Cholangiocarcinoma: A decade's experience at a community-based university hospital

ANDREW SZILAGYI, MD, FRCPC, BENJAMIN MITMAKER, MD, PHD, FRCSC, ESTHER LAMOUREUX, MD, FRCPC

ABSTRACT: Two young patients with cholangiocarcinoma associated with salmonella carriage and ulcerative colitis, respectively, were seen at a community-based university hospital. This experience prompted a review of all cases with this tumour seen in the past decade. Twenty-seven patients were found. Their clinical, laboratory, and histological features, and therapeutic outcome are described. Of the group, only 7.4% were younger than 30 years of age and 14.8% had recognized associated conditions. The most common definable tumour was a well differentiated hilar cholangiocarcinoma. Overall outcome was poor (six months). Survival was similar in patients undergoing palliative stents or surgery. In a small subgroup of surgically treated patients who received either radiotherapy or postoperative drainage, survival seemed to be better. **Can J Gastroenterol 1990;4(2):65-69**

Key Words: *Cholangiocarcinoma, Outcome, Salmonella, Ulcerative colitis*

Cholangiocarcinome

RESUME: Deux jeunes patients atteints d'un cholangiocardinome associédans un cas à l'état de porteur de salmonella, et dans l'autre à une rectocolite hémorragique, ont été remarqués dans un centre hospitalier universitaire dispensant les soins de santé communautaire. Cette expérience a entraîné une revue de tous les cas où une tumeur de ce type avait été relevée au cours des dix dernières années. Vingt-sept patients ont été recensés. Leurs caractéristiques cliniques et histologiques, les résultats des examens de laboratoire et les résultats thérapeutiques sont décrits. Dans ce groupe, 7,4% seulement des sujets étaient âgés de moins de 30 ans et 14,8% présentaient des conditions associées reconnues. La tumeur identifiable la plus courante était un cholangiocarcinome hilaire bien différencié. Dans l'ensemble, le pronostic était sombre (six mois). La survie était la même chez les patients ayant fait l'objet de mesures palliatives ou d'interventions chirurgicales. Dans un petit sous-groupe de patients ayant reçu un traitement chirurgical – radiothérapie ou drainage postopératoire, la survie semblait meilleure.

Department of Medicine, Divisions of Gastroenterology and Pathology; and Department of Surgery, Sir Mortimer B Davis Jewish General Hospital, McGill University, Montreal, Quebec

Correspondence and reprints: Dr A Szilagyi, 6000 Côte-des-Neiges, Suite 100, Montreal, Quebec H3S 1Z8.

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CHOLANGIOCARCINOMA IS THE second most common malignancy after primary hepatocellular carcinoma that affects the liver and biliary system. Surgical experience with such a neoplasm is limited, although the literature is relatively extensive on the subject. Treatment of this malignancy remains poor, despite the general trend towards a more aggressive surgical approach. A greater clinical awareness coupled with the newer investigative modalities for the biliary tract might conceivably find earlier lesions that are amenable to surgery and improve the dismal prognosis.

Clinical experience with two young men who developed cholangiocarcinoma in association with salmonella carriage and inflammatory bowel disease prompted a review of the general experience with these neoplasms at a community-based university hospital over the previous decade. Presentation, associated illness, and management of these cases reflect the current experience in the literature.

PATIENTS AND METHODS

The case histories of two patients are summarized. A computer-assisted search of medical records from January 1978 to August 1988 was conducted at the Sir Mortimer B Davis Jewish General Hospital. Charts were ac-

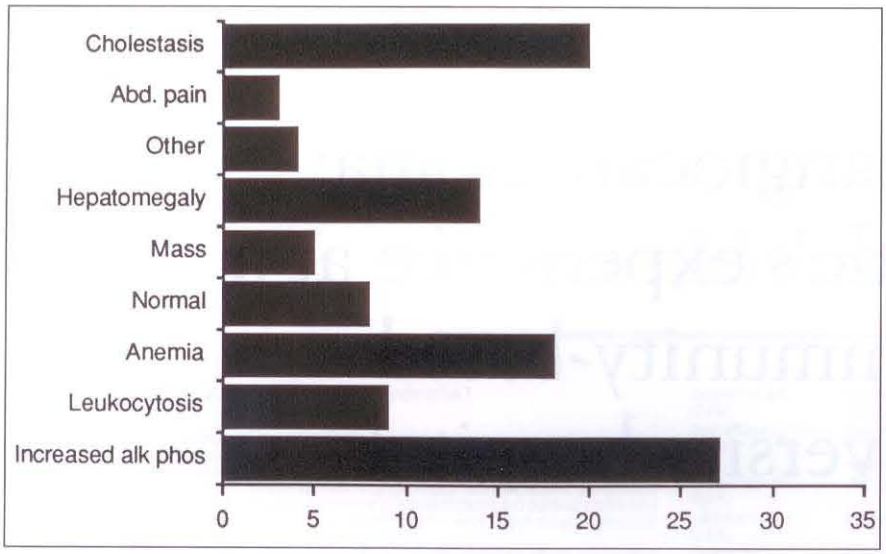

Figure 1) *The initial presenting clinical and laboratory features of 27 patients. 'Other' features refer to migratory thrombophlebitis (one patient), fatigue (one patient), shortness of breath (one patient) and hemoptysis (one patient). 'Normal' refers to normal physical findings*

