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Cholangiocarcinoma in Sclerosing Cholangitis. The Role of Liver Transplantation

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Our experience with patients who underwent orthotopic liver transplantation for sclerosing cholangitis at the University of Pittsburgh Health Center between March 1980 and March 1988 is reported here. Ten patients had an associated cholangiocarcinoma. Six of these patients died of recurrent, disseminated cancer, usually before one year. One patient died of sepsis, while three are alive and apparently free of tumor four months to almost two years later. Pre-operative identification of a possible cholangiocarcinoma and complete resection are of crucial importance. Adjuvant therapy, especially pre-transplant radiation with a prophylactic purpose is still being evaluated.

KEY WORDS: Liver transplantation - Cholangiocarcinoma - Recurrence.

Primary sclerosing cholangitis (PSC) is an unusual condition, characterized by a multiply segmental sclerosing and obliterative process involving the extra- or intrahepatic biliary tree, or frequently both.[1] Although found as a self-standing disease, it is commonly associated with inflammatory bowel disease (IBD) (mostly ulcerative colitis, or rarely Crohn's disease); the percentage of sclerosing cholangitis patients with IBD has been variously reported to be between 30 and 70%, with an average of 55%.[2 3 4 5] This disease affects men more frequently than women and it is diagnosed as a rule before the age of 50. The etiology is as yet unknown, though both an autoimmune component and a genotype predisposition seem to be suggested by the existing evidence. Immune complexes have been found in the serum of patients with sclerosing cholangitis, even in the absence of IBD,[6] while radiolabeled immune complexes have been found to be cleared more slowly from the serum of patients with PSC as opposed to normal controls.[7] Additionally, genetic studies have demonstrated what appears to be a predilection of HLA-B8 and HLA-Dr3 antigen types for development of PSC in the presence of IBD.[8]

It presents with intermittent right upper quadrant pain, fluctuating jaundice, but with a general progressive trend, increasingly bothersome pruritus, nausea and vomiting and frequently recurrent episodes of cholangitis. Although gallstones are not usually present, the gallbladder is generally abnormal, with the same inflammatory changes typical of PSC. The presence of gallstones, common duct stones or defects interpreted as evidence of choledocholithiasis will often lead to exploratory laparotomy. During the procedure, the bile duct(s) will be found difficult to cannulate or explore and an intraoperative contrast study will demonstrate the characteristic lesions. In a great number of patients, the diagnosis of irreversible liver disease will be made at this point as well.

The diagnosis is made by cholangiography (either retrograde or percutaneous transhepatic), which demonstrates the typical "beaded" bile ducts and is confirmed by biopsy, which shows the inflammatory, sclerosing process involving the ducts and the periductal tissues. Characteristically (but not exclusively), the alkaline phosphatase is elevated, while the other liver enzymes may be only marginally increased, if at all. Often, the first suspicion of biliary disease will be prompted by an incidental finding of elevated alkaline phosphatase. In advanced liver disease, the patients will have all the stigmata of end-stage secondary biliary cirrhosis, including ascites, esophageal varices, encephalopathy and hepatorenal syndrome.

The traditional treatment, either medical (D-penicillamine, [3] steroids, cholestyramine, azathioprine) or surgical (by means of various exploratory methods with drainage) [9 10] has had very poor results; in one series, 1/3 of the patients were dead within 57 months from diagnosis while another 1/3 had end-stage liver disease.[5]

During the last several years, orthotopic liver transplantation (OLTX) has emerged as the therapeutical modality of choice for a majority of the patients with advanced PSC.[11] The improved results with liver transplantation in general under a cyclosporine/prednisone regimen [12] as well as various technical refinements [13 14] have been responsible for making OLTX such a viable alternative.

In this context, one observation made by our group has been the unusually high incidence of cholangiocarcinoma (CHC) in patients undergoing OLTX for PSC.[9] While the

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increased incidence of bile duct carcinoma in IBD had already been noted,[15] there had been no emphasis on the high incidence of CHC in association with SC to our knowledge. We report here the incidence, characteristics and results with OLTX for SC in the presence of CHC.

Material and methods

One-hundred and eleven patients underwent OLTX for PSC at the University of Pittsburgh Health Center between March 1980 and March, 1988. Ten of the patients (9.1%) had CHC (Fig. 1). Three patients had known carcinoma at the time of transplantation. In the remaining seven patients, the carcinoma was an incidental finding during the pathological examination of the native hepatectomy specimen (Table I).

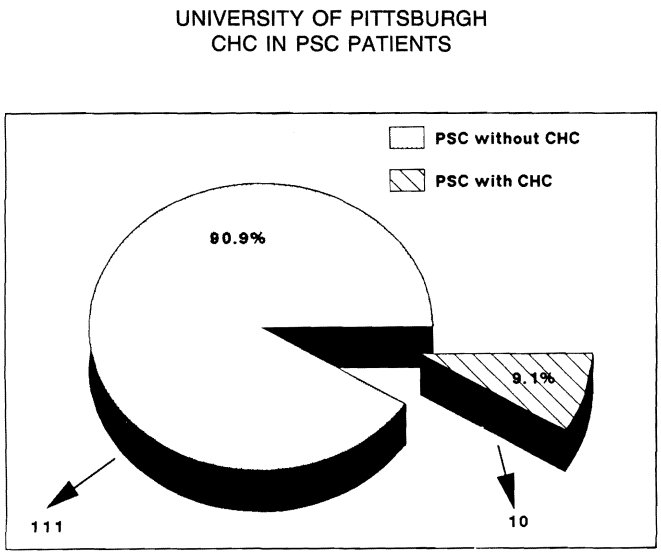

FIG. 1.—Percentages of sclerosing cholangitis patients with and without cholangiocarcinoma.

