Cholangiocarcinoma Complicating Primary Sclerosing Cholangitis

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Cholangiocarcinoma is more likely to develop in patients with primary sclerosing cholangitis. Our aims were to describe the clinical presentation, course, and management of patients afflicted with both cholangiocarcinoma and primary sclerosing cholangitis and to estimate the prevalence of cholangiocarcinoma in patients with primary sclerosing cholangitis. A retrospective analysis was conducted of 30 patients with both primary sclerosing cholangitis and cholangiocarcinoma managed at our institution during an 8-year period. Development of cholangiocarcinoma was heralded by rapid clinical deterioration with jaundice, weight loss, and abdominal discomfort. Cholangiocarcinoma complicating primary sclerosing cholangitis often was detected at an advanced tumor stage, which precluded effective therapy, and overall median survival was 5 months. Earlier recognition and treatment of cholangiocarcinoma in such patients will be necessary to increase survival rates. Seventy patients with primary sclerosing cholangitis were followed prospectively in a clinical trial of medical therapy for an average of 30 months. Twelve patients died and five were found at autopsy to have cholangiocarcinoma. The potential for cholangiocarcinoma to develop in patients with primary sclerosing cholangitis may indicate that liver transplantation should be considered earlier in the course of the disease.

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PRIMARY SCLEROSING CHOLANGITIS (PSC) is a chronic cholestatic disease characterized by obliterative inflammatory fibrosis of the bile ducts. The disease is usually slowly progressive, refractory to medical therapy, and frequently leads to cirrhosis and death from liver failure. Recent clinical observations[1] and careful pathologic study[2] suggest that cholangiocarcinoma may arise in patients with pre-existing PSC. Many clinicians, however, have been skeptical of the concurrence of these two diseases. A diagnosis of PSC often is categorically excluded by suggestions that all cholangiographic and clinical findings of PSC in patients suspected of having both diseases are explicable by the presence of multicentric or diffuse ductal cholangiocarcinoma. However histologic or autopsy evidence substantiating such claims generally have been absent. In contrast our experience with PSC suggests that cholangiocarcinoma is associated with PSC and is not uncommon.

Thus we tried to define further the association between cholangiocarcinoma and PSC. Our aims were twofold: first to describe the clinical presentation, course, and management of patients afflicted with both PSC and cholangiocarcinoma; and second to estimate the prevalence of cholangiocarcinoma in patients with primary sclerosing cholangitis.

Methods

We identified 30 patients evaluated at the Mayo Clinic between 1979 and 1987 with diagnoses of both primary sclerosing cholangitis and cholangiocarcinoma. A clinical diagnosis of PSC was supported by the following: classical radiographic features of PSC on cholangiography, elevation of the serum alkaline phosphatase to at least twice the upper limit of normal before cholangiocarcinoma development, and liver biopsy consistent with PSC. A diagnosis of cholangiocarcinoma required histologic or cytologic confirmation by biopsy or autopsy. Patient demographics, symptoms and signs, laboratory data, pathologic findings, operative management, and hospital morbidity and mortality were recorded for all patients. Follow-up was based on data abstracted from the clinical history. Patients still alive at the time of follow-up were evaluated clinically at the Mayo Clinic or were contacted by telephone or correspondence. Survival was calculated using the Kaplan–Meier product-limit method.[3]

To estimate the prevalence of cholangiocarcinoma associated with PSC, we evaluated all patients enrolled in

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a prospective clinical trial of medical therapy with D-Penicillamine (Merck Sharpe & Dohme, West Point, PA) for PSC.[4] Seventy patients were enrolled in the D-Penicillamine trial and the previously described diagnostic features of PSC were required for inclusion, with an additional requirement of established liver disease for more than 6 months' duration. Patients with intrahepatic cholangiographic abnormalities alone, cholangiographic changes highly suggestive of carcinoma, bile duct surgery or choledocholithiasis preceding the diagnosis of PSC, congenital bile duct abnormalities, a diagnosis of primary biliary cirrhosis, alcohol abuse, or a malignancy other than skin cancer were excluded. No patient was known to have cholangiocarcinoma when entered into the D-Penicillamine study. In each patient the diagnosis of cholangiocarcinoma was confirmed by biopsy or autopsy.

