Case Report

Drug fever induced by azathioprine in a haemodialysis patient

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Introduction

Azathioprine is extensively used in renal transplantation with the familiar side-effects of reduced resistance to infection, hepatotoxicity, and bone marrow suppression [1]. Fever as a toxic effect of azathioprine was reported in patients with autoimmune diseases receiving azathioprine alone or concurrently with other medications [2–4] and in one cardiac transplant [5], two renal transplants [6,7], and a haemodialysis patient given azathioprine prior to donor specific blood transfusion in preparation for a living-related kidney transplantation [8].

Case report

A 22-year-old man developed end-stage renal disease of unknown aetiology. After 6 months of haemodialysis he was scheduled to receive a live-related renal transplantation on 6 July 1997. In preparation for kidney transplantation he was started on azathioprine 3 mg/kg orally for 1 week prior to his scheduled surgery. Within 12 h of starting azathioprine he developed fever and he came to the Dialysis Unit with a temperature of 39.0°C. He denied other symptoms. His dialysis was regular three times per week with a Kt/V of 1.3. He was on regular medications of atenolol, rocaftol, calcium carbonate, and erythropoietin. Clinical examination was unremarkable and the arteriovenous fistula was not thrombosed or infected. After obtaining blood and urine samples for cultures 1.5 g ceftazidime and 120 mg gentamicin were given empirically intravenously at the end of haemodialysis session. He was admitted to the hospital and azathioprine discontinued. On admission temperature was 39.4°C, pulse 80 beats/min, blood pressure 130/85 mmHg. Hb 107 g/l, WBC 10.6 x 10⁹/l (normal differential count), platelets 256 x 10⁹/l, Na⁺ 140 mmol/l, K⁺ 4.0 mmol/l, Ca²⁺ 2.6 mmol/l, PO₄ 1.2 mmol/l, HCO₃ 29 mmol/l, bilirubin 8 µmol/l, ALT 12 U/l, AST 26 U/l, and albumin 41 g/l. The patient was HbsAg negative and HCV negative, and chest X-ray and echocardiogram were normal. Within 12 h of admission to hospital, fever subsided and the patient remained asymptomatic. All cultures were negative. Ceftazidime and gentamicin were discontinued and he was discharged from hospital on day 5.

A day later, azathioprine 3 mg/kg per day was started, planning for renal transplantation after 1 week. Next morning, again fever developed and the patient presented to the Dialysis Unit with a temperature of 39.0°C. He denied other symptoms. Blood and urine cultures revealed no growth of bacteria and on day 5 he was discharged from the hospital. He was warned against azathioprine.

One week later, he underwent renal transplantation with the immunosuppression of mycophenolate mofetil, cyclosporin, and prednisone. His transplant had smooth course and at 2 months post-transplantation serum creatinine was 130 µmol/l.

Comments

Hypersensitivity reactions following azathioprine have been reported in patients with connective-tissue diseases [3,4] and neuromuscular disease [2], usually receiving azathioprine together with heterogenous medications. In the adult renal transplant population one patient developed severe reaction to azathioprine [7] and another had hypersensitivity reaction mimicking Goodpasture’s syndrome [6]. Fever and rigors were observed in a haemodialysis patient after receiving 50 mg of azathioprine orally before donor-specific blood transfusion [8]. In these cases symptoms and
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Signs of reaction resolved completely on discontinuation of azathioprine.

It is difficult to distinguish drug-induced fever from fever of infectious origin, but drug reaction is usually accompanied by cutaneous manifestations, urticaria and eosinophilia [9] which are helpful in the diagnosis. However, drug fever is frequently a diagnosis of exclusion when fever subsides on withdrawal of the offending drug. In our patient fever was the sole symptom and there was no clinical or biochemical findings suggestive of azathioprine toxicity. As a haemodialysis patient having fever and chills, bacterial infection was presumed and empirical broad-spectrum antibiotic treatment started while investigating the source of fever. Bacterial infection is a major cause of mortality and morbidity in the haemodialysis population and vascular access is the main route for bacteremia [10]. In both occasions, fever subsided immediately after discontinuation of azathioprine. All cultures were negative and the patient remained asymptomatic. During the periods of fever he was taking his ordinary antihypertensive medications and vitamin D supplement. Azathioprine was the only new medication he received. The immediate resolution of fever after the discontinuation of azathioprine is suggestive of drug fever, and it is further supported by the recurrence of fever rechallenge with azathioprine.

In renal failure, the metabolites of azathioprine are expected to accumulate, enhancing toxic reactions, but in non-renal-failure patients, fever developed at significantly lower daily doses of azathioprine compared to hepatotoxicity and haematologic toxicity [2].

In conclusion, our patient was dialysis dependent and the toxic febrile reaction started within 12 h and subsided within 24 h of taking and discontinuing azathioprine respectively. Isolated fever without obvious cause in end-stage-renal failure patients receiving azathioprine prior to transplantation, justifies the consideration of azathioprine induced fever. This will avoid the costs of hospitalization, investigation of fever and delay of renal transplantation.

References

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