

Pancreatitis after renal transplantation

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SUMMARY Pancreatitis is seldom seen as a severe complication of renal transplantation. In a review on 1321 renal transplants, 23 cases with 12 deaths are reported (Johnson and Nabseth, 1970). Single case reports may be added. In our departments pancreatitis has proved to be a fairly frequent complication. It developed in 10 (7%) of 147 patients with renal transplantation one week to seven and a half years after transplantation (patients with primary hyperparathyroidism excluded). Three of the eight acute cases had haemorrhagic pancreatitis, in two of them leading to death. Two patients had chronic calcifying pancreatitis. Pancreatitis was complicated in one case by abscess formation and in two by severe haemorrhage into a pseudo-cyst. In two patients the diagnosis was made at necropsy only and death was probably not related to the acute pancreatitis. The exact pathogenesis of pancreatitis after renal transplantation cannot be precisely assessed. Possible contributing factors are treatment with corticosteroids, azathioprin, and L-asparaginase, early hypercalcaemia after transplantation, surgery, infections of bacterial or viral origin, and unknown immunological processes.

Pancreatitis is referred to as an infrequent and severe complication of renal transplantation. In a series of 1321 patients with renal transplants 23 cases (1.7%) with 12 deaths have been observed (Johnson and Nabseth, 1970). Other reports concern only single cases (Starzl, 1964; Tilney, Collins, and Wilson, 1966; Murray, Barnes, and Atkinson, 1967; Van Geertruyden and Toussaint, 1967; White, Morgan, and Hopton, 1970; Penn, Durst, Machado, Halgrimson, Booth, Putman, Groth, and Starzl, 1972; Renning, Worden, Stevens, and Reemtsma, 1972); Woods, Anderson, Frohuert, and Petrie, 1972). As pancreatitis appeared to be a more frequent complication of renal transplantation in the Departments of Medicine and Surgery A of the University of Zurich, it seemed of interest to us to report on its incidence, forms, evolution, and pathogenetic features.

Patients and Methods

From 1964 to 1972 160 cadaveric kidneys were transplanted to 147 patients. The technique

(Largiadèr, 1969) and postoperative treatment have already been described (Largiadèr, Linder, Senning, Scheitlin, Wegmann, and Van Rood, 1970). To be included in the study, patients had to fulfil the following criteria:

ACUTE PANCREATITIS

Serum-amylase above 1000 Somogyi units (normal 40 to 160 SU) together with typical clinical symptoms, or anatomical evidence of acute pancreatitis at laparotomy or necropsy.

CHRONIC PANCREATITIS

Calcification in the pancreatic region on radiographs, or anatomical evidence of chronic pancreatitis at laparotomy or necropsy, or repeatedly decreased faecal concentrations of chymotrypsin and trypsin.

As most patients had impaired renal function at the time of diagnosis, the urinary amylase concentration was not considered diagnostic. Patients with moderate and transient hyperamylasaemia (Penn *et al*, 1972), who usually had none of the typical symptoms of acute pancreatitis, were not included in the study. The quantitative estimation of pancreatic function by stimulation with pancreozymin and secretin could be performed in one case only. The faecal enzyme concentration was determined in all surviving patients.

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Renal Disease	Transplanted Patients	Patients with Pancreatitis
Glomerulonephritis	74	5
Chronic pyelonephritis	41	1
Congenital malformations with pyelonephritis	8	1
Polycystic kidney	12	1
Medullary cystic kidney	1	1
Cystic dysplasia	1	1
Nephrosclerosis Fahr	1	—
Alport syndrome	2	—
Haemolytic uraemic syndrome	2	—
Glomerulonephritis with Goodpasture syndrome	1	—
Fabry's disease	1	—
Primary hyperparathyroidism	1	—
Cystinuria	1	—
Systemic lupus erythematosus	1	—
Total	147	10

Table I Underlying renal disease in 147 patients with renal transplantation and 10 patients with subsequent pancreatitis

Results

Of the 147 transplanted patients (92 men and 55 women), 10 (7%) (seven men and three women) developed pancreatitis (table I). Clinical and laboratory data for the 10 cases are given in table II.

