedronate, prednisolone, erythropoietin as well as calcium and vitamin D supplements. Her baseline serum creatinine was 150 μmol/L (reference range, RR: 50-110 μmol/L) prior to this presentation.

On examination, she was alert, orientated and afebrile. She was found to be hypotensive (blood pressure of 70/40...
Azathioprine was ceased and broad spectrum antibiotics were administered to the intensive care unit (ICU) for vasopressive symptoms such as nausea, vomiting, diarrhea, fever, myalgia, tachycardia (heart rate 120 beats/min) and in respiratory distress (respiratory rate of 28 breaths/min and oxygen saturation of 91% on room air). Jugular venous pressure was elevated. Both heart sounds were present without murmurs. Respiratory examination revealed bibasal fine crepitations and a generalized wheezing.

Preliminary investigations showed acute on chronic renal failure with a serum creatinine level of 506 μmol/L, hypernatremia with a serum sodium level of 122 mmol/L (RR: 135-145 mmol/L) and a markedly elevated C-reactive protein (CRP) at 450 mg/L (RR: <10 mg/L). Full blood count and cardiac enzymes were unremarkable. Her ANCA was negative and her coagulation profile was deranged with INR: 4.9 (RR: 0.9-1.2) and APTT: 50 seconds (RR: 24-38 sec). Chest X-ray revealed upper lobe vascular diversion and bilateral alveolar infiltrates which was consistent with pulmonary edema and ECG showed sinus tachycardia. The initial transthoracic echocardiogram demonstrated a marginally dilated left ventricle with mild to moderate global systolic dysfunction. The ejection fraction was 45% (Table 1). The left atrium was dilated and there was moderate elevation of right heart pressures. No thrombus or vegetations were noted.

The patient was treated for presumed septic shock and admitted to the intensive care unit (ICU) for vasopressor support. Azathioprine was ceased and broad spectrum antibiotics including piperacillin/tazobactam and azithromycin were commenced. Ganciclovir was added to cover possible cytomegalovirus infection. Intravenous hydrocortisone (100 mg) was administered twice daily. Nevertheless, her condition continued to deteriorate in the next two days. She required mechanical ventilation. A repeat echocardiogram showed further worsening of her left ventricular function with an ejection fraction of only 11%. There was no evidence of pericardial effusion or endocarditis. An intra-aortic balloon pump (IABP) was inserted which significantly improved cardiac output. Continuous venous-venous hemodialysis was commenced because of oliguric renal failure. Her condition slowly improved and she was extubated and IABP was discontinued on day 6 of the ICU admission. Hemodialysis was no longer required on day 8. Septic workup did not yield any organisms. All blood and bronchoscope aspirate cultures were negative, as were all viral PCR; consequently, intravenous antibiotics were discontinued.

Throughout her ICU stay, she developed tender, dusky and papular lesions on the dorsum of both hands and on the anterior surfaces of both thighs. Punch biopsies of the lesions were performed. The findings were consistent with neutrophilic dermatosis (Sweet’s syndrome) (Fig. 1).

It was concluded that her multi-organ (cardiac, renal and gastrointestinal) failure as well as the skin lesions were due to azathioprine hypersensitivity. On further follow-up, her renal function had returned to the baseline level. Mycophenolate mofetil (250 mg twice a day) was chosen for the maintenance therapy of her MPA in addition to her usual prednisolone dose. Her repeat echocardiogram showed an ejection fraction of 67%. All skin lesions had resolved.

**Discussion**

Azathioprine hypersensitivity is an uncommon idiosyncratic and dose-independent clinical syndrome. This condition most commonly occurs in the first four weeks of azathioprine therapy (3, 4). The lag time to symptoms may vary from 1 to 56 days upon initiation of azathioprine therapy (4); however, a few reports indicate that azathioprine hypersensitivity can be delayed by more than a year, warranting hypersensitivity reactions to be considered independent of treatment initiation (5). It manifests along a wide clinical spectrum from local neutrophilic disease to a systemic syndrome (1). Clinical features include gastrointestinal symptoms such as nausea, vomiting, diarrhea, fever, myal-