All three patients with known tumor at the time of OLTX died of recurrence four to 17 months (mean 11 months) after transplantation. Three of the patients with incidental carcinoma died of disseminated recurrent carcinoma at 4.5, 12 and 14.5 months respectively; all three had resection margin involved with tumor. A fourth patient died of sepsis 2.5 weeks after transplantation. The remaining three are still alive and apparently free of tumor four months to almost two years after the transplant (Table I).

Discussion

As evidenced by our results, the prognosis of sclerosing cholangitis patients undergoing OLTX in the presence of cholangiocarcinoma is poor (Fig. 2). This is in agreement with the results obtained with transplantation for primary bile duct carcinoma.[16,17] In our experience, none of the patients with known tumor at the time of transplantation survived. Furthermore, half of the patients with incidental tumors died within a year.

Interestingly enough, unlike non-transplant patients in whom cholangiocarcinoma is a very slowly progressing disease, that usually kills by obstructive sepsis, in our series the patients succumbed to very rapid and florid carcinomatosis. This phenomenon is explained by the fact that the immunosuppressed transplant patient cannot mount any effective anti-tumoral defence.

Post-operative treatment with radiation and/or chemotherapy has so far been clearly ineffective in preventive recurrence. On the other hand, the patients with incidental carcinoma and resection margins free of tumor seem to have a much better prognosis, though the numbers are still very small and the follow-up limited.

Based on these results, we believe that every effort must be made in order to diagnose the presence of cholangiocarcinoma pretransplant and, if the tumor is found, to try to document its extension. Repeated brush biopsies during pretransplant percutaneous transhepatic cholangiogram (PTC) or endoscopic retrograde choledochopan-

TABLE I.—*List of all the patients with cholangiocarcinoma in this series.*

Name	Age	Sex	Tumor	Tx date	Margin	Recurrence	Site(s)	Status	Interval (*)
C.P.	33	F	Known	05/13/1980	Free	Yes	Bile duct, liver, jejunum	Dead	12 months
J.N.	47	F	Known	10/08/1985	Free	Yes	Liver, bones, lungs	Dead	17 months
G.M.	35	F	Known	12/17/1985	Involved Lymph nodes Small bowel	Yes	Carcinomatosis	Dead	4 months
M.M.	24	M	Incidental	06/07/1986	Free	No	NA	Alive	24 months
P.R.	37	M	Incidental	06/09/1986	Free	No	NA	Alive	24 months
B.D.	58	M	Incidental	06/19/1986	Free	Yes	Bile duct, liver, bones	Dead	13 months
G.B.	61	M	Incidental	08/30/1986 09/03/1986	Free	Yes	Bones, liver, peritoneum	Dead	15 months
B.S.	61	M	Incidental	12/18/1986 Liver transplant Kidney transplant	Free	No	Died of sepsis on POD 6	Dead	<1 month
S.R.	56	M	Incidental	12/12/1986	Involved	Yes	Liver, bones	Dead	5 months
J.L.	42	M	Incidental (gallbladder)	01/22/1988	Free	No	NA	Alive	6 months

(*) In months to death or follow-up length.

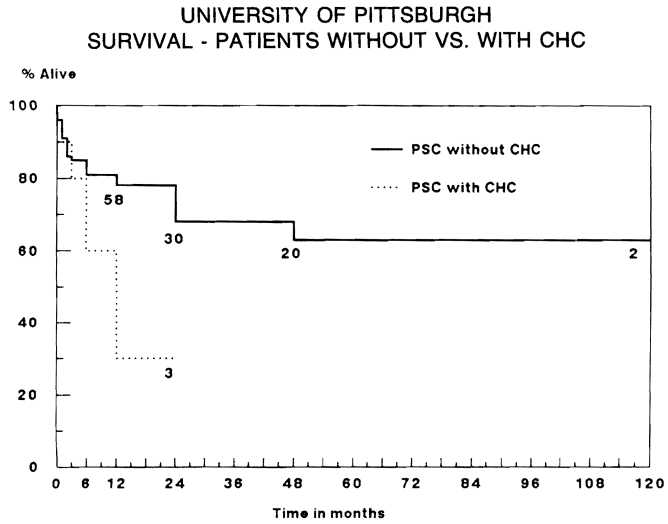

FIG. 2.—Survival of patients with cholangiocarcinoma (dotted/dash line) versus that of patients without cancer (solid line).

creatogram (ERCP) must be obtained in every patient who is being considered for liver transplantation candidacy. If a tumor is found, an attempt to evaluate the extension, via PTC or even pretransplant exploratory laparotomy with biopsy should be seriously considered, since only complete resection of the tumor may offer a chance of survival. Pretransplant radiation therapy (either by external beam or internal implantation) may play a role in allowing the resection of the tumor-involved liver and in the improvement of survival, but this approach is only now being evaluated and several more years will be needed before any firm conclusion can be drawn. Last but not least, as there seems to be a direct correlation between the duration of PSC and the higher incidence of cholangiocarcinoma, it may be justified to recommend liver transplantation at an earlier time than otherwise indicated by the patient's general condition.

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