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CASE REPORT

Azathioprine-induced shock in a patient suffering from undifferentiated erosive oligoarthritis

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ABSTRACT

Shock due to a hypersensitivity response to azathioprine is unpredictable, occurs seldom and bears a potentially fatal outcome. Azathioprine is widely used in the treatment of autoimmune diseases and in solid organ transplantation. Here, we present a patient who suffered from undifferentiated erosive oligoarthritis and was treated with azathioprine. This patient developed anaphylactic shock which was interpreted as a side effect of azathioprine. Although rare, similar cases were described since 1980.

KEYWORDS

Azathioprine, azathioprine-induced shock, hypersensitivity, shock, undifferentiated oligoarthritis

INTRODUCTION

Azathioprine (AZA) is a frequently prescribed drug, used in the treatment of autoimmune and chronic inflammatory diseases. Moreover, it is used in the prevention of allograft rejection after solid organ transplantation. AZA is an imidazole derivative of 6-mercaptopurine (6-MP) and together with 6-MP and 6-thioguanine (6-TG) forms the three major thiopurines. The adverse effects of AZA can be subdivided into two types: allergic and nonallergic. The nonallergic adverse reactions are dose-dependent and are thought to be related to thiopurine metabolites and include myelosuppression and hepatotoxicity. The allergic-type reactions are rare, dose-independent and occur within weeks following the drug introduction. A broad spectrum of reactions can occur, ranging from pancreatitis, hepatitis, skin rash, fever, arthralgias, malaise, nausea, diarrhoea and abdominal pain to the development of anaphylactic reactions.[1,2] Only a few cases of AZA-induced shock have been reported previously.[3-14] AZA-induced shock is characterised by an unpredictable clinical course with a potentially fatal outcome. The 6-mercaptopurine component has been suggested to be responsible for the induction of toxic side effects, while the imidazole component more likely underlies the hypersensitivity reaction.[3,5-7,14,15]
Here, we present a patient in whom AZA induced a circulatory collapse with an atypical clinical presentation, probably triggered by patient's own rechallenge with this drug.

CASE REPORT

A 46-year-old Caucasian man with a two-year history of undifferentiated erosive oligoarthritis presented with a 72-hour history of persistent fever up to 40°C, nausea and vomiting. In the past, he had suffered from recurrent episodes of arthritis, localised in both ankles and in the left knee and had been treated with different courses of disease-modifying antirheumatic drugs including high-dose prednisone, methotrexate and salazopyrine without sufficient response. At presentation, he was on prednisone 15 mg/day orally. He had no known drug allergies. The fever was abrupt in onset and not accompanied by chills. Two weeks earlier, AZA had been introduced at a dose of 50 mg/day and then increased to 100 mg /day three days before presentation. After the first two doses of 100 mg, he began to feel unwell. He developed severe nausea and vomiting and stopped taking the AZA. However, one day before hospitalisation he rechallenged himself by taking

AZA again. Within a few hours he developed high fever without rigors, accompanied by general malaise, arthralgia, myalgia and nausea. At presentation, he was not acutely ill, had a regular pulse rate of 146 beats/min and a blood pressure of 160/85 mmHg. No signs of active arthritis were detected, nor was a rash observed. The remainder of the physical examination was unremarkable. Laboratory tests showed a C-reactive protein of 210 mg/l and a white blood cell count of 6.6 x 10^9/ml with 0.02 x 10^9/ml eosinophils. There were no signs of renal dysfunction or liver enzyme abnormalities. Serum amylase was normal. Urine examination did not show white blood cells or micro-organisms. Chest X-ray revealed a normal cardiac silhouette without infiltrate(s). The patient was admitted under the clinical diagnosis of drug fever due to AZA, which was immediately stopped. Within twelve hours, the patient's clinical condition and haemodynamic status changed dramatically. He developed dizziness, nausea and vague upper abdominal pain, located in the epigastric and right upper quadrants. Quite suddenly, a profound hypotensive shock with a decrease in the blood pressure to 80/50 mmHg occurred. Respiratory function was normal and pulmonary examination revealed no crackles or expiratory wheezes. No jugular venous distension was noted. Abdominal examination was normal without signs of peritonitis. At that moment, liver enzymes were elevated: aspartate aminotransferase 384 U/l, alanine aminotransferase 232 U/l and total bilirubin 21 umol/l, without a rise in serum amylase or lipase. No leucocytosis and no signs of haemorrhage were observed. Abdominal ultrasound showed gallbladder wall thickness and some pericholecystic fluid but no gallstones. The pancreas and common bile duct looked normal. No dilation of intra- and extra-hepatic bile ducts was seen.

Patient's clinical condition was then ascribed to an acute cholecystitis complicated by sepsis. Fluid resuscitation and antibiotic treatment consisting of amoxicillin-clavulanic acid and gentamycin, and supplemental intravenous hydrocortisone (3 x 50 mg) did not lead to a prompt clinical improvement. A percutaneous cholecystectomy was performed, but the gallbladder appeared not to be inflamed, perforated or gangrenous. In spite of this, within 24 hours of admission, the patient's haemodynamic status stabilised. When all blood, urine, throat and gall cultures appeared to remain sterile, the antibiotics were stopped. Within two days, the patient recovered completely. Retrospectively, this patient seemed to have suffered from AZA-induced hypersensitivity shock, probably triggered by his own rechallenge.