cepted for review with the diagnosis of biliary duct cancer or cholangiocarcinoma. A database was constructed including age, sex, date of diagnosis, discharge, length of follow-up, surgery, types of underlying disease, clinical presentation, physical findings, preoperative laboratory values, biopsy or autopsy findings and any other modality of therapy. Available pathological material was reviewed by one of the authors to ensure the correct diagnosis. Statistical analysis was carried out by using Wilcoxon Rank Sum test. Significance was accepted when $P<0.05$.

CASE ONE

A 22-year-old Indonesian man complained for three weeks of recurrent epigastric and right upper quadrant pain. Two weeks prior to admission he became jaundiced. Medical history included extensive travel in southeast Asia and the Pacific islands. Six months prior to admission he was treated for syphilis. On admission, he was normotensive, afebrile and jaundiced. Abdominal palpation revealed mild epigastric and right upper quadrant tenderness without hepatomegaly. Stools were positive for occult blood. Biochemistry showed a total bilirubin of 168 nmol/L with a 66% conjugated fraction. Alkaline phosphatase was 225 iu/L while the serum aspartate aminotransferase was 55 iu/L. The hemoglobin was 126 g/L, white count was 7.1 x 10^9/L and coagulation studies were normal. Hepatitis B surface antigen test was negative.

Subsequent stool cultures were positive for salmonella group C, and two ova of *Ascaris lumbricoides* were detected. Radiological investigation revealed a normal chest x-ray. An abdominal ultrasound showed dilated intrahepatic ducts confined to the left lobe. An abdominal computerized tomography scan confirmed these findings. Retrograde cholangiography could not better define the lesion. A bone scan and a barium meal were reported as normal.

The patient was taken to the operating room, where a polypoid tumour of the distal common bile duct was localized. This lesion was found to extend to the hilum. Pathology confirmed a well differentiated, mucin-producing, papillary adenocarcinoma with regional lymph node metastases showing a desmoplastic reaction. Stains on histology for markers of hepatitis B were negative. The tumour was not resectable and a cholecystectomy and choledochojejunostomy/gastrojejunostomy with enteroenterostomy were carried out. Cultures of bile at the time of surgery also grew salmonella group C. No parasites were found.

The postoperative course was complicated by a febrile episode; however, urine and blood cultures were negative. He was subsequently discharged and returned one month later to Indonesia.

CASE TWO

A 21-year-old immigrant from Romania presented after a seven week history of vague right upper quadrant pain and mild weight loss. He had a six year history of poorly controlled ulcerative colitis until one year prior to admission, when his symptoms improved on sulfasalazine. A barium enema and flexible sigmoidoscopy at that time confirmed the diagnosis. Two weeks prior to admission, physical examination and abdominal ultrasound were normal. However, biochemistry showed marked anicteric cholestasis. He was subsequently admitted for work-up of this abnormality.

On physical examination, vital signs were normal. He was somewhat cachectic and the liver edge was now palpable 2 cm below the costal margin. Stools were negative for blood.

Biochemistry revealed an alkaline phosphatase of 116 iu/L, gamma-glutamyl transpeptidase of 404 iu/L and bilirubin of 15 µmol/L. Hemoglobin was normal. Hepatitis B surface antigen was negative.

An hepatobiliary scintigraph revealed incomplete emptying of the right lobe. A liver-spleen scan showed hepatomegaly and a possible mass in the region of the porta hepatis. An abdominal computed tomography scan revealed an extensive hypodense area in the right lobe. He refused endoscopic cholangiography.

At surgery, the entire right lobe of the liver was found to be replaced by tumour. There were numerous metastatic nodules to the peritoneum as well as lymph node masses at the root of the mesentery. Biopsies of the liver, nodules and lymph nodes confirmed the presence of a well differentiated adenocarcinoma consistent with bile duct origin.

He made an uneventful recovery

TABLE 1
Disease processes associated with cholangiocarcinoma in 27 patients under review

Gallstones	5 patients
Salmonella carriage	2 patients
Ulcerative colitis	1 patient
Choledochal cyst	1 patient
Linitis plastica	1 patient

One of these patients also had previous bronchogenic cancer 11 years previously

following surgery, and refused any adjuvant radiotherapy. He died seven months after diagnosis was established. An autopsy was refused.