The mean age of all patients at transplantation was 36.7 ± 12.0 years and the mean age of pancreatitis patients 35.4 ± 8.6 years. There was no predilection for sex or age. As is shown in table I, the underlying renal disease seemed not to be related to the development of pancreatitis. The interval between transplantation and pancreatitis was one week to seven and a half years (table II): in three cases it occurred within weeks of transplantation, in three within six months, and in four more than three years after transplantation. In two patients the diagnosis of pancreatitis was made at necropsy only. In three cases pancreatitis was in conjunction with some other severe complication of transplantation.

Forms of Pancreatitis

Eight patients developed acute pancreatitis. Two of them had a single episode, another suffered three attacks. Two patients showed acute pancreatitis with multiple abscesses and three had haemorrhagic necrotizing pancreatitis. The evolution of the disease is shown in tables II and III. Two of the patients with haemorrhagic pancreatitis died; the third, in whom haemorrhagic pancreatitis occurred one week after transplantation, developed two further episodes

	Patient Number									
	1	2	3	4	5	6	7	8	9	10
Sex	Male	Male	Male	Male	Female	Female	Female	Male	Male	Male
Age at transplant (years)	33	48	31/33	42	47	26	41	21	33	31
Renal disease	Glomerulonephritis	Glomerulonephritis	Cystic dysplasia	Medullary cystic kidneys	Polycystic kidneys	Pyelonephritis	Glomerulonephritis	Glomerulonephritis	Pyelonephritis	Glomerulonephritis
Pancreatitis	Acute haemorrhagic	Acute haemorrhagic	Acute haemorrhagic	Acute recurrent	Acute	Acute	Acute with abscesses	Acute with abscesses	Chronic calcifying	Chronic calcifying
Occurrence after transplantation (mth)	2½	4½	½	½	1½	89	37	6	58	51
Result	Death	Death	Recovery	Recovery	Recovery	Recovery	Death from other cause	Death from other cause	Free of symptoms	Pseudocyst operated, free of symptoms 106-1
Serum creatinine ($\mu\text{mol/l}$)	530.4	141.4	256.4	972.4	442.0	122.8	176.8	238.7	114.9	—
Gallstones	—	—	—	—	Cholecystectomy 3 years before transplantation	—	—	—	—	+
Alcohol	—	—	—	—	—	—	—	—	—	—
Abdominal surgery (nephrectomy and transplantation excluded)	—	—	—	Vagotomy Pyloroplasty	—	—	—	—	—	—
Duodenal ulcer	—	—	—	+	—	—	—	—	—	—
Early posttransplantation hypercalcaemia	—	—	—	+	—	—	—	+	—	—
Hepatitis B antigen	—	—	—	—	+	—	?	?	—	—
Increase or start of corticosteroids	+	—	+	+	+	—	—	—	—	+
Antilymphocytic globulin during pancreatitis	+	—	+	+	+	—	—	—	—	—
Hypertension (>150/100 mm Hg)	+	—	—	—	+	—	+	—	—	—

Table II Clinical and laboratory data on patients with pancreatitis after renal transplantation

End Result and Complication	Pancreatitis	
	Acute	Chronic
Death from pancreatitis	2	—
Death from other cause	2	—
Recovery or absence of symptoms	4	2
Shock	3	1
Pseudocyst formation	—	1
Abscess formation	2	—
Laparotomy for pancreatitis	2	1
Exocrine insufficiency	—	—

Table III End results and complications of pancreatitis

with haemorrhagic ascites and paralytic ileus, which led to two laparotomies with drainage of the pancreatic region. He fully recovered eventually. The other three patients with acute pancreatitis recovered uneventfully. The two patients with multiple pancreatic abscesses had been clinically asymptomatic and were diagnosed at necropsy only. One of them died of cerebral haemorrhage 37 months after transplantation, the other six months after transplantation of septicaemia after rupture of the transplanted ureter and of a mycotic aneurysm of the internal iliac artery. Necropsy disclosed acute pancreatitis with a huge pancreatic abscess in the first patient and many small pyogenic abscesses and haemorrhagic areas in the pancreas of the second patient. All patients who survived the acute pancreatitis are well at the time of this report and show normal serum and urinary amylase levels and normal faecal trypsin and chymotrypsin concentrations.

