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Case report

Emergency surgical treatment of complicated acute pancreatitis after kidney transplantation with acute rejection: Case report and literature review

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HIGHLIGHTS

- Acute pancreatitis is a rare but frequently fatal complication and challenging therapeutical situation in patients following kidney transplantation.
- Several etiological agents are listed, which also include the effect of immunosuppressive medication.
- Patient care requires reduction of immunosuppressive medication and very close co-operation between the surgeon, nephrologist, intensivist and anaesthetist.

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ABSTRACT

Introduction: Acute pancreatitis is a rare but frequently fatal complication in patients following kidney transplantation. The first case of acute pancreatitis in patients following a kidney transplant was described by Starzl in 1964. The incidence of acute pancreatitis is stated at between 1 and 5%. The mortality rate amongst these patients reaches as high as 50–100%.

Presentation of case: Here we present a case of acute pancreatic abscess in a caucasian female – shortly following a kidney transplant complicated by the development of acute rejection, in which immunosuppressant therapy is a potential etiological agent. Emergency surgical treatment was indicated, which included drainage of the abscesses irrigation of the abdominal cavity. Immunosuppressive medication was considered a possible etiological factor, and as a result administration of tacrolimus and mycophenolate mofetil was discontinued. This was successful and three months later, diagnostic rebiopsy of the graft was performed without signs of rejection.

Discussion: The etiology of this illness is multifactorial. The clinical manifestation of acute pancreatitis in patients following kidney transplantation is the same as in the remainder of the population. However, in patients following transplantation with long-term immunosuppression, it usually manifests a more rapid development and a more severe, frequently fatal course.

Conclusions: With regard to the patient's comorbidities, early surgical therapy was indicated – drainage and closed lavage and immunosuppressive medication as a suspected tobe ethiological factor was discontinued. This course of treatment led to a complete recovery with preservation of good function of the cadaverous kidney.

1. Introduction

Acute pancreatitis is a rare but frequently fatal complication in patients following kidney transplantation. The first case of acute pancreatitis in patients following a kidney transplant was described

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by Starzl in 1964 [1]. Several etiological agents are listed, which also include the effect of immunosuppressive medication. Here we present a case of acute pancreatic abscess in a patient shortly following a kidney transplant complicated by the development of acute rejection, in which immunosuppressive therapy is a potential etiological agent, as well as a review of the literature listening the potential etiological agents and management of therapy of acute pancreatitis in patients following kidney transplantation.

2. Presentation of case

A 67 year old caucasian female, underwent renal transplantation from a deceased donor due to chronic renal failure based on the biopsy of unconfirmed chronic glomerulonephritis. Immunosuppression consisted of 2 doses of basiliximab and standard dosages of tacrolimus, mycophenolate mofetil and prednisolone. After the operation, there was a late onset of graft function and the patient was haemodialysis dependent. A biopsy performed 7 days after transplantation confirmed severe combined acute cellular (2B according to Banff 2007 classification) and antibody mediated C4d positive rejection, which was treated intravenously with rabbit antithymocyte globulin (700 mg in 7 doses á 100 mg) in parallel with plasmapheresis [7] and intravenous immunoglobulins (total dose 75 mg). This treatment was successful, with recovery the graft function. At the same time, clinically asymptomatic elevation of amylase and lipase was registered, probably in connection with the combination of pharmaceuticals. No pathology of the pancreas was observed upon ultrasound examination. A solitary stone was found inside the gall bladder, but the bile ducts were not dilated. The patient was treated by conservative therapy. The dose of mycophenolate mofetil was reduced in view of its possible role in inducing pancreatic irritation [6,8–11] and in order to prevent deterioration of the patient's condition due to infection. Corticosteroids were not discontinued given that the patient had been taking them for a long time and had developed corticosteroid-dependence.

Three months after the renal transplant, the female was admitted to the surgery clinic presenting with progressive sharp pain throughout the entire abdominal region persisting for three days, with temperatures exceeding 39 C and shivering. At the time of admission, immunosuppressive treatment consisted of tacrolimus (Advagraf, 5 mg o.p.d.), mycophenolate mofetil (Mycophenolate mofetil- SANDOZ, 500 mg b.i.d), prednisolone (Prednison, 20 mg o.p.d.).