**Table 1.** Serial Measurement on Echocardiography

<table>
<thead>
<tr>
<th>Parameter (Reference Range)</th>
<th>At presentation</th>
<th>2 days after presentation</th>
<th>On follow up after cessation of AZA</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF (50% - 85%)</td>
<td>49.6%</td>
<td>11.4%</td>
<td>66.9%</td>
</tr>
<tr>
<td>LVDd (3.6 - 5.6cm)</td>
<td>5.8</td>
<td>4.7</td>
<td>3.1</td>
</tr>
<tr>
<td>LVDs (2.3 - 4.0cm)</td>
<td>not measured</td>
<td>4.5</td>
<td>3.2</td>
</tr>
<tr>
<td>IVSd (&lt; 1.1cm)</td>
<td>1.0</td>
<td>1.2</td>
<td>1.0</td>
</tr>
<tr>
<td>LVPWd (&lt; 1.1cm)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Abbreviations: EF: ejection fraction, LVDd: left ventricle internal diameter end-diastole, LVDs: left ventricle internal diameter at end-systole, IVSd: interventricular septal wall thickness at end-diastole, LVPWd: left ventricle posterior wall thickness at end-diastole, AZA: azathioprine
gia, pancreatitis and hepatitis. Skin lesions such as neutrophilic dermatosis (6, 7) and cardiac failure are also recognized (4). Diagnosis is often delayed and symptoms are frequently ascribed to septic causes or to exacerbation of the underlying illness treated by azathioprine. Skin findings may be an important early clue to the diagnosis of azathioprine hypersensitivity and aid in prompt recognition and treatment of this potentially life-threatening adverse drug effect (1). Prognosis is generally good with cessation of azathioprine. Nevertheless, reintroduction of azathioprine should be avoided as this may lead to more serious reactions within hours of the rechallenge (3, 8).

In the present case, the most prominent manifestation of azathioprine hypersensitivity was cardiac failure and cardiogenic shock requiring ICU management including IABP. Hypotensive shock has been described before as one of the clinical features of azathioprine hypersensitivity and Sweet’s syndrome (2, 6, 8). To date, only one case of azathioprine hypersensitivity-induced multi-organ failure including cardiac failure has been reported (9). However, Sweet’s syndrome has been reported to involve the myocardium and cardiac valves in three previous cases (10-12). We suggest that azathioprine hypersensitivity be considered as a differential diagnosis for patients on azathioprine presenting with hypotension and cardiac failure. Echocardiography could help ascertain the diagnosis. The present case demonstrates that congestive heart failure associated with azathioprine hypersensitivity can be completely reversible when azathioprine is discontinued.

Classic Sweet syndrome, also known as acute febrile neutrophilic dermatosis is a reactive pustular dermatosis. This syndrome is generally associated with malignancy, autoimmune diseases such as inflammatory bowel disease and drugs. Azathioprine and ANCA-positive vasculitis have been associated with Sweet’s syndrome (13). In some settings, it is difficult to ascertain the exact etiology such as when patients have an underlying disease that can be associated with Sweet’s syndrome and then treated with a drug that can also induce this dermatological syndrome.

Drug-induced Sweet’s syndrome has also been reported with granulocyte colony-stimulating factor (14), all-trans-retinoic acid (15), hydralazine (16) and trimethoprim-sulfamethoxazole (17). The present case has all of the features (except for a documented fever) consistent with the criteria for drug-induced Sweet’s syndrome as proposed by de Fonclare and co-authors (18).

Azathioprine undergoes thiol methylation to 6-mercaptopurine (6-MP) and glutathionyl imidazole. Enzymatic conversion of 6-MP to cytotoxic thioguanine nucleotides is part of the dose-dependent side effects, such as myelosuppression and hepatotoxicity (19). In contrast, hypersensitivity reactions are most likely due to the imidazole side-chain, as demonstrated by several case studies where 6-MP did not induce hypersensitivity reactions in patients sensitized to azathioprine (20-22). Nonetheless, there is currently no data available to explain how imidazole would lead to compromised cardiac function.

In summary, the present case highlights the importance of maintaining a high index of clinical suspicion for hypersensitivity reactions with azathioprine therapy, in particular if azathioprine had been initiated within the preceding few weeks of onset of symptoms. Given the described cardiac effects, it would be prudent to exclude azathioprine hypersensitivity as the cause of hypotension and cardiac failure following the initiation of azathioprine.

The authors state that they have no Conflict of Interest (COI).

References


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