PANCREATITIS FOLLOWING LIVER TRANSPLANTATION[1]

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Since 1981, when the liver transplantation program was initiated at the University of Pittsburgh, we have been impressed with the prevalence of pancreatitis occurring following liver transplantation in patients transplanted for hepatitis B–related liver disease. To either confirm this clinical impression or refute it, the records of the 27 HbsAg⁺ patients and those of an additional 24 HbsAg⁻ but HbcAb and/or HbsAb⁺ patients who underwent orthotopic liver transplantation were reviewed to determine the prevalence of clinical pancreatitis and hyperamylasemia (biochemical pancreatitis) following liver transplantation (OLTx). Post-OLTx hyperamylasemia occurred significantly more frequently in HbsAg⁺ patients (6/27) than it did in the HbsAg⁻ patients (0/24) ($P<0.05$). More importantly, clinical pancreatitis occurred in 14% (4/27) of the HbsAg⁺ patients and 0% (0/24) of the HbsAg⁻ patients. Interestingly, in each case, the pancreatitis was associated with the occurrence of acute hepatitis B infection of the allograft.

Based upon these data, we conclude that pancreatitis occurring after liver transplantation is more common in patients transplanted for active viral liver disease caused by hepatitis B than in those with inactive viral liver disease. These observations suggest that pancreatitis occurring in, at least some cases following liver transplantation for viral liver disease, may result from hepatitis B virus infection of the pancreas.

The frequency of pancreatitis following renal transplantation has been reported to vary between 0.4% and 7% and to be associated with a mortality between 20–70% (1–6). Mechanisms proposed as putative causes for the pancreatitis include: the immunosuppressive medications utilized especially glucocorticoids and/or azathioprine, unidentified viral infections, postoperative hyperparathyroidism, vasculitis, and intraoperative pancreatic trauma. Since 1981 when the liver transplantation program was initiated at the University of Pittsburgh, pancreatitis has been observed occasionally in liver allograft recipients. Its occurrence in HbsAg⁺ patients with postoperative hepatitis B infection of the allograft has been particularly impressive. To evaluate this possible association, a retrospective analysis of the incidence of post-orthotopic liver transplantation (OLTx)* pancreatitis in HbsAg⁺ patients compared with that found in a control group of HbsAg⁻ patients with laboratory evidence of prior hepatitis B exposure was performed. The results of this study are reported here.

* Abbreviation used: OLTx, orthotopic liver transplantation.

MATERIALS AND METHODS

Subjects. All of the in-patient and out-patient records of the 27 HbsAg⁺ patients who underwent orthotopic liver transplantation at the Presbyterian University Hospital of the University of Pittsburgh Health Science Center between January 1st, 1981 and December 31st, 1986 were reviewed. Twenty-four of these 27 patients (89%) underwent OLTx for advanced cirrhosis with chronic hepatic insufficiency, while three (11%) were transplanted for hepatocellular carcinoma with clinically stable cirrhosis. The records of 24 patients who had serologic evidence of prior hepatitis B infection, and who underwent OLTx during the same time period, were reviewed as a control population. Each of these latter 24 patients was HbsAg⁻ and was HbcAb⁺ and/or HbsAb⁺, and had not been immunized with a pancreatitis B virus vaccine. Nineteen of these 24 patients had OLTx for advanced postnecrotic cirrhosis with chronic hepatic insufficiency, and five (19%) underwent the procedure because of hepatocellular carcinoma in an individual with stable cirrhosis. Table 1 demonstrates the historical, clinical, and laboratory data available on these two groups of liver transplant recipients. The follow-up data are to May 31st, 1987.

Clinical evaluation. The presence or absence and degree of hepatic encephalopathy in each subject prior to OLTx was determined clinically as well as prospectively by hepatology fellows using established criteria and was scored from 0–2 as follows (7):

Grade 0: No clinically evident encephalopathy
Grade 1: Clinical stage 1–2 encephalopathy.
Grade 2: Clinical stage 3–4 encephalopathy

Similarly, the presence or absence of ascites prior to OLTx was scored prospectively by hepatology fellows on a scale running from 0–2 as follows:

Grade 0: No ascites evident by ultrasonography
Grade 1: Mild-to-moderate amount of ascites responsive to diuretic therapy
Grade 2: A large volume of ascites poorly controlled by diuretic therapy