Results

Thirty patients, 19 men and 11 women, with a mean age of 43 ± 10 years (range, 20 to 61 years) were found to have both PSC and cholangiocarcinoma at our institution between 1979 and 1987. This group of patients included five patients who were part of the D-Penicillamine trial. The diagnosis of PSC preceded the diagnosis of cholangiocarcinoma by a mean of 52 ± 43 months (range, 0 to 165 months) in 21 patients. Twelve patients had PSC for at least 2 years before diagnosis of cholangiocarcinoma. Synchronous diagnoses were made in nine patients.

Twenty-six patients (including all nine with synchronous diagnoses of PSC and cholangiocarcinoma) had classical radiographic features of PSC on cholangiography. Four patients did not have cholangiographic confirmation of PSC but each had long-standing liver disease with elevation of serum alkaline phosphatase for 4 to 7 years before diagnosis of cholangiocarcinoma. In addition each of these patients had chronic ulcerative colitis (CUC).

Twenty-five patients (83%) had inflammatory bowel disease. Twenty-four of these patients had CUC. The diagnosis of CUC preceded the diagnosis of PSC by a mean of 18 ± 11 years for 21 patients (range, 1 to 39 years) and followed the diagnosis of PSC by a mean of 4 ± 4 years for three patients (range, 1 to 8 years). One patient had undergone proctocolectomy for Crohn's colitis 22 years before PSC development.

Symptoms

Twenty-three of thirty patients were alive when the diagnosis of cholangiocarcinoma was established. Symptoms at the time of diagnosis of cholangiocarcinoma are listed in Table 1. The most common symptoms were jaundice, weight loss, and abdominal discomfort.

Cholangiocarcinoma was detected before death for 10 of 12 patients for whom the diagnosis of PSC preceded that of carcinoma by at least 2 years. Jaundice developed rapidly in seven of these patients and was present 1 to 4 months before detection of carcinoma. Eight of these patients had weight loss of 7 to 32 pounds during the course of 1 to 6 months. During the interval between the diagnosis of PSC and cholangiocarcinoma, a twofold increase in serum alkaline phosphatase occurred in 7 of these 10 patients. No other laboratory values were found to change consistently during the interval between diagnoses.

TABLE 1. *Symptoms in Patients with PSC and Cholangiocarcinoma*

Symptoms	*Patients (n = 23)
Jaundice	18
Weight loss	16
Abdominal discomfort	14
Pruritus	12
Fatigue/malaise	12
Fever	8
Anorexia	4
Gastrointestinal bleeding	2

* Patients with diagnosis of cholangiocarcinoma at autopsy are excluded.
PSC, primary sclerosing cholangitis.

Twenty-one patients underwent operative or percutaneous liver biopsy at the time of diagnosis of cholangiocarcinoma. Histologic criteria for staging of PSC are cholangitis or portal hepatitis, stage I; periportal fibrosis or periportal hepatitis, stage II; septal fibrosis, bridging necrosis or both, stage III; and biliary cirrhosis, stage IV.[5] The extent of liver disease at the time of diagnosis of cholangiocarcinoma was stage I–1 (5%), stage II–8 (38%), stage III–6 (29%), and stage IV–6 (29%).

Diagnosis

The diagnosis of cholangiocarcinoma was established operatively in 15 patients (2 during aborted orthotopic liver transplants when lymph node metastases were discovered) and nonoperatively by percutaneous needle biopsy in 6, by laparoscopy in 1, by biopsy of subcutaneous metastases in 1, and at autopsy in 7 (including the 5 patients in the D-Penicillamine study).

Location

Cholangiocarcinomas arose intrahepatically in six patients and extrahepatically in 18 patients. The location of origin was indeterminate in six patients. The distribution of extrahepatic cholangiocarcinoma was primarily proximal, with six tumors arising at the hilus and four in the common hepatic duct. Four tumors arose in the common bile duct, and four tumors arose in the gallbladder or cystic duct. Three patients had clear evidence for multicentric

cholangiocarcinoma: separate lesions in remote locations confirmed by biopsy.

Metastases

Nineteen patients (63%) had metastatic disease present at the time of diagnosis of cholangiocarcinoma. Fourteen patients (47%) had intra-abdominal metastases only, and five patients (16%) had both intra- and extra-abdominal disease. Locations of metastases are listed in Table 2.