HOSPITAL EXPERIENCE

Twenty-seven patients including the two index cases were collected from the decade under review. Their demographic features are shown in Figure 1. Only two patients were younger than 30 years old (the present cases).

Although most patients noted jaundice or pruritus, abdominal pain was not prominent initially. However, pain was exacerbated as the disease progressed. Four patients presented with symptoms or findings other than those focused on the biliary tract. One of these patients presented with a migratory thrombophlebitis for two months prior to admission. Another patient presented with a chief complaint of progressive fatigue. Two patients presented with symptoms referred to the respiratory tract, progressive shortness of breath and hemoptysis. On physical examination, 19 patients had hepatomegaly or a mass and eight had normal findings. On biochemistry, all 27 patients exhibited features of cholestasis. The majority were anemic and one-third had leukocytosis. However, there were no patients with sepsis.

A search for associated conditions in this group of patients revealed 10 with such features (Table 1). In addition to salmonella infection and inflammatory bowel disease, one patient had a previously resected choledochal cyst. A 65-year-old woman had both salmonellosis in the past and a bronchogenic carcinoma surgically treated 11 years earlier. A 74-year-old woman had concomitant linitis plastica which was clearly differentiated from another primary biliary tract tumour. No patient had concomitant cirrhosis of the liver, but five had previous cholecystectomies.

The anatomic origin of cancer could be clearly distinguished in only 16 of the 27 cases (Table 2). Microscopic diagnosis was established in 18, of which 17 were reviewed by a second pathologist. In cases where it was not possible to make a histological confirmation, the diagnosis was based on a combination of radiological and intraoperative observations.

The types of treatment given and their outcomes are listed in Table 3. There was no significant difference in survival between patients who were treated by stent or surgery alone. Of the 15 surgical procedures, two patients with attempted resection were lost to follow-up one month post surgery. The remaining operative procedures consisted of the Longmire operation (10 patients), left hepatic lobar resection (one patient), a Whipple's operation (one patient) and multiple bypass procedure (one patient). Of these 13 patients, three also received 4000 rads of cobalt therapy, and two had additional drainage procedures at a later date postoperatively. Although there were no apparent clinical differences with regard to age, clinical presentation and pattern of tumour at surgery, survival in this subgroup was significantly better than in the other eight patients who underwent attempted resection without other interventions (P=0.045). One patient who survived 15 months received only chemotherapy because of extensive liver invasion. Five patients received no specific therapy. Three patients died within several days to a month of diagnosis. One patient was lost to follow-up two months after diagnosis of extrinsic liver spread. Case 2 died seven months after diagnosis.

TABLE 2
Pathological features of cholangiocarcinoma

Anatomic distribution		Microscopic diagnosis	
Main duct	3 patients	Well or moderately differentiated	15 patients
Klatskin (hilar)	9 patients	Poorly differentiated	1 patients
Peripheral	4 patients	Papillary	2 patients
Undeterminable	11 patients	No pathology	9 patients*

** Diagnosis based on a combination of clinical (computed tomography, ultrasound, endoscopic retrograde cholangiopancreatography or transhepatic cholangiography) and intraoperative features*

DISCUSSION

There are three features of interest in this study. First, the two case reports highlight possible contrasts between younger and older patients with cholangiocarcinoma. Second, the series raises discussion about possible underlying illnesses which may predispose to cholangiocarcinoma. Finally, treatment and outcome in this series can be compared with the current experience in the literature.

In the present series, 7.4% of patients were younger than 30 years old, and the mean age was 65.1, comparable with that found in the literature (1-6). Although there was more associated illness, the outcomes in the two young patients were not different from the group.

TABLE 3
Outcome of cholangiocarcinoma by therapeutic intervention

Therapy	No of patients	Survival in months (range)
Nil	4	1.8 (0.06-7)
Stent only	6	7.2 (1.25-12)
Chemotherapy (mitoxantrone)	1	15
Surgery only	8	5.4 (0.5-19)
Surgery and radiotherapy	3	20.4 (6.3-33)
Surgery with late drainage	2	8 (7-9)

Three of 27 patients were lost to follow-up. One patient received no therapy due to extensive disease and two patients who underwent Longmire procedures were lost to follow-up one month postoperatively

TABLE 4
Diseases known or suspected of association with cholangiocarcinoma

Diseases	References
Anatomical abnormalities or surgical procedures	
Choledochal cyst	4,19-21
Choledochoenteric anastomoses	35
Liver cyst, congenital hepatic fibrosis	10
Caroli's disease	10
Biliary atresia	10, 36
Inflammatory conditions	
Ulcerative colitis	11,12,37,38
Crohn's disease	13,14
Sclerosing cholangitis	15
Infectious	
Clonorchis sinensis	9, 10
Opisthorchis viverrini	9
Salmonella	16, 18
Radiographic agents	
Thorotrast	39
Other liver diseases	
Hemochromatosis	7
Cirrhosis	7
Hepatolithiasis	8

Previously associated conditions are listed in Table 4. The prevalence of 14.8% noted in the present series compares well with the 10% quoted in the literature for North America (7). Although gallstones and other cancers were noted at 25.9% in the present series, these conditions (with the exception of hepatolithiasis) are not thought to predispose to biliary cancer (26). In southeast Asia, liver flukes are also considered important (8-9).