DISCUSSION

An uncommon but potentially fatal side effect of AZA treatment is the onset of a hypersensitivity reaction that can lead to shock with involvement of multiple organ systems. However, this occurs in only a minority of the patients receiving this drug. A search in the Medline database for publications back to 1980 revealed fourteen case reports referring to AZA-induced shock.[4-14] Detailed description of these patients is given in *table 1*. Severe hypotension requiring inotropic support and intravascular volume suppletion was described in almost all these cases.[4-6,8,9,14] Onset of symptoms was unpredictable, starting from one day to two months after institution of therapy. Rechallenge led to an acute response with occurrence of fever, nausea, and hypotension within hours.[6-14] As in our case, more indolent vague abdominal symptoms were also reported as the presenting symptoms of such episodes. Except for the use of AZA, no other cause for the circulatory shock was found in our patient. The diagnosis of AZA-induced shock in this case is supported by a close relationship in time between the onset of symptoms and institution of therapy as well as patient's own rechallenge.

Neither AZA, 6-MP nor 6-TG has intrinsic activity; they must undergo extensive metabolism to ultimately produce the 6-thioguaninenucleotides (6-TGNs), which are structurally similar to purine bases and in this way interfere with *de novo* synthesis of proteins and nucleic acids. Two key enzymes seem to be important in this regard: thiopurine (*S*)-methyltransferase (TPMT) and the dephosphorylating enzyme inosine triphosphate pyrophosphatase (ITPase). TPMT has been shown to exhibit genetic polymorphism with three known variant alleles highly associated with defective phenotype of TPMT in Caucasians. Low TPMT status results in overproduction of 6-TGNs and hence probable overdosing, and high TPMT status results in overproduction of 6-methylmercaptopurine and hence likely hepatotoxicity. An impaired activity of ITPase may lead to pancreatic toxicity, rash, neutropenia and gastrointestinal symptoms probably due to the accumulation of a metabolite, 6-thioinosine triphosphate. It has been hypothesised that 6-TG is less intensively metabolised by TPMT and that ITPase is probably not involved in its metabolism. Therefore, 6-thioguanine (6-TG), an agent leading more directly to the formation of 6-TGNs, may be an alternative in AZA or 6-MP intolerance. Theoretically, 6-TG may therefore be beneficial in patients with high TPMT status or in patients with impaired ITPase activity. Although the benefit of performing TPMT status measurement is still a matter of debate, some recommendations have been made. If a patient has a high TPMT status, then administration of full doses of thiopurines from the start is possible. Patients with normal TPMT activity may receive 2 to 2.5 or 1 to 1.5 mg/kg per day of AZA or 6-MP, respectively. Patients with intermediate TPMT activity should have an empiric dose reduction of 50%, while patients with low TPMT activity should only be treated with great caution and at very low

Table 1. *Well-described case reports with azathioprine-induced shock back to 1980*

Reference	Subject sex/age	Disease	Daily treatment dose (mg/day)	Clinical presentation	Time to onset of symptoms (days)	Azathioprine-induced shock after rechallenge
3	♂ 40	PA	100	Hypotension, fever, rash, diarrhoea	16	No rechallenge
4	♂ 49	AIH	50	Hypotension nausea, vomiting, liver enzyme abnormalities	14	No rechallenge
5	♀ 17	LCV	100	Fever	15	Yes
6	♀ 68	BP	150	Nausea, vomiting, diarrhoea	21	Yes
6	♀ 62	PN	50	Nausea	21	Yes
7	♂ 31	MS	150	Fever, rash	14	Yes
8	♀ 45	RA	100	Hypotension, fever, vomiting, liver enzyme abnormalities	6	Yes
9	♀ 30	SS	100	Fever	7	Yes
10	♀ 50	RA	50	Hypotension, fever	14	Yes
10	♀ 51	RA	75	Hypotension, vomiting	56	Yes
11	♂ 27	SLE	50	Nausea, vomiting	NR	Yes
12	♂ 56	PA	75	Fever	7	Yes
12	♂ 62	RA	75	Fever	8	Yes
13	♀ 32	MCTD	50	Hypotension, fever, chills, diarrhoea, liver enzyme abnormalities	14	Yes
Our case	♂ 46	EOA	100	Nausea, vomiting	14	Yes

PA = psoriatic arthritis; AIH = autoimmune hepatitis; LCV = leucocytoclastic vasculitis; BP = bullous pemphigoid; PN = polyarteritis nodosa; MS = multiple sclerosis; RA = rheumatoid arthritis; SS = systemic sclerosis, MCTD = mixed connective tissue disorder; EOA = erosive oligoarthritis; NR = not reported.

doses initially, approximately 10% of the standard dose.[2,16] We attempted to determine the TPMT status in our patient. Since this patient was switched to therapy with leflunomide with a good response, he refused to undergo TPMT status measurement.

The diagnosis of hypersensitivity reaction caused by AZA can usually only be made retrospectively since other possible causes of hypotension, such as sepsis or haemorrhage, should be excluded first. AZA-induced shock should be considered in the diagnostic work-up of unexplained circulatory collapse. Considering the rarity of this complication, a high clinical suspicion is needed to establish this diagnosis.

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