The initial laboratory results were characterised by a significantly increased level of serum amylase (4.25 μkat/l) and lipase (1.55 μkat/l); bilirubin, ALT, AST, ALP and GGT were within the norm. The level of potassium was 5.3 mmol/l, creatinine 384 μmol/l and urea 21.9 mmol/l. Inflammatory parameters were extremely elevated – leukocytes 14.48 $\times$ 10^9/l, CRP 433 mg/l, procalcitonin 40 μg/l. The serum levels of calcium and parathyroid hormones were within the normal range. Acute infections were serologically excluded – CMV, Epstein-Barr virus, herpes simplex, varicella zoster virus and acute hepatitis. Acute contrast-enhanced CT scan (CECT) [Fig. 1,2] described acute pancreatitis with an unfocussed image of the contours of the body and tail of the pancreas, and multiple subphrenic abscess collections to the right and left, with a maximum of collection in the bursa omentalis, as well as fluid between the loops of the small intestine (see Figs. 3 and 4).

Objective manifestations of peritonism, elevated inflammatory parameters, septic temperatures and the CECT image of pancreatic abscess were decisive in indicating surgical treatment. The surgical procedure consisted of transverse laparotomy, drainage of the abscess subphrenically on the left and right, sample collection for cultivation, severance of ligamentum gastrocolicum with opening of bursa omentalis and drainage of abscess and irrigation of the abdominal cavity and four quadrants drainage.

Immunosuppressive medication was also considered as a possible etiological factor, and as a result administration of tacrolimus and mycophenolate mofetil was discontinued. Only corticoids were administered intravenously. The cultivation of the abscesses of the abdominal cavity demonstrated Escherichia coli. A combination of meropenem + metronidazole was administered. Progressive increase in azotemia and manifestations of graft failure, which required continual CVVHD were observed. On the sixth postoperative day, the patient's condition was sufficiently stabilised to allow extubation, and support of vasopressors was no longer required. Spontaneous diuresis was renewed. Follow-up CECT scan 9 days after the surgical revision revealed [Fig. 2.] only a residue following evacuation of the pancreas, without progression of inflammatory changes in the pancreas and peripancreatic fat saturation with streaks of fluid. There was significant regression of the inflammatory parameters and stabilisation of laboratory values. On the third postoperative day, immunosuppressive therapy with tacrolimus was renewed. The dose of corticoids was progressively reduced. 14 days after surgical revision the patient was back on full sustenance, the surgical wound was locally bandaged with a VAC system and the patient was transferred to the nephrological department and subsequently discharged for home care.

Three months later, diagnostic rebiopsy of the graft was performed without signs of rejection. Up to the present time no other recurrence of acute pancreatitis has been registered. Immunosuppressive medication consisted of tacrolimus and prednisolone (Prednison 5 mg/day), and graft function is very good.

3. Discussion

Acute pancreatitis is a potentially fatal illness. It is described in 1–5% of patients following a kidney transplant [2–4]. The cause of the development of this illness is multifactorial. Acute pancreatitis is caused by disorders of the bile duct and alcoholism, additional obstructive factors include disorders of the duodenum (annular pancreas, periampullary polyps and intraluminal duodenal

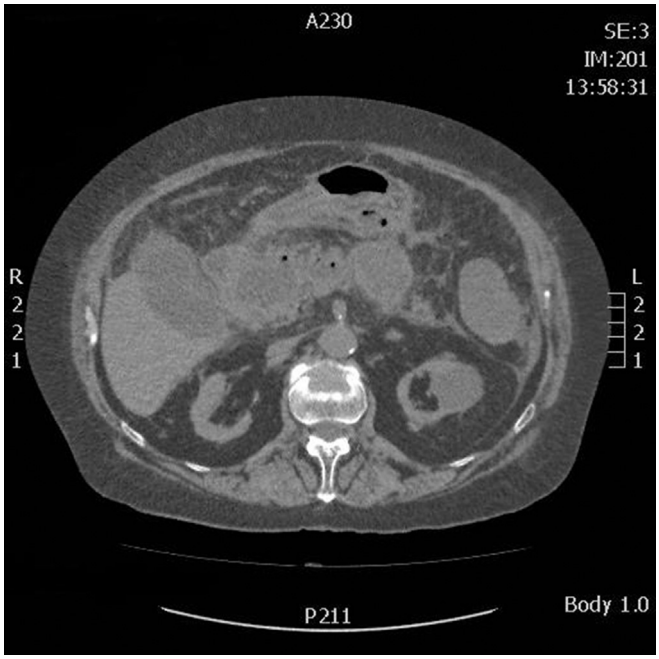

Fig. 1. Initial CECT scans.