Finally, the patients' functional status immediately prior to OLTx was also scored prospectively on a scale ranging from 0–3 as follows:

Grade 0: Living at home and working
Grade 1: Living at home but unable to work due to hepatic disease
Grade 2: Hospitalized
Grade 3: Hospitalized in an intensive care unit

Diagnostic testing. All preoperative laboratory and diagnostic tests were performed according to an established protocol. Posttransplantation data were obtained as clinically indicated. Amylase determinations are routinely made on all patients with abdominal pain and at the time of each readmission regardless of the presenting complaints or physical findings. No laboratory or diagnostic testing for the sole purpose of this investigation was performed. Serum amylase measurements were performed by the clinical pathology department of Presbyterian University Hospital using the Kodak Enzymatic Amylase Kit, which uses paranitrophenol maltopentaoside as the substrate (Eastman Kodak Co., Rochester, NY).

All of the pathologic specimens reported here were examined by a single pathologist skilled in the interpretation of liver transplantation and pancreatitis B liver histopathology.

Definition of pancreatitis. For the purpose of this investigation "pancreatitis" was defined as an elevation of the serum amylase to a level

greater than twice the upper limit of the normal range in association with radiographic and/or clinical symptomatology suggesting pancreatitis—specifically abdominal pain with or without nausea and/or vomiting. Elevations of the serum amylase to levels greater than twice the normal value but without radiologic or clinical evidence consistent with pancreatitis was defined as *hyperamylasemia* or biochemical pancreatitis.

Statistical analysis. Statistical analysis was performed using the Students' *t* test for unpaired samples. Chi-square methods were used to evaluate the association, as well as differences in proportions; the Yates' correction for continuity was incorporated when appropriate. A *P* value less than 0.05 was considered to be significant.

RESULTS

There was no difference between the HbsAg⁺ group and the HbsAg⁻ group with respect to the percentage of patients undergoing OLTx in each year of the investigation (Table 2). There was no difference in the patient survival rate between the HbsAg⁺ and HbsAg⁻ groups (data not reported).

The prevalence of pancreatitis in the HbsAg⁺ group (4/27) was arithmetically but not significantly greater than the prevalence in the HbsAg⁻ group (0–24). However, the prevalence of pancreatitis plus hyperamylasemia in the HbsAg⁺ group (6/27)

was statistically greater than in the HbsAg⁻ group (0/24) ($P<0.05$).

Six patients in the HbsAg⁺ group were readmitted to Presbyterian University Hospital with acute hepatitis B infection of the allograft with jaundice. Four of these also had clinical pancreatitis. Interestingly, among patients transplanted for HbsAg⁺ disease, post-OLTx pancreatitis occurred more frequently in those who manifested a picture of clinical acute hepatitis B virus infection of the allograft (4/6) than in those without clinically evident hepatitis B infection in the allograft (0/21) ($P<0.01$). Shown in Table 3 are the clinical data on the 4 patients with pancreatitis and two of the patients with hyperamylasemia.

DISCUSSION

The HbsAg⁺ study group and the HbsAg⁻ but HbcAb⁺ or HbsAb⁺ control group were reasonably similar with respect to the historical, clinical, and laboratory data assessed and reported in Table 1. However, the HbsAg⁺ group had a greater percentage of male patients ($P<0.02$), a greater ascites score ($P<.05$), and a poorer performance status score ($P<0.05$) than did the HbsAg⁻ group. The differences in performance status and ascites scores between the two groups document the poorer clinical condition of the HbsAg⁺ patients with respect to the HbsAg⁻ at the time of transplantation. Despite these differences, there was no difference in survival between the two groups. Since the percentage of patients undergoing OLTx in each year of the study was similar for both groups, the duration of survival was also similar for both groups.

Three of the four cases of pancreatitis had clinical, laboratory and radiologic evidence for acute pancreatic inflammatory dis-

TABLE 1. Patient data

	HBsAg(+) (n=27)	HBsAg(−) (n=24)
Age	43.0 ± 2.3ᵃ	40.1±3.1
% Male	89% (24/27)ᵇ	58% (14/24)
Ascites score (0–2)	1.5±0.2ᵇ	1.0±0.2
Encephalopathy score (0–2)	1.2±0.2	1.1±0.2
Status (0–3)	2.0±0.2ᵇ	1.5±0.1
History of variceal bleeding	44% (12/27)	38% (9/24)
Albumin (g/dl)	2.7±0.1	2.8±0.1
Prothrombin time (sec [Control = 11.7])	16.3±0.6	16.0±0.5
Absolute lymphocyte count (cells/mm³)	1057±132	963±129
Creatinine (mg/dl)	1.4±0.2	1.0±0.1
Bilirubin (mg/dl)	10.5±2.8	7.2±2.1

ᵃ Mean±SEM.
ᵇ $P<0.05$.