Seventeen patients underwent abdominal exploration (two subsequent to percutaneous biopsy) and eight patients were found to have intra-abdominal metastatic disease. Six patients had involvement of regional (choledochal, hepatic artery, and celiac trunk) lymph nodes; one had multiple hepatic metastases, and one had peritoneal carcinomatosis.

Treatment and Survival

Overall median survival was 5 months following the diagnosis of cholangiocarcinoma, excluding seven patients with autopsy diagnosis and two patients lost to follow-up (Fig. 1). Survival with respect to treatment is depicted in Figure 2.

Only one patient underwent potentially curative resection. This 32-year-old woman had a cholangiocarcinoma in the common bile duct and is alive and free of disease 26 months after pancreatoduodenectomy. She had no regional lymph node involvement.

Seven patients (one lost to follow-up) underwent palliative resection. Resection was incomplete due to involvement of the bile duct at the margin of resection in five patients. One patient with regional lymph node involvement underwent palliative left lateral hepatectomy and is alive after 2 months. The remaining patient had multifocal disease with low-grade carcinoma present in the distal common bile duct and right hepatic duct. A palliative resection of the distal common bile duct lesion was performed, but the patient had advanced cirrhosis and died from gastrointestinal hemorrhage 3 months later. Median survival after palliative resection was 10 months.

TABLE 2. *Site of Metastases Present at Time of Diagnosis of Cholangiocarcinoma in Patients with PSC and Cholangiocarcinoma*

Site	No. of Patients
Regional lymph nodes	13
Liver	7
Lung	2
Skin	2
Peritoneum	1
Bone	1

PSC, primary sclerosing cholangitis.

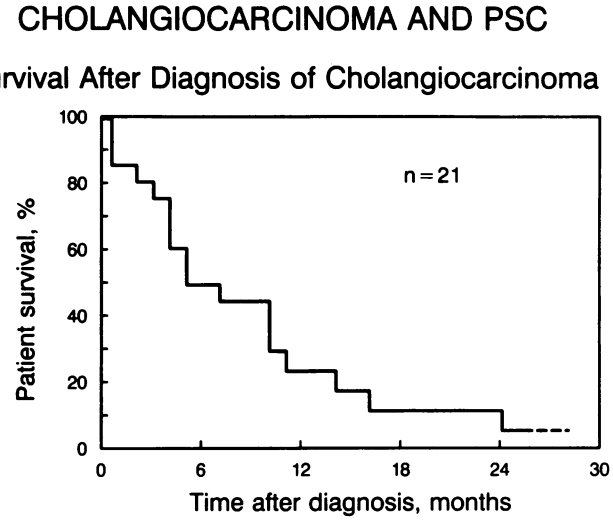

FIG. 1. Survival after diagnosis of cholangiocarcinoma.

Four patients received radiotherapy after palliative resection. One was lost to follow-up and the others survived 7, 10, and 16 months.

Nine patients had palliation of bile duct obstruction by intubation techniques (operative, endoscopic, and percutaneous) and had a median survival time of 5 months. Two patients received external beam radiation therapy; one survived 14 months, and the other is alive after 1 month. One patient received intraoperative and external beam radiotherapy and survived 24 months.

Six patients (one lost to follow-up) had advanced disease that was not amenable to operative palliation or intubation. They had a median survival of 4 months. Two received radiotherapy and survived 4 and 10 months.

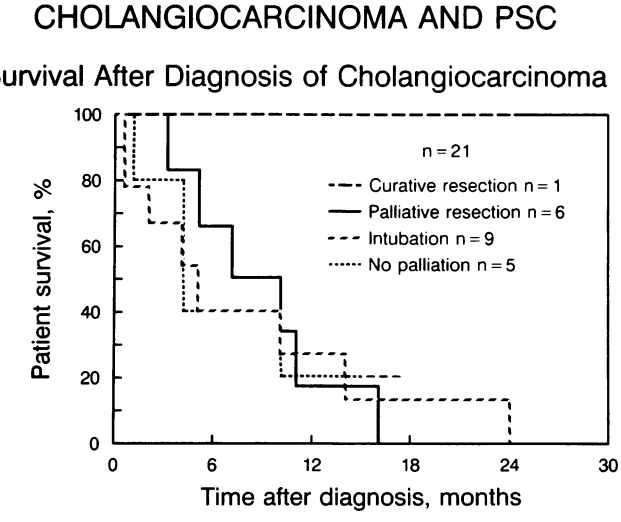

FIG. 2. Survival after diagnosis of cholangiocarcinoma by treatment modality.

