Case Report

Post-renal transplant azathioprine-induced pancreatitis

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Introduction

Acute pancreatitis is a rare but often lethal complication in post-transplant patients. Azathioprine is one of the incriminated agents out of the multiple possible aetiological factors.

We present a case who developed acute necrotizing pancreatitis while on immunosuppression, which included azathioprine, for more than a year in the post-transplant period, and review the literature regarding possible aetiopathogenesis and management of post-transplant drug-induced pancreatitis.

Case

In December 1996, a 48-year-old man with chronic renal failure due to glomerulonephritis received a renal transplant from a live genetically unrelated donor. Immunosuppressive regimen comprised cyclosporin, azathioprine, and corticosteroids. The post-operative course was unremarkable, with satisfactory renal function. There was no episode of rejection or infection during this period.

In January 1998 the patient was admitted with acute epigastric pain, non-colicky, characteristically radiating to the back and decreasing on stooping forward. Serum amylase was raised (320 Somogyi units/dl). Dynamic CAT scan of the abdomen showed features of acute pancreatitis with minimal ascites (Figure 1). At the time the patient was admitted, he was receiving cyclosporin (3.5 mg/kg body weight) with serum cyclosporin concentration of 198 ng/ml, azathioprine 75 mg/day, and prednisolone 10 mg/day. To control hypertension nifedipine 20 mg t.d.s. and Minipress 2.5 o.d. were being administered. He was kept on conventional conservative management: fasting, intravenous fluids, antibiotics, and analgesics.

The results of relevant laboratory investigations are as follows. Serum calcium was 9.7 mg/dl, serum albumin 3.7 g/dl, serum inorganic phosphate 4 mg/dl, serum cholesterol 160 mg/dl, and total lipid level 600 mg/dl. Serological investigations for hepatitis B and hepatitis C virus were negative. Cytomegalovirus (CMV) IgM antibodies by micro-ELISA test were negative. Urine smear showed no cells suggestive of CMV inclusions. There was no evidence of alcohol intake, biliary-tract disease, hyperlipidaemia, hypercalcaemia, or viral infection. Therefore, azathioprine was suspected to be the possible cause and was discontinued. Cyclosporin was increased to 5 mg/kg/day and steroids were continued for immunosuppression. The function of the transplanted kidney remained unaffected. The patient improved with conservative management, and oral intake was commenced after 7 days.

Azathioprine (75 mg/day) was reintroduced in the subsequent week with the intention of continuing it as a part of immunosuppressive regimen. About 30 h after the first dose the patient developed epigastric
pain and abdominal distention. Ultrasonography showed multiple hypoechoic areas in head, body, and tail of the pancreas with peri-pancreatic fluid collection. Azathioprine was withdrawn and conservative management was reinstituted with addition of parenteral hyperalimentation. Ultrasound-guided aspiration of peri-pancreatic fluid was performed and was found to be sterile. Blood cultures were also negative.

There was no improvement in the patient’s condition even after 3 weeks of conservative management. He developed fever with chills and rigors in the 4th week of conservative management. Dynamic CAT scan demonstrated multiple intra-pancreatic and peri-pancreatic collections (Figure 2). Ultrasound-guided therapeutic aspiration of a pseudocyst of the pancreas was performed and culture of this fluid grew *Proteus mirabilis*, which was resistant to most groups of antibiotics. At laparotomy, multiple cystic collections containing pus and necrotic material were found in the region of the body and tail of the pancreas, as well as in the mesentery. Necrosectomy along with drainage of the lesser sac and feeding jejunostomy were performed. Elective mechanical ventilation was performed for a day. Irrigation through drains positioned in the lesser sac was started after 48 h of exploration and continued for a duration of 5 weeks. The patient gradually improved and was discharged after 7 weeks of surgery.

Magnetic resonance cholangiopancreaticography (MRCP, Figure 3) performed 4 months after laparotomy revealed an irregular pancreatic duct with ill-defined peri-pancreatic fat, a sequela of the previous pancreatitis. There has been no recurrence of symptoms in 1 year of follow up.

Discussion

Acute pancreatitis is reported in 1–2.5% of patients after organ transplantation [1–3] but a higher incidence of about 5% has also been reported [4]. The multiplicity of possible aetiological factors such as alcohol, biliary tract disease, viral infections, and the surgery itself usually prevent the recognition of single causative factor in most cases. Hypercalcaemia, hyperparathyroidism, hyperlipidaemia, uraemia, and malignant hypertension have been reported to play some role in post-renal transplant patients. However, the most interesting aetiological agents to be implicated in post-transplant pancreatitis are the very drugs that have permitted clinical transplant to become a practical reality, the immunosuppressive azathioprine and corticosteroids [5].