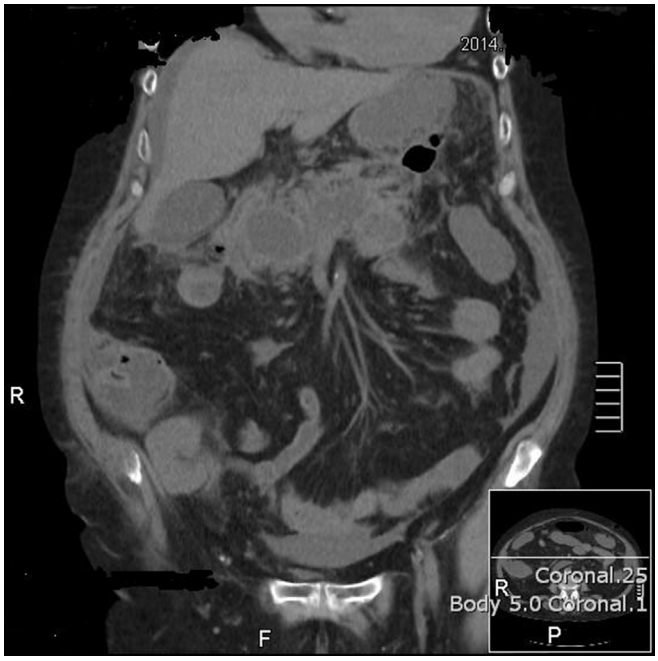

Fig. 2. Initial CECT scans.

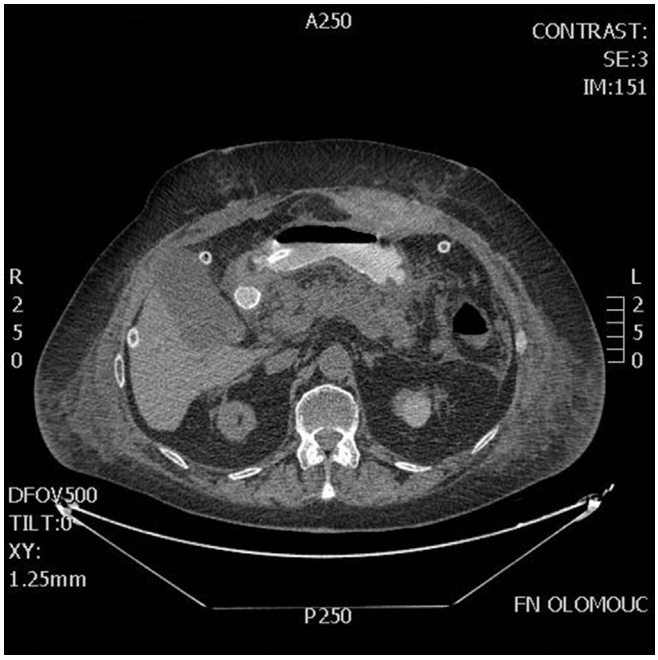

Fig. 3. Control CECT scans with reduced peripancreatic fluid collections.

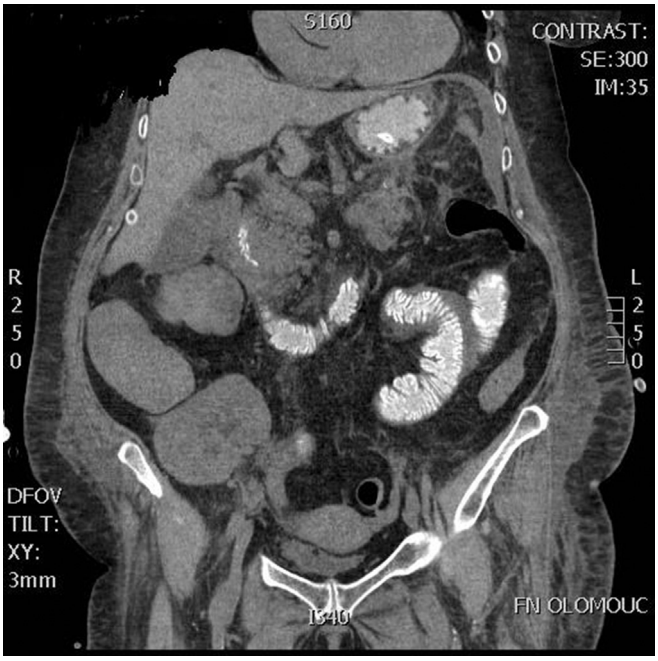

Fig. 4. Control CECT scans with reduced peripancreatic fluid collections.

diverticulum), tumours, congenital anomalies and in addition to alcohol, toxic causes include various drugs. Classification of types of drug-induced pancreatitis has been presented by *Trivedi and Pitchumoni*. [5] [Tables 1 and 2].