TABLE 2. Distribution of OLTx procedures performed yearly

Year	HBsAg(+) (n=27)	HBsAg(−) (n=24)
1981	0% (0/27)	0% (0/24)
1982	11% (3/27)	17% (4/24)
1983	4% (1/27)	0% (0/24)
1984	11% (3/27)	13% (3/24)
1985	22% (6/27)	13% (3/24)
1986	52% (14/27)	58% (14/24)

TABLE 3. Clinical data on the four cases with pancreatitis and two cases with hyperamylasemia

Case No.	Hepatitis status	OLTx date	Onset of pancreatitis posttransplantation (days)	Liver biopsy	Amylase (IU/L)	CT/sonographic findings	Course
1	HBsAg⁺ HBeAg⁺	2-16-82	122	Chronic viral hepatitis	360	Edematous pancreas	Died
2	HBsAg⁺ HBeAg⁺	5-11-85	220	Acute viral hepatitis	325	Unremarkable	Alive
3	HBsAg⁺ HBeAg⁺	5-31-85	192	Acute viral hepatitis	497	Pancreatitis	Alive
4	HBsAg⁺ HBeAg⁺	6-5-86	103	Acute viral hepatitis	377	Pancreatic phlegmon and pseudocyst	Died
5	HBsAg⁺ HBeAg⁺	11-4-86	75	Not done	546	Not done	Died
6	HBsAg⁺ HBeAg⁺	11-15-86	20	Not done	560	Not done	Alive

ease. The fourth case of pancreatitis had only laboratory and clinical evidence highly suggestive of acute pancreatitis. Elevations of the serum amylase value in patients with nonpancreatic abdominal pain are certainly well recognized (8-11). However, in two large studies in patients with abdominal pain and serum amylase values greater than twice the upper normal limit were found to be quite specific for pancreatitis (12, 13); in the most recent study, an elevated amylase (>2× ULN) had specificities of 98.4% and 100% when determined and calculated using two assay techniques. Patients 5 and 6 had elevations of the serum amylase to levels similar to those of cases 1-4 and may have represented subclinical pancreatitis—but, because of the lack of symptoms or radiologic evidence of pancreatitis, they can only be classified as having hyperamylasemia. Nonetheless, we have observed three definite, one highly probable, and two possible cases of pancreatitis in the 27 individuals in the HbsAg⁺ group—the one probable and three definite cases occurred in association with acute recurrent hepatitis B infection of the allograft. Over the same period, we observed no cases of pancreatitis or hyperamylasemia in the HbsAg⁻ control group of patients studied. Based upon this experience, we conclude that there is greater risk of post-OLTx pancreatitis in HbsAg⁺ patients than there is in HbsAg⁻ patients, and that pancreatitis is often associated with recurrent acute B virus hepatitis of the allograft.

There are many other possible causes for the observed cases of pancreatitis. Postoperative pancreatitis can occur with any intraabdominal operation—and, one might expect, with the magnitude of dissection required for liver transplantation, to observe postoperative pancreatitis not infrequently following liver transplantation. With the exception of the hyperamylasemia seen in case 6 all of our cases occurred at greater than two months post-OLTx, making postoperative pancreatitis resulting from intraoperative pancreatic trauma an unlikely cause of the pancreatitis observed in this investigation (14). Moreover operative trauma does not explain the occurrence of pancreatitis in HbsAg⁺ patients and its absence in HbsAb⁺ patients. All post-OLTx patients are on multiple medications, several of which are well known to be associated with pancreatitis. All post-OLTx patients receive large doses of corticosteroids and most also receive intermittent treatment with furosemide, two drugs known to cause pancreatitis (15-21). The use of azathioprine has been associated with pancreatitis as well (22-25). Of the six cases herein reported, only patient 5, who developed hyperamylasemia, was actively taking or had ever taken azathioprine. The other medications potentially responsible for pancreatitis in this series were used equally by both groups.