Association with ulcerative colitis is well established and estimated to be 0.4 to 1.6% (11,12). Recently, cholangiocarcinoma was also described in Crohn's disease (13,14). While sclerosing cholangitis is considered an antecedent, it is not a requirement (15). As well, the tumour has a variable time course with inflammatory bowel disease activity.

Salmonella carriers appear to have a higher risk for biliary cancer (16,17). However, the best documentation for progression to cholangiocarcinoma from the carrier state occurs in a single case report (18). Case 1 was likely a carrier, since both stool cultures and bile cultures were present with the same strain of salmonella in the absence of acute gastrointestinal symptoms. Furthermore, no other associated conditions were found. the authors are not aware of ascaris causing this neoplasm, and no eggs or worms were found at surgery.

Although choledochal cysts usually present in childhood (4,19), as in the single case, up to 20% may occur in adults (4,20). A triad of right upper quadrant mass, pain and intermittent jaundice occurs in 20% (21). Cholangiocarcinoma may occur in any portion of the dilated biliary tree and usually arises following incomplete surgical manipulation (4).

TREATMENT AND OUTCOME

Prognosis is poor, and dependent on factors listed in Table 5 (1,7,10,22). Surgical management is dictated by site, with distal lesions being more amenable (23,24). In general, 15 to 61% of tumours are resectable. While 100% of distal sites are amenable to surgery, only 33 and 10% of lesions, respectively, located in the middle or hilar biliary tree, are thus manageable (3,22-24). More recently, an aggressive approach for hilar lesions, including anastomosis of the intrahepatic ducts with a defunctional enteric link, has had a marginal impact on survival (5,25-27). In the current series, resection was attempted in only 48%, although two-thirds of the patients had surgery. The finding that the majority of tumours (56%) were in a hilar location contributed to the low rate of attempted resection.

Polypoid (28) and squamous cell cancers (29) both appear also to contribute to better survival than nodular, sclerosing or diffusely infiltrating types.

In the hope of avoiding high postoperative morbidity and mortality there is a search to better define resectability. While Comprodon (6) outlined an intraoperative approach prior to attempted resection, the increased use of nondirect visualization of the biliary tree recently prompted Lynn et al (30) to outline a radiological approach. In the latter study, proximal and mid duct tumours proved unresectable. These results, however, need to be better refined in view of the 10 and 33% respective resectability rates reported by Alexander et al (3) for the same lesions. Furthermore, in cases where resection is not possible, either endoscopically or surgically placed stents appear to improve quality of life over more definitive surgically palliative operations (31,32).

TABLE 5
Variables determining survival in cholangiocarcinoma

Location in biliary tree
Surgical resectability with or without hepatic resection
Gross appearance of tumour
Presence of metastases
Palliative potential – surgical, percutaneous, endoscopic
Use of radiotherapy
Use of chemotherapy

Other modalities of therapy are not well established. Iridium or cobalt therapy can prolong median survival to 11 months (1). However, morbidity is substantial. Iwasaki (30) reported that intraoperative electron beam radiation resulted in a 17% two year survival versus 9% without such treatment (38).

Single agent therapy with mitomycin C or 5-fluorouracil, or combination with bis-chloronitrosourea, adriamycin and ftorafur showed a 30% response rate and a median prolongation of survival by 9.5 months (1). In another small study, external radiation was combined with adriamycin, 5-fluorouracil and ^{131}I labelled anti-carcinoembryonic antigen. However, only 7.4% complete and 25.9% partial remissions were achieved (34). No unified consensus of opinion exists on the use of such therapy at this time.

CONCLUSION

In summary, cholangiocarcinoma remains a poorly treatable neoplasm. The present survey found 14.8% of patients to have associated predisposing disease, and another 25.9% gallstones or other cancers occurring synchronously or metachronously. In this series, two patients were younger than 30 years old. Both had associated conditions and their courses were not dif-

ferent from the rest. In the survey, 48% of patients were resected, and there is a possibility that perioperative radiotherapy may be useful. The literature review also suggests that at this time surgical resection of well defined lesions offers the best chance for prolonged survival. The role of adjuvant therapy, although hopeful, is not settled.

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