There are frequently multiple causes of acute pancreatitis. In addition to the above, in patients following kidney transplantation, the most interesting connection is between acute pancreatitis and the use of immunosuppressive medication. Documentation of drug-induced pancreatitis (DIP) is more definite if other likely causes of pancreatitis are not present, if there is recovery after drug withdrawal, and if pancreatitis recurs with the reintroduction of the drug. Over 100 drugs have been implicated as a cause of AP, mostly from case and anecdotal reports [5,12,13,17]. Azathioprine, sulfonamides, steroids, furosemide and opiates have been identified as drugs causing pancreatitis on the basis of consistent statistical data.

The revised Atlanta classification of acute pancreatitis from 2012 [14,20] identified two phases of the disease: early and late. Severity is classified as mild, moderate or severe. Local complications of AP are peripancreatic fluid collections, pancreatic and peripancreatic necrosis (sterile or infected), pseudocyst and walled-off necrosis (sterile or infected).

The clinical manifestation of acute pancreatitis in patients following kidney transplantation is the same as in the remainder of the population. However, in patients following transplantation with long-term immunosuppression, it usually manifests with a more rapid development and a more severe, frequently fatal course. More than half of the patients with acute pancreatitis following kidney transplant have severe pancreatitis, versus 20–30% incidence in non-transplant cases of pancreatitis. Mortality has been reported to range from 50 to 100% in immunocompromised patients, as compared with a much lower mortality rate of 5–10% in non-immunosuppressed patients [1,3,15,16]. The diagnosis is based on the clinical picture, laboratory results, and the gold standard is contrast-enhanced CT, or if this is unavailable or contraindicated then MRI. Infected necroses in necrotising pancreatitis, pancreatic abscess and postacute pancreatic pseudocyst are indications for surgical therapy. The following techniques are currently in use for the debridement of pancreatic/extrapancreatic necrosis: 1. open necrosectomy with postoperative closed continuous lavage of the lesser sac and the abdominal cavity, 2. open necrosectomy with open packing and planned relaparotomy, 3. retroperitoneal or ventral laparoscopic necrosectomy with staged lavage, 4. endoscopic transgastric necrosectomy and lavage and drainage, 5. percutaneous interventional drainage and lavage [18,19]. Nowadays there is clearly no more doubt that surgery is not the first choice of treatment for patients suffering from severe acute pancreatitis. Patients with early severe acute pancreatitis and CECT-proven extended necrosis (>50%) of the pancreas should have surgical

Table 1
Proposed classification for medications associated with drug-induced pancreatitis [5].

Class I drug:
- At least 20 reported cases of acute pancreatitis
- At least 1 case with positive rechallenge
Class II drug:
- >10 but <20 reported cases of acute pancreatitis with or without positive rechallenge
Class III drug:
- All medications implicated in pancreatitis (i.e., class I, class II) and those with ≤10 reported cases or unpublished reports in pharmaceutical or Food and Drug Association files

Table 2
Medications associated with pancreatitis (Trivedi and Pitchumoni).

Class I drugs:
- Didanosine, Asparaginase, Azathioprine, Valproic acid, Pentavalent antimonials, Pentamidine, Mercaptopurine, Mesalamine, Various estrogens, Opiates, Tetracycline, Cytarabine, Steroids, Sulfamethoxazole/trimethoprim, Sulfasalazine, Furosemide, Sulindac
Class II drugs:
- Rifampicin, Lamivudine, Octreotide, Carbamazepine, Acetaminophen, Phenformin, Interferon α_{2-b}, Enalapril, Hydrochlorothiazide, Erythromycin, Cyclopenthiazide

debridement if organ failure is nonresponsive to maximum intensive care treatment for more than 1 week [19]. In the case of acute pancreatitis in patients after kidney transplantation, aggressive surgical therapy is preferred because prolonged conservative therapy is related to increased mortality [19].

4. Conclusions

The presented case described a female following a kidney transplant complicated by acute rejection, with clinical manifestations of acute pancreatitis and CT verified pancreatic abscesses with cardiovascular, pulmonary, renal and hepatic dysfunction. With regard to the comorbidities, early surgical therapy was indicated – drainage and closed lavage. This treatment led to a complete recovery, with the preservation of good function of the cadaverous kidney.