Published reports have identified about 50 drugs that can either definitely or possibly be held responsible for acute pancreatitis. Definite conclusion can only be made where there is consistent statistical data, reliable rechallenge evidence, and experimental studies demonstrating a possible mechanism. Azathioprine, thiazides, sulphonamides, frusemide, oestrogens, and tetracycline have definite association with pancreatitis [5,6]. The definitive co-relation was based upon carefully documented studies showing pancreatitis developing during treatment with the drug, improvement upon withdrawal of the drug, and often occurring again if the drug was re-introduced. Experimental studies in mice also suggest that azathioprine causes biochemical and histological evidence of acute pancreatitis [7], and aggravates acinar cell necrosis [8].

Some authors, however, consider that there is only a possible, rather than a proven, association between azathioprine and acute pancreatitis. Azathioprine is at the most a co-factor in inducing pancreatitis, since all these patients have additional possible factors for the disease [9]. Our patient was on treatment with azathioprine at the time of acute attack, and his condition improved upon withdrawal of the drug. Rechallenge with azathioprine led to flare-up of symptoms, confirmed by serial CAT scan and surgery, thus establishing the role of azathioprine in the aetiology of acute pancreatitis. In spite of an early improvement, the patient
progressed to severe pancreatitis upon reinstatement of azathioprine. Azathioprine-induced pancreatitis has also been reported in a number of clinical settings other than transplantation. Reports of patients suffering from inflammatory bowel disease [10,11], chronic active hepatitis [12], and SLE [13] developing pancreatitis attributed to azathioprine are available in the literature.

Acute pancreatitis has been reported in patients having high serum trough levels of cyclosporin [14] and in animal studies with high dose of cyclosporin (60 mg/kg/day) [8]. The evidence, however, is not sufficient in clinical [15] or experimental [16] studies to hold cyclosporin responsible for acute pancreatitis. Although there is no definite evidence, yet, corticosteroids are also believed to have a causal relationship with pancreatitis [5]. Our patient continued to receive steroids and cyclosporin during the course of his illness with no adverse effects. However, a synergistic effect with azathioprine cannot be ruled out. There was no evidence of alcohol abuse, biliary-tract disease, hyperlipidaemia, or hypercalcaemia in our patient, and a serological test for CMV infection was negative.

Drug-induced pancreatitis usually runs a benign course, and all signs and symptoms disappear over a period of 1–11 days upon withdrawal of the offending agent [10,17]. However, in post-transplant immunosuppressed patients it runs a more severe and sometimes lethal course. More than half of post-transplant patients who develop pancreatitis have severe pancreatitis [1], as against 20–30% incidence in non-transplant cases of pancreatitis. Mortality has been reported to range from 50 to 100% in immunocompromized patients as compared to much lower mortality rate of 5–10% in non-immunosuppressed patients [1–4,18]. One hypothesis is that the diminished immunocompetence of these post-transplant patients results in an initially attenuated inflammatory response with a decrease in tissue perfusion and delayed or ineffective clearing of damaged tissue, leading to extensive necrosis, haemorrhage, and infection [1,19].

Clinical manifestations in post-transplant pancreatitis are similar to general population. The severity of pancreatitis may be difficult to assess clinically. Serial dynamic CAT scans are vital to assess the severity of disease. CAT scans showing any degree of necrosis of pancreas, extension of oedema or fluid in peripancreatic tissue or multiple fluid collections are defined as severe pancreatitis [1]. Little is known about the pathogenesis of drug-induced pancreatitis. A number of studies in patients with Crohn’s disease with pancreatitis characteristically showed a latent period of about 3 weeks after exposure to the drug for onset of symptoms, rapid defervescence of pain upon cessation of drug, and recurrence after a shorter interval at rechallenge [5,10,20], irrespective of the dose of drug given. This trend is best explained by an allergic mechanism. There is usually no associated eosinophilia, fever, malaise, or joint pains. Thus type II (cytotoxic complement-mediated) or type IV (sensitized T-lymphocyte-mediated) response seems most likely. In contrast to the striking timing of onset of acute pancreatitis in Crohn’s disease (the 3rd week of therapy) it has not been a regular feature in renal transplant patients and the time gap is much longer [1,3,10]. Our patient was on azathioprine therapy for 13 months at the time of manifestation of acute pancreatitis. Drug hypersensitivity as the possible mechanism is further supported by the fact that most of the patients do not show any other adverse effects of azathioprine [10]. Leukopenia was not seen in our patient.

In view of higher mortality in post-transplant pancreatitis, aggressive management should be instituted. Prolonged conservative therapy is associated with high mortality [3]. Serial dynamic CAT scans are helpful in assessing the severity of pancreatitis. Early and perhaps repeated operations may be life saving in cases with severe disease. Milder forms of pancreatitis can be given a trial of conventional medical management: fasting, intravenous fluids, or parental nutrition and analgesia. Reintroduction of the offending drug should always be avoided.

References


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