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Hepatolithiasis-associated cholangiocarcinoma: Results from a multi-institutional national database on a case series of 23 patients

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Abstract

Aims: Few papers focused on association between hepatolithiasis (HL) and cholangiocarcinoma (CCC) in Western countries. The aims of this paper are to describe the clinical presentation, treatment, and postoperative outcomes of CCC with HL in a cohort of Western patients and to compare the surgical outcomes of these patients with patients with CCC without HL.

Materials and methods: Among 161 patients with HL from five Italian tertiary hepato-biliary centers, 23 (14.3%) patients with concomitant CCC were analyzed. The results of surgery in these patients were compared with patients with CCC without HL.

Results: The 60.9% of patients with HL received the diagnosis of CCC intra- or postoperatively, with a resectability rate of 91.3%. The post-operative morbidity was 61.6%. The 1- and 3-year survival rates were 78.6% and 21.0%, respectively. The recurrence rate was 44.4% and the 3-year disease-free survival rates were 18.8%. The comparison with patients with CCC without HL showed a higher resectability rate ($p = 0.02$) and a higher frequency of earlier stage ($p = 0.04$) in CCC with HL. Biliary leakage was more frequent in CCC with HL group ($p = 0.01$) compared to CCC without HL group. We found no differences in overall and disease-free survival between the two groups.

Conclusions: Patients with HL and CCC showed a high resectability rate but a higher morbidity. Nevertheless, overall and disease-free survival of patients with CCC and HL showed no differences compared to those of patients with CCC without HL. Also in Western countries, HL needs a careful management for the possible presence of CCC.

Keywords: Cholangiocarcinoma; Hepatolithiasis; Liver surgery

Introduction

Cholangiocarcinoma (CCC) is the second most common primary liver cancer.[1] Several risk factors have been identified for the development of CCC, including primary sclerosing cholangitis, choledochal cysts, Caroli's disease, and liver fluke infection. Hepatolithiasis (HL) is associated with a high incidence of CCC and it is one of the major risk factors for the development of CCC.[1–3] The incidence of

Abbreviations: HL, hepatolithiasis; CCC, cholangiocarcinoma.

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HL shows a regional distribution, with a greater prevalence in South-East Asian countries. In contrast, HL is fairly uncommon in Western countries with an incidence to 1.3%.[4,5]

Epidemiological, pathological, and genetic studies have seemed to prove the relationship between HL and CCC. It has been suggested that biliary carcinogenesis is caused by prolonged inflammation of the biliary epithelium secondary to biliary stones, bile stasis, and bacterial infections.[6]

In the literature, few papers have focused specifically on the association between HL and CCC in Western countries.[7–9] No data are available on the clinical presentation, treatment, and outcome of patients with both conditions.

The aim of the present paper is to describe the clinical presentation, treatment, and postoperative outcomes of CCC associated to HL in a cohort of patients recruited from a multi-institutional database from tertiary referral centers. Moreover, the long-term results of surgical resection in these patients were compared with the results in patients with CCC without HL.

Material and methods

From January 1st, 1997 to December 31st, 2011, 161 patients affected by HL were recruited prospectively in five Italian tertiary hepato-biliary centers (Department of Surgery, Division of General Surgery 'A', GB Rossi Hospital, University of Verona, Verona; Department of Hepato-Biliary–Pancreatic and Digestive Surgery, Ospedale Mauriziano 'Umberto I', Turin; Department of Surgery – Liver Unit, Scientific Institute San Raffaele, Milan; Hepatobiliary Surgery Unit, Department of Surgery, Catholic University of the Sacred Heart School of Medicine, Rome; Department of Surgery and Organ Transplantation, Ospedale Sant'Orsola-Malpighi, University of Bologna, Bologna). All the institutions are members of the Italian Chapter of the International Hepato-Pancreato-Biliary Association (IHPBA). From this dataset, 23 (14.3%) patients with concomitant CCC were included into this study. The diagnosis of CCC was pathologically confirmed in all patients.

We defined HL as concretions existing in the intrahepatic bile ducts. Although the confluence of the hepatic ducts is situated outside of the parenchyma of the liver, for convenience we included in this study HL of any bile duct proximal to the confluence of the right and left hepatic ducts, as reported by other Authors in literature.[10]

The following clinical variables were analyzed: age; gender; symptoms; medical history (previous operations on the bile duct, liver fluke infestation, underlying hepatic disease); clinical characteristics of HL (location, time between diagnosis and treatment); laboratory data including serum bilirubin, gamma-glutamyl transferase , preoperative liver function test (indiocyanine green retention rate), presence of tumor markers, histological differentiation, lymph node involvement, and the presence of metastasis. The imaging modalities that were used for the diagnosis of CCC were recorded and analyzed.

After surgery, a computed tomography or magnetic resonance scan was performed every three or six months for follow-up examination of the patients. One patient was lost to follow-up, and the median duration of follow-up was 15 months (range 3–121 months).

To evaluate the long-term results of surgical resection of CCC associated with HL, we compared the results of surgery on our cohort with those for a cohort of 414 patients submitted to surgical resection for CCC without HL (peri-hilar or intrahepatic). The data of patients affected by CCC without HL were obtained from a multi-institutional database held by two of the five hepato-biliary tertiary centers (Verona and Bologna) during the same time period. The median follow-up period in these patients was 18 months (range 3–275 months).

Statistical analysis

The data were collected and analyzed with the statistical software SPSS (version 18.0; SPSS, Chicago, Ill., USA). Continuous variables were compared using an independent two sample *t*-test. The differences between categorical variables were analyzed with Pearson's chi-squared test. Survival analyses and survival plots were carried out using the Kaplan–Meier method. We considered the day of treatment to be time zero, and data from patients alive at the end of the follow-up period were considered to be censored. Univariate analyses of survival were performed with the Kaplan–Meier method, using the log-rank test to verify the significance of differences. Multivariate analysis of survival was carried out with Cox's regression model. A value of $p < 0.05$ was considered significant.

A propensity score match analysis (1:3) was performed between patients with HL and CCC and patients with CCC alone in order to better define the prognostic value of HL in patients with CCC.

Results

Demographic data

Among the 161 patients with HL observed during the study period 23 with CCC (14.3%) were included into the study. Among these, 14 were men and 9 were women with a mean age of 63.9 years (range 42–82 years). The patients' characteristics are described in detailed in Table 1. The clinical features are summarized in Table 2. No differences were found between these patients and patients with CCC alone.

Symptoms at presentation

The mean time from the diagnosis of HL and of malignancy was 61.2 months (range 1–372 months). Seventeen patients (73.1%) developed symptoms due to HL before the diagnosis of CCC. The mean time span between the onset of symptoms and diagnosis of CCC was 17.3 months (range 0–72 months). In most cases HL patients were