Azathioprine-induced pericarditis in a patient with ulcerative colitis

C DAVID SIMPSON MD

Azathioprine, a purine analogue, has been used for many years in the treatment of idiopathic inflammatory bowel disease (IBD). Despite the development of newer immunomodulatory agents that are useful in acutely ill patients, azathioprine retains a place in the management of patients requiring a persistently high dose of corticosteroids for disease control (1). Although a number of potentially serious adverse effects of the purine analogues are well known, studies assessing toxicity of azathioprine in rheumatoid arthritis (2) and 6-mercaptopurine (the active metabolite of azathioprine) in IBD (3) have shown a surprisingly low incidence of serious toxicity. To our knowledge this is the first reported case of azathioprine-induced pericarditis in a patient with ulcerative colitis.

CASE PRESENTATION

A 31-year-old man with a two-year history of typical ulcerative colitis initially responded well to oral mesalamine and steroid enemas, but had two flare-ups in the first year requiring systemic corticosteroids despite ongoing maintenance therapy with mesalamine. After a subsequent severe flare-up it proved impossible to wean him from systemic corticosteroids; whenever his dose of oral prednisone went below 20 mg/day he would develop very frequent bloody diarrhea with marked tenesmus. He had no extra-intestinal manifestations of IBD and no other relevant past or current medical history except for reflux esophagitis (well controlled with H2 blockers).

Because of inability to wean him from prednisone in 1991,
Pathologic or viral pericarditis was considered. The literature search produced no reports of an association between azathioprine and pericarditis. There have been case reports of a wide variety of clinical syndromes associated with the common manifestations of azathioprine hypersensitivity, including a number of gastrointestinal syndromes such as pancreatitis (8) and cholestatic jaundice (10).

Azathioprine hypersensitivity mimicking potential complications of underlying IBD has been reported (11). A recent meta-analysis of azathioprine and 6-mercaptopurine in inflammatory bowel disease found that, when specified, the most common extra-intestinal manifestation of IBD unrelated to medical therapy was Restarting azathioprine after he had been asymptomatic while taking that drug for one week. Over the next two days he developed a low grade fever, and on the third day he again developed pleuritic chest pain and a pericardial rub. Azathioprine was stopped and these symptoms and signs resolved over 24 h and did not recur. Figure 1 shows his temperature curve in relation to azathioprine dosing. Subsequently it continued to prove impossible to wean the patient from systemic steroids, and he ultimately underwent colectomy with good results.

DISCUSSION

Although there have been rare case reports of pericarditis as an extra-intestinal manifestation of IBD unrelated to medication (4), the clinical course in this case provides conclusive evidence that azathioprine was the cause of pericarditis. A number of drugs are well documented to cause pericarditis. There is a relatively high incidence of hypersensitivity reactions, including pericarditis, to sulfasalazine (5) but there have also been a number of reports of pericarditis caused by mesalamine either because of a hypersensitivity reaction (6) or because of the development of a lupus-like syndrome (7). Although the aminosalicylates have far fewer adverse effects than sulfasalazine, the drug they were originally designed to replace, it is becoming increasingly clear that they can provoke a number of adverse clinical syndromes, including acute pancreatitis (8). However, the clinical course in this case makes it impossible to implicate mesalamine as the cause of the pericarditis.

Azathioprine is well known to cause a number of infrequent but significant adverse effects, such as bone marrow suppression. As well, azathioprine hypersensitivity is well recognized although uncommon. Hypersensitivity is seen most often in patients with immune-mediated diseases and is usually associated with fever; symptoms typically resolve readily once the drug is discontinued. The onset of symptoms usually occurs between one and two weeks after starting the drug, but on rechallenge symptoms may develop rapidly and be more severe. The clinical picture can be quite variable although chills, arthralgias and myalgias commonly accompany fever. The clinical course in this case is typical for a hypersensitivity reaction to azathioprine (9), and this is believed to be the mechanism for the development of pericarditis. There have been case reports of a wide variety of clinical syndromes associated with the common manifestations of azathioprine hypersensitivity, including a number of gastrointestinal syndromes such as pancreatitis (9) and cholestatic jaundice (10).

Azathioprine hypersensitivity mimicking potential complications of underlying IBD has been reported (11). A recent meta-analysis of azathioprine and 6-mercaptopurine in Crohn’s disease found that, when specified, the most com-

Figure 1  Temperature curve starting on the day a pericardial rub was first noted. ‘A’ indicates azathioprine was given that day

he was started on azathioprine 100 mg/day two weeks before presentation. Other medications were prednisone 20 mg/day, mesalamine 1200 mg tid and ranitidine 150 mg bid.

Ten days after starting the azathioprine he felt vaguely unwell with low back pain and fatigue. Over the ensuing three days he developed worsening back pain, headache, diaphoresis and chills. The night before admission he developed severe arthralgias involving the knees, hips and ankles without any frank signs of arthritis. His colitic symptoms were unchanged with eight to 10 daily episodes of small volume diarrhea with hematochezia. On examination at admission he had a temperature of 38°C and appeared cushingoid. Respiratory, cardiovascular, abdominal and musculoskeletal examinations were all normal. Routine laboratory investigations were normal except for a mild increase in liver enzymes: gamma-glutamyl transpeptidase 159 U/L (normal 10 to 50), alkaline phosphatase 158 U/L (normal 40 to 105), aspartate aminotransferase 96 U/L (normal 10 to 35) and alanine aminotransferase 86 U/L (normal 10 to 35). Bilirubin was normal. Chest x-ray was normal and cultures of throat, urine, stool and blood were negative. Viral serology was not obtained.