Ethical approval

No ethical approval.

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Author contribution

All authors participated in data collection, analysis, writing and editing of the manuscript.

Conflict of interest statement

None.

Guarantor

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Consent

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

References

[1] T.E. Starzl, Experience in Renal Transplantation, WB Saunders, Philadelphia. PA, 1964, p. 111.
[2] D.P. Slakey, C.P. Johnoson, D.J. Czeperle, et al., Management of severe pancreatitis in renal transplant recipients, Ann. Surg. 225 (1997) 217–222.
[3] L. Fernandez-Cruz, E.M. Targarona, E. Cugat, A. Alcaraz, F. Oppenheimer, Acute pancreatitis after renal transplantation, Br. J. Surg. 76 (1989) 1132–1135.
[4] T. Kenmochi, T. Asano, H. Shimada, T. Ochiai, K. Isono, Clinical and experimental studies of acute pancreatitis after renal transplantation, Transplant. Proc. 24 (1992) 1578–1580.
[5] C.D. Trivedi, C.S. Pitchumoni, Drug-induced pancreatitis. an update, J. Clin. Gastroenterol. 39 (2005) 709–716.
[6] H.A. Villarreal, L.D. Wells, B.A. Neuschwander-Tetri, Azathioprine induced acute pancreatitis in mice, Gastroenterology 105 (1995) A 398.
[7] T. Foitzik, B. Fargacs, E. Ryschich, et al., Effect of different immunosuppressive agents on acute pancreatitis. A comparative study in an improved animal model, Transplantation. 65 (8) (1998) 1030–1036.
[8] B. Tasdogan, H.F. Kucuk, N. Kurt, et al., Effect of mycophenolate mofetil on cerulein-induced acute pancreatitis, Eur. Surg. Res. 45 (2010) 146–150.
[9] R.L. Murphy, G.A. Noskin, E.D. Ehrenpreis, Acute pancreatitis with aerosolized pentamidine, Am. J. Med. 88 (1990) 53N–56N.
[10] B.A. Oguenseinde, E. Wimmers, B. Washington, et al., A case of tacrolimus (FK506)- induced pancreatitis and fatality 2 years postcadaveris renal transplant, Transplantation. 76 (2003) 448.
[11] Z. Nieto, P. Russ, G. Everson, et al., Acute pancreatitis during immunosuppression with tacrolimus following an allogenic umbilical cord blood transplantation, Bone Marrow Transplant. 26 (2000) 109–111.
[12] M.K. Müller, M. Wojcik, H. Coone, M.V. Singer, Inhibition of insulin release by FK506 and its prevention by rioprostil, a stable prostaglandin E1 analogue, Transpl. Proc. 23 (1991) 2812–2813.
[13] Y. Echigo, K. Inoue, M. Kogire, et al., Effects of cyclosporine and tacrolimus (FK506) on acute pancreatitis in mice, Arch. Surg. 13 (1995) 64–68.
[14] E.L.I. Bradley, A clinically based classification system for acute pancreatitis, Arch. Surg. 128 (1993) 586–590.
[15] P.M. Taft, A.C. Jones, G.M. Collins, et al., Acute pancreatitis following renal allotransplantation. A lethal complication, Can. J. Surg. 25 (1982) 547–549.
[16] V. Siwach, V. Bansal, A. Kumar, et al., Post-renal transplant azathioprine-induced pancreatitis, Nephrol. Dial. Transpl. 14 (1999) 2495–2498.
[17] C.M. Edwards, J.D.T. Morgan, J.V.T. Tilsed, et al., Impaired acute phase response: a risk factor for life threatening posttransplant pancreatitis? Transpl. Proc. 24 (6) (1992) 2769.
[18] B.M. Rau, A. Bothe, H.G. Beger, Surgical treatment of necrotiying pancreatitis by necrosectomy and closed lavage: changing patient characteristics and outcome in 19-year, single-center series, Surgery 138 (2005) 28–39.
[19] H.G. Beger, B.M. Rau, Indications for surgical management, in: H.G. Beger, S. Matsuno, J.L. Cameron (Eds.), Diseases of the Pancreas. Current Surgical Therapy, Springer-Verlag, Berlin Heidelberg, 2008, p. 216.
[20] P.A. Banks, T.L. Bollen, C. Dervenis, et al., Classification of acute pankreatitis-2012: revision of the Atlanta classification and definitions by international consensus, Gut 62 (2013) 102–111.