Two patients had chronic calcifying pancreatitis. They are asymptomatic for the time being and have normal faecal enzyme concentrations. One of them (case 9) was found to have a greatly increased level of serum amylase (1760 SU) without clinical symptoms 58 months after transplantation. Two years later pancreatic stimulation with pancreozymin and secretin gave normal results. The other patient (case 10) experienced colicky pains in the right upper quadrant and was shown to have gallstones. Four weeks after successful cholecystectomy with careful revision of the common bile duct the first episode of acute pancreatitis developed. Later, after another attack, a pseudocyst with haemorrhage had to be operated upon. Tiny spots of calcification, diffusely scattered over the whole pancreas, which had developed within four weeks of the first attack, diminished considerably in the following year. These calcifications did not seem to be situated in larger pancreatic ducts, but it cannot be excluded that such a ductal stone led to the second acute episode of pancreatitis with pseudocyst formation. Hypercalcaemia was not present at any time in this patient. Almost total clearance of calcifications after drainage of a pseudocyst of the body of the gland is

unusual. Single cases in which calcifications diminished considerably have been reported by Tucker and Moore (1963) and by Reynolds (1958).

Discussion

As serum amylase and lipase determinations are not routinely performed in transplanted patients, the true incidence of pancreatitis is not known. The frequency of pancreatitis was 7% in this study and corresponds to that of 5.6% reported by Penn *et al* (1972). Johnson and Nabseth (1970) report an incidence of 1.7% among 1321 transplant patients. The relatively high incidence in our series may partly be explained by the two cases detected only at necropsy and the two patients with chronic calcifying pancreatitis. No such cases are included in the literature. The mortality of 20% in the present series seems to be somewhat lower than the mortality of 50 to 60% found by other authors. But the difference should not be overemphasized as the number of pancreatitis patients is small in all series.

Possible Aetiological Factors

The aetiology of pancreatitis in patients with renal transplantation varies. In addition to the common causes, contributing causes such as acute or chronic rejection, continuous immunosuppression, impaired response to infections, as well as the use of various drugs have to be considered.

Gallstones were present in one patient only (case 10). As chronic calcifying pancreatitis with pseudocyst followed cholecystectomy and revision of the common bile duct and repeated cholangiography gave no evidence of a remaining stone in the common duct, gallstones are not very likely to be the cause of this case of chronic pancreatitis (Ammann, Akovbiantz, Deyhle, Hahnloser, Largiadèr, and Wellauer, 1974). Another patient (case 5) had cholecystectomy with revision of the common bile duct because of asymptomatic gallstones three years before transplantation. The patient has refused cholangiography at the present time, so that a common duct stone cannot be excluded, but clinical and biochemical evidence did not support this possibility.

None of our patients had a history of chronic or excessive alcohol intake.

Operations, especially in the upper abdomen, including nephrectomy, can be the cause of damage to the pancreas and of acute pancreatitis (Dunphy, Brooks, and Ackroyd, 1953; Starzl and Porter, 1967; Van Geertruyden and Toussaint, 1967; Penn *et al*, 1972). In two of our patients the interval between operation and the onset of acute pancreatitis was very short, thus favouring this pathogenesis.

There were no cases of malignant hypertension; three patients showed moderately increased blood pressure, which is not thought to have contributed to the development of acute pancreatitis.

Hypercalcaemia as a possible cause of acute pancreatitis developed in two patients after transplantation (cases 4 and 8). Hyperlipaemia was not present in any of the patients. Uraemia predisposes to pancreatitis. The cause is unknown (Merrill and Hampers, 1970). Four of our patients had urea values of above 16.6 mmol/l. Serum creatinine was normal in only three cases. It is thus possible that impaired renal function contributed to the development of either acute or chronic pancreatitis.