Infectious pancreatitis is well known to occur with the mumps virus and has been reported in association with other viral and/or parasitic infections, such as Mycoplasma pneumoniae, Coxsackie B and ECHO virus (26-29), and a variety of fungal and Ascaris lumbricoides (30). None of the patients herein reported had evidence of a systemic infection, though infectious pancreatitis is always an etiologic possibility in any patient on immunosuppressive medication.

Each of the above-identified causes is a possible explanation for the development of post-OLTx pancreatitis in the cases we report. However, none explains the strikingly different prevalence of pancreatitis between the HbsAg⁺ and HbsAg⁻ groups or the 67% prevalence of pancreatitis in transplant patients who had "recurrent" acute hepatitis B infection. Pancreatitis caused by hepatic necrosis and pancreatitis caused by hepatitis B pancreatic infection are more likely causes of the pancreatitis observed in this study, as they explain the observed close relationship of pancreatitis and recurrent hepatitis B infection. An association between pancreatitis and hepatic failure is well recognized also. (31-34). In these reports, acute pancreatitis is seen most commonly in association with viral hepatitis, but it has been reported to occur with other forms of hepatic failure as well, especially acetaminophen overdose and halothane toxicity. In the only study to specifically evaluate the etiology of the hepatic failure and the prevalence of pancreatitis, acute pancreatitis was found to be more common with viral hepatitis than in cases of halothane hepatotoxicity. Geokas et al. found autopsy evidence of acute pancreatitis in 2 of 33 (6%) patients who died of halothane hepatotoxicity and in 7 of 16 (44%) patients who died from fulminant viral hepatitis (31). The reasons for this relationship between hepatic failure and acute pancreatitis are as yet unknown; postulated causes include intrapancreatic hemorrhage (33), vascular thrombosis from disseminated intravascular coagulation (33), glucocorticoid therapy (35)—and, most interestingly, concommitant viral infection of the pancreas (31, 33, 34, 36,-38). Due to the greater but not exclusive association of viral hepatitis with acute pancreatitis, viral pancreatic infection may be an important mechanism responsible for the pancreatitis associated with hepatic failure. It should be noted, however, that this certainly is not the only cause possible and several other mechanisms are also likely.

Four of the patients described herein with pancreatitis had evidence of increased activity of their pretransplant hepatitis B virus infection: all four patients had liver histopathologic data showing hepatic necrosis and had seroconverted to HbeAg⁺ (3/4) when first studied and/or developed an increase in their HbsAg ratio (4/4) over that same period. This increase in hepatitis B viral replication is not particularly surprising, as increases in hepatitis B viral replication have been shown to occur in patients taking chemotherapy (39) and corticosteroids (40), as well as in those on immunosuppressive medications following renal transplantation (41-42). The fact that hepatitis B viral infection of the allograft is common (43, 44) shows not only that immunosuppressive therapy can lead to a state of increased viral replication in liver tissue, but also that it can result in the dissemination of hepatitis B virus infection to extrahepatic sites. Pancreatic involvement with hepatitis B virus has been demonstrated by the finding of hepatitis B viral antigens in pure pancreatic juice and pancreatic acinar cells of patients with chronic hepatitis B virus infection (45-46). We suggest that immunosuppressive stimulation of this pancreatic hepatitis B virus infection maybe a likely cause of the pancreatitis seen in the patients reported in this investigation. The true cause of the pancreatitis may be different for each individual case and may even be multifactoral in any given case. However, the observed association of pancreatitis with recurrent acute hepatitis B infection supports hepatitis B pancreatic infection as a possible etiologic agent responsibly for of the pancreatitis seen in the patients studied.

In summary, we reported an arithemetically greater prevalence of "pancreatitis" and a significantly increased prevalence of "hyperamylasemia" after liver transplantation in HbsAg⁺ patients as compared with patients with postnecrotic cirrhosis who are HbsAg⁻ and HbcAb or HbsAb⁺. Moreover, we find a

significant association between the development of "recurrent" acute hepatitis B infection and the development of postoperative pancreatitis in the patients studied. We suggest that the pancreatitis seen in HbsAg⁺ patients following OLTx may be caused, at least in part, by this immunosuppression and resultant accelerated hepatitis B pancreatic infection.

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