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Short communication

Tacrolimus Induced Acute Exacerbation of Chronic Calcifying Calculous Pancreatitis in a Kidney Transplant Patient - Case Report and Literature Review

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Abstract

Introduction. The purpose of this case report is to describe our experience in the treatment of potential tacrolimus-induced pancreatitis in a renal transplant patient.

Case report. We present a case of a 35-year Caucasian female kidney transplant patient who developed an acute exacerbation of chronic calcifying calculous pancreatitis twice in the early posttransplant period. Before undergoing a kidney transplant, she had been hospitalized on three occasions due to episodes of acute pancreatitis, which was successfully treated with conservative therapy. The second episode of acute exacerbation of chronic pancreatitis, which occurred two months after kidney transplantation, was much more severe than the first, which occurred on the sixth day after transplantation, and was complicated by the formation of multiple pseudocysts in the head and body of the pancreas, with a further tendency to grow. The resulting compression on the surrounding structures required surgical drainage of the cysts. Furthermore, tacrolimus was switched to parenteral cyclosporine due to intolerance of oral food and fluid intake, and oral cyclosporine therapy was continued after recovery. The patient was discharged without recurrent clinical and laboratory signs of acute exacerbation of chronic pancreatitis during the further follow-up of 6 months.

Conclusion. Tacrolimus is the most likely cause of acute exacerbation of chronic pancreatitis in our patient. Switching from tacrolimus to cyclosporine should be considered.

Keywords: acute exacerbation of calcifying calculous chronic pancreatitis, kidney transplant, tacrolimus, pancreatic pseudocysts

Introduction

Tacrolimus (or FK506), a calcineurin inhibitor (CNI) introduced in the field of transplantation in the 1990s, is the cornerstone of most immunosuppressive regimens in solid organ transplantation, and its use has revolutionized the future of kidney transplantation. It has been associated with better graft survival, a lower incidence of rejection, and improved drug tolerance with fewer side effects than cyclosporine [1]. According to a review article by Jones MR *et al*. acute pancreatitis due to medications generally is rare (incidence of 0.1% to 2%), with common drugs being tetracyclines, isoniazid, macrolides, metronidazole, and angiotensin-converting enzyme inhibitors [2].

Drug-induced pancreatitis is classified (class I - IV) based on the number of cases reported, demonstration of a consistent latency period (time from initiation of the drug to development of pancreatitis), and reaction with rechallenge [3]. A population-based case-control study by Floyd A *et al*. pancreatitis, reported in solid organ transplantation and allogeneic stem cell transplantation cases, was related to immunosuppressive agents. However, only azathioprine has been confirmed to be the cause of pancreatitis with solid evidence so far [4]. We report a rare but clinically important case of tacrolimus-induced acute exacerbation of chronic calcifying calculous pancreatitis in a renal transplant patient.

Case report

35-year-old Caucasian female kidney transplant patient developed an acute exacerbation of chronic calcifying calculous pancreatitis during tacrolimus therapy. She was diagnosed with autosomal dominant polycystic kidney disease (ADPKD) with liver and ovarian cysts in 2009. Nine relatives also have ADPKD, and all have had kidney transplants. From December 2018, due to end-stage renal disease, she was started to replace renal function with peritoneal dialysis, initially with continuous ambulatory peritoneal dialysis (CAPD) and from June 2019 with automated peritoneal dialysis (APD) as the treatment modality. In August 2019, she was

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hospitalized for persistent upper abdominal pain with nausea. Laboratory tests showed elevated serum amylase of 462 U/L (normal range 23-91) and lipase of 1130 U/L (normal range 13-60), suggesting acute pancreatitis without a clearly defined etiology.

Further radiological diagnosis in terms of multi slice computed tomography (MSCT scan) corroborated the suspicion of chronic calcifying calculous pancreatitis (numerous mineral stones of the pancreas were descrybed, with a dilated central pancreatic duct (Wirsung) up to 7 mm and also a dilated accessory pancreatic duct (Santorini) and also dilated choledochal duct up to 10 mm, without visible signs of obstruction in terms of lithiasis or tumor. The applied symptomatic and supportive therapy was accompanied by clinical improvement but serum amylase and lipase remained elevated. In September 2019, on the advice of the gastroenterologist, she underwent magnetic resonance cholangiopancreatography (MRCP) which revealed a dilated choledochal duct up to 6 mm with suspected choledocholithiasis and a possible diagnosis of pancreatic divisum (noting that the ducts were not fully visible). In November 2019, she was readmitted to the hospital for clinical and laboratory signs of acute exacerbation of chronic pancreatitis (abdominal pain and elevated serum amylase 3774 U/L and lipase 7400 U/L). Endoscopic ultrasound (EUS) revealed calcifications in the head of the pancreas, with a tortuous main pancreatic duct and with possible protein plugs, without lithiasis. Although laboratory and microbiological analysis showed no signs of acute peritonitis, acute exacerbation of chronic pancreatitis was understood as a possible complication of peritoneal dialysis. She was switched to hemodialysis. During the aforementioned hospitalization, clinical improvement occurred with symptomatic and supportive therapy.