Corticosteroids are accepted as a cause of pancreatitis (Lazarus and Bencosme, 1956; Stumpf, Wilens, and Somoza, 1956; Baar and Wolff, 1957; Carone and Liebow, 1957; Oppenheimer and Boitnott, 1960; Dreiling, Janowitz, and Perrier, 1964). All patients were on this drug when they developed pancreatitis. Furthermore pancreatitis occurred in three patients simultaneously with the increase of the dosage of corticosteroids for the treatment of acute rejection and in two cases immediately after instituting immunosuppressive treatment after transplantation. It is suggested therefore that corticosteroids may be an important aetiological factor in posttransplantation pancreatitis. The pathogenesis of corticosteroid-induced pancreatitis is not clear. Since aseptic bone necrosis (Crues, Blennerhassett, Macdonald, Maclean, and Dossetor, 1968; Briggs, Hampers, Merrill, Hager, Wilson, Birtch, and Murray, 1972), another well known complication of corticosteroid treatment in renal transplantation, is thought to be due to occlusive vascular processes, the same cause might contribute to the pathogenesis of pancreatitis. But in this series only case 2 had concomitant aseptic bone necrosis. All patients had azathioprin. Only a few reports exist on the relationship between acute pancreatitis and this drug. Nogueira and Freedman (1972) report one patient with regional enteritis in whom acute pancreatitis developed at the time the azathioprin treatment was started. Another episode of pancreatitis occurred after challenge with azathioprin. A similar case was reported by Kawanishi, Rudolph, and Bull (1972). The role of azathioprin in acute pancreatitis after renal transplantation is also discussed by Hume (1966).

Antilymphocytic globulin is not known to cause pancreatitis. In our series five patients had never had antilymphocytic globulin whereas four were treated with this serum throughout the attack of pancreatitis. L-asparaginase has been incriminated as a cause of acute pancreatitis (Shaw, Barnes, Madden, and Bagshawe, 1970). Only one of our patients was given

this drug for severe rejection before pancreatitis developed. In the earlier days of renal transplantation we frequently administered L-asparaginase without noticing pancreatic complications. Some patients were receiving other drugs at the time or shortly before pancreatitis but none of these is known to cause pancreatitis.

Infections of bacterial and viral origin are frequent in patients receiving immunosuppressive drugs. A pathogenetic role of infective agents, especially of cytomegalic virus, has been raised in acute pancreatitis (Van Geertruyden and Toussaint, 1967; Johnson and Nabseth, 1970; Penn *et al.*, 1972). Cytomegaly was not found in the necropsy material investigated. The serological titres assessed in two patients were negative. In two other patients who died after renal transplantation cytomegalic inclusion bodies were found in pancreatic cells without any histological signs of acute pancreatitis. Cases 1 and 8 had severe bacterial infections at the time of pancreatitis.

Hepatitis B-antigen was positive in one of eight patients at the time of pancreatitis; in another it became positive six months after pancreatitis. Hepatitis-B-antigen has been incriminated in periarteritis nodosa (Baker, Kaplan, Benz, Sidel, and Wolfe, 1972). A similar immunological mechanism could be responsible for the development of pancreatitis. There were no other signs favouring the diagnosis of periarteritis nodosa in these patients, however. Other immunological mechanisms have to be considered. Cross-reacting antibodies are suggested to damage the renal transplant and the organs of the receptor (Fujii and Nelson, 1963). It might further be speculated that unknown protective mechanisms, which prevent the pancreas from autodigestion, are depressed by immunosuppressive drugs.

In conclusion, it is not possible to find a single factor responsible for the frequency of pancreatitis after renal transplantation. Certain factors, such as immunological processes, the administration of corticosteroids and azathioprin, are present in all cases and various other contributing factors are usually present. The institution of corticosteroid therapy or the increase of corticosteroid dosage may play an important aetiological part. Prevention of pancreatitis should be attempted by careful surgery, omission of L-asparaginase, the prevention of post-transplant hypercalcaemia, the prescription of the lowest possible dose of corticosteroids, prompt and adequate treatment of rejection, and a vigorous approach to infections.

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