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Azathioprine hypersensitivity in a renal transplant recipient

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Abstract. Hypersensitive reactions to azathioprine have been reported infrequently, and always in nontransplanted patients. Here, a renal transplant recipient with a severe hypersensitive reaction to azathioprine is described. We suggest that, until recently, hypersensitivity to azathioprine was suppressed in transplant recipients by the association of high doses of corticosteroids. Since the introduction of cyclosporin, azathioprine therapy is usually associated with corticosteroids in a much lower dose, so an increasing occurrence of azathioprine hypersensitivity in transplanted patients might be expected.

Key words: Azathioprine, hypersensitivity to – Hypersensitivity, azathioprine, kidney transplantation

Before the introduction of cyclosporin (Sandimmun), azathioprine (Imuran) associated with corticosteroids was the mainstay of immunosuppressive therapy after renal transplantation. Bone marrow depression and hepatotoxicity are the most frequently described side effects. Hypersensitive reactions have only very rarely been described in the transplant literature, although recently several cases have been reported in nontransplanted patients. We report here a case of high fever, rigors, myalgias, and severe diarrhea with hypotension in a renal transplant patient in association with azathioprine therapy.

Case report

A 23-year-old male patient was admitted to our hospital on 9 January 1989 because of high fever with rigors and severe diarrhea. On 2 March 1984 he received a cadaveric kidney graft because of terminal renal failure due to oligomeganephronia. The patient was treated with cyclosporin and corticosteroids. During the first 7 postoperative months there were six periods of increase in serum creatinine (in three cases, acute rejection was proven by biopsy), each time successfully treated with high doses of steroids. In July 1984, renal biopy suggested chronic cyclosporin toxicity, and azathioprine – 100 mg daily – was started. Cyclosporin was stopped and methylprednisolone was continued at a dose of 16 mg daily. Azathioprine was subjectively well tolerated but had to be stopped after 2 months because of prolonged leukopenia, and cyclosporin treatment was reinstituted. Renal function remained stable over the following years, with a mean serum creatinine of 2.5 mg/dl.

In November 1988 (day 1710 post-transplantation), azathioprine was added to the immunosuppressive regimen because of a slow deterioration of renal function. After the first intake, the patient experienced episodes of nausea daily, later leading to severe vomiting. After 2 weeks of irregular intake of azathioprine he developed diarrhea, with chills and fever (37.6 °C). He was admitted to the hospital and the clinical diagnosis of gastroenteritis was made. Azathioprine therapy was discontinued. One month later, a rechallenge with azathioprine was attempted (day 1759 post-transplantation). Azathioprine (50 mg) was given at 5 p.m. Within an hour after intake the patient felt nauseous, vomited, and presented with diarrhea. At 7 p.m. he developed high fever (40 °C) with chills. On admission at 9 p.m. he complained of frontal headache, rigors, myalgias, and colicky abdominal pain. He was hypotensive with a blood pressure of 80/50 mm Hg, responding to intravenous fluid administration. He passed 15 motions of watery stool over the next 12 h. Fever and symptoms resolved spontaneously within 24 h. Cultures of blood and urine were sterile. A culture of stool yielded normal intestinal flora. The white blood cell count was 15000/mm^3 (1% eosinophils). There was an increase in serum creatinine from 2.6 to 3.5 mg/dl, which resolved after fluid replacement. Liver function tests were normal. The serum amylase level was 182 IU/l (normal value 10–160 IU/l). A rectoscopy was normal, with normal rectal mucosa on biopsy. The diagnosis of azathioprine hypersensitivity was made and the treatment with azathioprine was discontinued.

Discussion

Over the past 25 years, the side effects of azathioprine have been well documented. Dose-dependent bone marrow depression with associated infectious complications is one of the most frequently seen. Hypersensitive reactions, as described in our patient, are only rarely mentioned.

The clinical features of azathioprine hypersensitivity have been reviewed elsewhere [9]. In most cases fever, often with rigors, myalgias, arthralgias, and skin rash have been seen. More severe adverse reactions with extreme hypotension, which require replacement with large

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amounts of fluid [4] and even inotropic medication [8], have been reported. Impairment of renal function may occur, usually secondary to profound hypotension, but two cases of interstitial nephritis have been published [7, 10]. Pancreatitis is mentioned most often, but not exclusively, in patients with inflammatory bowel disease who are treated with azathioprine [11]. High fever and severe diarrhea mimicking infectious gastroenteritis, as in our patient, have been documented in several patients with rheumatoid arthritis [1] or inflammatory bowel disease [3]. An immunologically mediated allergic mechanism for this adverse reaction is difficult to demonstrate by in vivo or in vitro tests [6] and is, therefore, mostly postulated on clinical grounds. It only occurs after a variable latency period, usually more than 1 week of therapy. Once established, the symptoms recur rapidly after rechallenge with doses as low as 5 mg [5]. On rechallenge, this reaction can be very severe and potentially life-threatening. In our patient, it seems very likely that the symptoms could be attributed to azathioprine hypersensitivity since they only occurred after a prior, asymptomatic period of intake and, once established, recurred on rechallenge. This feature, together with the severe systemic symptoms (high fever with chills and hypotension) resembling other well-known allergic reactions, favors an allergic etiology rather than a direct toxic effect of azathioprine on gut mucosa in our patient.

Although there are more than 50 well-documented cases of hypersensitivity to azathioprine in the literature, nearly all concern patients with immune-mediated disorders. Only recently a case of azathioprine hypersensitivity was reported in a cardiac transplant patient to whose immunosuppressive regimen azathioprine was added when cyclosporin toxicity was suspected (the dose of prednisone was not mentioned) [9]. To our knowledge there is no report of azathioprine hypersensitivity in a renal transplant recipient. This is surprising considering the widespread use of azathioprine over more than 20 years of renal transplantation and notwithstanding the fact that its possible occurrence in these patients was already anticipated in one of the first reports of azathioprine hypersensitivity in a patient treated for glomerulonephritis [7]. Yet, until now, only pulmonary toxicity has been mentioned in renal allograft recipients receiving azathioprine. On both clinical and histological grounds, it seems more likely that pulmonary injury is caused not by an allergic, but by a dose-dependent, toxic mechanism [2].

One could suggest that some cases of azathioprine hypersensitivity did occur in renal transplant recipients but were misdiagnosed as an infectious complication for which azathioprine therapy was stopped. Yet, this seems unlikely in renal transplant patients. For many years azathioprine was such an essential immunosuppresive drug for patients receiving a renal allograft that it was always restarted even after a severe infection.

We can only speculate as to why this hypersensitive reaction to azathioprine has not been previously described in the renal transplantation literature. Before the introduction of cyclosporin, azathioprine was associated with corticosteroids in a far larger dose (up to 100 mg prednisone) in renal transplant patients than in patients with immune-mediated disorders. In the latter, steroids are usually prescribed, if at all, in a lower dose. It is possible that the higher dose of corticosteroids prevented the development of an allergic reaction to azathioprine in renal transplant recipients. This might explain why this reaction could occur in our patient since azathioprine was started while the dose of steroids was relatively low (16 mg methylprednisolone). Since, nowadays, azathioprine is usually started when cyclosporin toxicity is suspected and then added to an immunosuppressive regimen with a low dose of steroids, we can expect this hypersensitive reaction to occur more frequently in the future. Azathioprine hypersensitivity should be considered in renal transplant patients presenting with fever.

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