In July 2020, she was hospitalized again due to clinical (abdominal pain and vomiting) and laboratory (elevated serum amylase 3630 U/L and lipase 8829 U/L) signs of acute exacerbation of chronic pancreatitis which again improved on symptomatic and supportive therapy. A fecal elastase test was performed, and the finding was within normal range, indicating normal pancreatic exocrine function.

After completion of appropriate pretransplant diagnostics, the patient underwent the deceased donor kidney transplantation in June 2021, with a standard immunosuppression protocol that included induction of basiliximab 20 mg (day 0 and +4) with tacrolimus, mycophenolate mofetil (MMF), and steroids as maintenance therapy. On the sixth posttransplant day, the patient complained of abdominal pain. Laboratory tests revealed an increase in serum amylase (2089 U/L) and lipase (2951 U/L), indicating an acute exacerbation of chronic pancreatitis, which was gradually improved with supportive and symptomatic therapy applied. In August 2021, she was hospitalized again for an acute exacerbation of chronic pancreatitis, with a more complicated clinical picture of severe abdominal pain accompanied by vomiting and diarrhea. Laboratory tests showed an increase in C-reactive protein (CRP) up to 197 mg/L, in addition to elevated amylase (731 U/L) and lipase (264 U/L. In addition, an abdominal MSCT examination was performed on two occasions. On the first occasion, multiple pseudocysts were seen in front of the head and body of the pancreas in addition to acute pancreatitis, the largest of which was approximately 13 cm in diameter, and five days later, progression of the cysts to a size of 17 cm, with an indentation between the large curvature of the stomach, spleen, trunk, and tail of the pancreas was described. Since endoscopic drainage of the cysts was no longer possible, the surgeon performed medial laparotomy and cystogastrostomy and drainage of the pseudocysts according to Jurasz [5], and the procedure passed without complications. Further, the patient was transferred to the intensive care unit (ICU), and after improvement of clinical condition, she was transferred to the ward for transplant patients to continue the previously started treatment. In the meantime, due to intolerance of oral food and fluid intake, oral immunosuppressive therapy with tacrolimus was switched to parenteral therapy with cyclosporine, and the dose of intravenous steroids was increased, while MMF was also gradually excluded from therapy. Switching from tacrolimus to cyclosporine, in addition to empiric and targeted antibiotics (ciprofloxacin and linezolid) and other supportive therapies, resulted in an improvement in clinical condition and a gradual decrease in laboratory parameters of pancreatic inflammation. The use of oral cyclosporine was continued with dose adjustment depending on the drug concentration in the blood. MMF was also gradually returned to therapy with oral steroid therapy dose reduction and the patient was discharged from the hospital without any discomfort. Oral supplementation of pancreatic enzymes was introduced.

At the outpatient nephrological controls, the patient was subjectively well, with stable graft function and no objective clinical deterioration and laboratory indicators of acute pancreatitis. On the control ultrasound of the pancreas, pseudocysts regression size was described.

Review of the literature

In a case report by Liu X *et al*. they presented a 24-year-old male patient who had undergone kidney transplantation and who, among others, had immunosuppressive therapy with tacrolimus, and on the tenth after transplantation, he developed clinical, laboratory, and radiological signs of acute pancreatitis. After excluding other possible causes, they concluded that tacrolimus was the definite inducer of pancreatitis because his symptoms decreased and laboratory tests improved after exclusion of tacrolimus, which was

temporarily switched by cyclosporin. Furthermore, tacrolimus was on day 61 again returned to therapy with consequent laboratory and radiological relapse of acute pancreatitis. The patient has switched from tacrolimus to cyclosporine again, followed by normalization of laboratory tests and after all, he was discharged home with no relapse of acute pancreatitis [6].

Xu J *et al*. presented a case of a 45-year-old male who underwent kidney transplantation and received immunosuppressive therapy of tacrolimus, and on day 67 after transplantation, he developed acute pancreatitis with an extremely high blood tacrolimus concentration. They also excluded other possible causes and speculated tacrolimus was the probable inducer of pancreatitis. After tacrolimus was discontinued and alternated with cyclosporine, the patient gradually recovered and was discharged home with no relapse [7].

Mallory and Kern have established a criterion for a definite association of any drug with pancreatitis. This includes (a) appearance of this complication during treatment with the drug, (b) disappearance upon with drawal of the drug, (c) exclusion of other causes, and (d) relapse upon reintroduction [8].

In our patient, 3 of 4 criteria are fulfilled, so we can assume with a high degree of probability that the last two acute exacerbations of chronic pancreatitis were triggered by tacrolimus.

Conclusion

The goal of this article is to emphasize that clinicians should be aware of the possibility of tacrolimus-induced pancreatitis during tacrolimus treatment in renal and other transplant patients.

Conflict of interest statement. None declared.

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