Prevalence

Seventy patients with PSC were followed prospectively for a mean of 30 months in a randomized trial of medical therapy with D-Penicillamine. During this period, 15 patients died. All died with liver failure and 12 had autopsies. Cholangiocarcinoma was found at autopsy in five of these cases. No patient in the study had a diagnosis of cholangiocarcinoma made while alive. Thus cholangiocarcinoma occurred in at least 7% (5 of 70) of the patients in the study and in 42% (5 of 12) of the autopsied patients. All five patients with cholangiocarcinoma had advanced PSC with cirrhosis and portal hypertension at the time of death and all five patients had long-standing chronic ulcerative colitis (mean duration, 20 years). Patients with cholangiocarcinoma and PSC tended to be older (mean, 50 *versus* 38 years, $p = 0.06$, two-tailed t test) and tended to have had chronic ulcerative colitis longer (mean, 20 *versus* 8 years, $p = 0.05$, two-tailed t test) than patients with PSC alone. Other clinical and biochemical information did not distinguish in which patients cholangiocarcinoma would be more or less likely to develop.

Discussion

The results of our study suggest an association between PSC and cholangiocarcinoma. Cholangiocarcinoma frequently arose in patients with PSC and was heralded by rapid clinical deterioration with progressive jaundice, weight loss, and pain. Cholangiocarcinoma occurring in the setting of PSC was nearly always detected at an advanced stage that precluded potentially curative resection. Therapeutic options were limited and survival was short.

Many clinicians have considered concurrent diagnoses of PSC and cholangiocarcinoma to be mutually exclusive. This attitude is based on the premise that the characteristic cholangiographic and clinical features of PSC are explicable by the presence of diffuse infiltrating ductal cholangiocarcinoma. However there is little evidence to support this premise. Cholangiocarcinoma is, indeed, capable of extensive periductal infiltration but spread of tumor is usually radial from its origin and is limited radially to 5 cm.[6] Diffuse cholangiocarcinoma, which can masquerade as PSC with a similar extrahepatic and intrahepatic radiographic appearance, is distinctly uncommon. Extensive periductal infiltration was present in only 4 of 22 patients with sclerosing cholangiocarcinoma in the series reported by Weinbren and Mutum.[6] Furthermore long-term survival after onset of symptoms of hepatobiliary disease, extending for 20 years in some of our patients, is inconsistent with our knowledge of the natural history of cholangiocarcinoma with an expected survival range of 6 to 12 months for most patients after diagnosis.[7] Clearly cholangiocarcinoma that is cholangiographically similar to PSC represents an advanced stage with an expected short survival time and, therefore, categorically excluding the diagnosis of PSC is inconsistent with these findings.

Conversely there is pathologic evidence that cholangiocarcinoma may arise in the setting of PSC. Wee et al.[2] demonstrated histologic changes of PSC distant from malignant areas and the presence of carcinoma *in situ* in areas with fibrous cholangitis in patients with long-standing hepatobiliary disease and CUC. The relationship between cholangiocarcinoma and chronic ulcerative colitis (CUC) is well known. Studies by Ritchie et al.[8] and Akwari et al.[9] demonstrated that the incidence of cholangiocarcinoma in patients with CUC far exceeded that in the general population. Furthermore a recent study from the Cleveland Clinic estimated that the relative risk of cholangiocarcinoma developing in patients with CUC was 31.3 times greater than the risk to the general population.[1] We believe that this increased risk is due to the concomitant presence of PSC. Indeed, in the study by Wee et al.,[2] which re-examined the patients studied by Akwari et al.,[9] cholangiocarcinoma was never found in the absence of PSC.

We found that cholangiocarcinoma was present in at least 7% (5 of 70) of the patients and 42% of the autopsied patients with PSC followed prospectively for an average of 30 months. Although surprisingly high, these figures probably underestimate the true incidence of cholangiocarcinoma in patients with PSC. Because cholangiocarcinomas in the D-Penicillamine study were found only at autopsy, it is possible that additional tumors remain undetected.