The day after admission the patient developed anterior pleuritic chest pain for the first time and a pericardial friction rub was heard. Serial electrocardiograms showed only nonspecific ST-T changes. Creatine phosphokinase values were normal. An echocardiogram done five days after the onset of the rub showed a small pericardial effusion, confirming the clinical diagnosis of acute pericarditis. The patient’s azathioprine medication was held for one day; on that day he felt better with no further chest pain and a marked reduction in arthralgias. When a review of standard reference texts did not reveal any known association between pericarditis and azathioprine, azathioprine was restarted. Two days later he again developed fever, pleuritic chest pain and arthralgias, and azathioprine was discontinued. Over the ensuing 24 h his pleuritic chest pain, pericardial rub, arthralgias and fever all resolved and he felt well over the next week aside from his ongoing colitic symptoms. During this whole period the mesalamine and prednisone were continued. Rheumatoid factor was negative and antinuclear antibody level was not significant with a titre of 1/100. A literature search produced no reports of an association between azathioprine and pericarditis, and therefore the possibility of coincidental idiopathic or viral pericarditis was considered. The literature search was conducted using the MEDLINE database (1982 to October 1991) using the key words ‘azathioprine’, ‘hypersensitivity’ and ‘pericarditis’. A manual search of the reference lists from relevant articles was also conducted.

Because the patient did not want surgery, azathioprine therapy was restarted after he had been asymptomatic while not taking that drug for one week. Over the next two days he developed a low grade fever, and on the third day he again developed pleuritic chest pain and a pericardial rub. Azathioprine was stopped and these symptoms and signs resolved over 24 h and did not recur. Figure 1 shows his temperature curve in relation to azathioprine dosing. Subsequently it continued to prove impossible to wean the patient from systemic steroids, and he ultimately underwent colectomy with good results.

DISCUSSION

Although there have been rare case reports of pericarditis as an extra-intestinal manifestation of IBD unrelated to medication (4), the clinical course in this case provides conclusive evidence that azathioprine was the cause of pericarditis. A number of drugs are well documented to cause pericarditis. There is a relatively high incidence of hypersensitivity reactions, including pericarditis, to sulfasalazine (5) but there have also been a number of reports of pericarditis caused by mesalamine either because of a hypersensitivity reaction (6) or because of the development of a lupus-like syndrome (7). Although the aminosalicylates have far fewer adverse effects than sulfasalazine, the drug they were originally designed to replace, it is becoming increasingly clear that they can provoke a number of adverse clinical syndromes, including acute pancreatitis (8). However, the clinical course in this case makes it impossible to implicate mesalamine as the cause of the pericarditis.

Azathioprine is well known to cause a number of infrequent but significant adverse effects, such as bone marrow suppression. As well, azathioprine hypersensitivity is well recognized although uncommon. Hypersensitivity is seen most often in patients with immune-mediated diseases and is usually associated with fever; symptoms typically resolve readily once the drug is discontinued. The onset of symptoms usually occurs between one and two weeks after starting the drug, but on rechallenge symptoms may develop rapidly and be more severe. The clinical picture can be quite variable although chills, arthralgias and myalgias commonly accompany fever. The clinical course in this case is typical for a hypersensitivity reaction to azathioprine (9), and this is believed to be the mechanism for the development of pericarditis. There have been case reports of a wide variety of clinical syndromes associated with the common manifestations of azathioprine hypersensitivity, including a number of gastrointestinal syndromes such as pancreatitis (9) and cholestatic jaundice (10).

Azathioprine hypersensitivity mimicking potential complications of underlying IBD has been reported (11). A recent meta-analysis of azathioprine and 6-mercaptopurine in Crohn’s disease found that, when specified, the most com-
mon adverse effects were allergic reactions consisting of fever and/or rash and arthritis in 2% of patients (12).

The cause and mechanism of azathioprine hypersensitivity are unknown. Immune mechanisms have been postulated, and the clinical features of most reported cases are consistent with an allergic etiology (13). The size of the azathioprine molecule makes it a poor immunogen, raising the possibility that it acts as a hapten. It is intriguing that there are case reports of such a wide variety of clinical syndromes in association with what appear to be the more typical manifestations of azathioprine hypersensitivity. Also, reported cases have occurred despite the concomitant use of systemic steroids in doses as high as prednisone 45 mg/day (9).

There have been many cases of azathioprine hypersensitivity associated with hypotension, possibly due to cytokine release (13). Specific associated cardiac syndromes are exceedingly rare. Having extended the literature search outlined in the 'Case Presentation' to include up to June 1996, I conclude that this is the first reported case of pericarditis caused by azathioprine. This case highlights the necessity of considering the diagnostic possibility of azathioprine hypersensitivity in any patient being treated with this drug who develops any febrile illness soon after institution of therapy.

REFERENCES