Although our estimate of prevalence may have been influenced by a referral bias to our tertiary care center, other studies also have recognized a similar prevalence of cholangiocarcinoma arising in patients with PSC. Chapman et al.[10] reviewed 29 patients with PSC. Eleven of these patients died with a mean survival of 7 years from the time of diagnosis, and three were found to have cholangiocarcinoma. Similarly Aadlund et al.[11] reported cholangiocarcinoma in 4 of 45 patients (8.9%) with PSC. All were found at autopsy with a frequency of 33% (12 autopsies). Marsh et al.[12] recently reported the University of Pittsburgh experience with orthotopic liver transplantation for PSC. Five of fifty-five patients (9%) were found to have previously unrecognized cholangiocarcinoma at the time of transplantation. This prevalence of cholangiocarcinoma in patients with PSC is strikingly similar to our own.

We fully recognize that the clinical distinction between patients with both PSC and cholangiocarcinoma and those with PSC alone is often difficult. Although jaundice, weight loss, and abdominal discomfort were present in 75%, 70%, and 61% of the patients with both diseases, these symptoms are not specific and occur in a similar proportion of patients with PSC alone.[10,13] Our impres-

sion, however, is that cholangiocarcinoma in patients with PSC may be heralded by more rapid clinical and biochemical deterioration than we have seen with PSC alone. Increasing jaundice and decreasing clinical performance status often prompted hepatobiliary imaging, which led to intervention and diagnosis in some of our patients.

We could not identify any laboratory features that reliably indicated the presence of cholangiocarcinoma in patients with PSC. Serum alkaline phosphatase tended to increase during the interval between the diagnosis of PSC and cholangiocarcinoma when an interval existed, but this change was not consistent. Similarly the histologic stage of PSC did not correlate patients with cholangiocarcinoma. The distribution of cholangiocarcinoma between stage II, III, and IV disease was nearly equal. Lack of correlation to the stage of PSC is not surprising given the variable natural history of PSC.[13]

The prognosis for patients with PSC and cholangiocarcinoma is poor. Median survival was only 7 months following the diagnosis of cholangiocarcinoma. Survival was short because of the advanced stage of cholangiocarcinoma at the time of diagnosis. Metastatic disease was common and was present in 63% of the patients at the time of diagnosis. Metastases or local extent of disease precluded potentially curative resection in all but one patient.

Clearly there is a need for earlier detection and effective therapy for patients in whom cholangiocarcinoma develops in the setting of PSC. Operative resection may be effective in few patients. Delayed diagnosis, tumor multicentricity, and advanced stage of disease frequently preclude potentially curative resection. Earlier diagnosis aided by screening or heightened clinical awareness could improve the effectiveness of operative resection. However survival rates may remain poor due to the natural history of PSC, and operative intervention has not been shown to retard the clinical progression of PSC.

Orthotopic liver transplantation is the only therapeutic alternative that offers both radical eradication of tumor and a potential cure for PSC. However recurrent disease developed within 1 year in three of five patients who underwent liver transplantation for both PSC and cholangiocarcinoma in the University of Pittsburgh experience.[12] Thus until we are better able to detect cholangiocarcinoma arising in the setting of PSC or to predict its development, it may be better to offer liver transplantation earlier for patients with PSC. Whereas the indications for liver transplantation now are based on clinical criteria for patients with PSC, the potential for cholangiocarcinoma to develop may now be an indication for considering earlier intervention.

We believe an association clearly exists between PSC and cholangiocarcinoma. We wonder whether the chronic inflammatory process of PSC predisposes bile duct epithelium to malignant transformation. The association of chronic inflammation and gastrointestinal carcinoma is not unique. Chronic inflammation caused by cholelithiasis[14] and *Clonorchis sinensis*[15] have been associated with carcinoma of the gallbladder and bile ducts, respectively. Because PSC so often occurs in patients with CUC, we wonder whether similar mechanisms of carcinogenesis for colon cancer with CUC and bile duct cancer with PSC exist. Further studies are needed to define the association between PSC and cholangiocarcinoma and to determine if PSC is a premalignant condition.

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