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Differentiation of benign and malignant hilar bile duct stenosis

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ABSTRACT

Background: Failure to differentiate benign and malignant hilar bile duct stenosis may lead to inappropriate treatment. We retrospectively analyzed the methods for differentiation.
Materials and methods: A total of 53 patients with hilar bile duct stenosis were included, comprising 41 malignant cases (hilar cholangiocarcinoma) and 12 benign cases (six primary sclerosing cholangitis and six IgG4-associated sclerosing cholangitis). Data of clinical histories, laboratory tests, imaging studies, and liver pathologies were collected, and comparison was made between benign and malignant groups.
Results: Compared with malignant group, patients in the benign group were more likely to have multiorgan involvement of clinical histories ($P < 0.001$). There was no difference on bilirubin, liver enzyme, and serum tumor marker between the two groups, whereas serum IgG4 levels were higher in the benign group ($P = 0.003$). Patients in the benign group were more likely to have pancreatic changes ($P < 0.001$) and multiple-segmental bile duct stenosis ($P < 0.001$) on imaging. Compared with the malignant group, patients in the benign group were more likely to show severe periportal inflammation in noninvolved liver ($P < 0.001$), fibrosis around intrahepatic bile duct ($P < 0.001$), and more IgG4-positive plasma cells ($P < 0.001$) on liver pathology.
Conclusions: Benign lesion should be considered for patients with history of multiorgan involvement, pancreas changes, or multiple-segmental bile duct stenosis on imaging. Liver biopsy could be helpful for differential diagnosis before surgery.

Introduction

Hilar bile duct stenosis is not common, and the most usual causes include hilar cholangiocarcinoma (HCCA) and sclerosing cholangitis (SC). Imaging results in patients with SC (including primary sclerosing cholangitis [PSC] and IgG4-associated sclerosing cholangitis [IAC]) may resemble those of HCCA, including thickening of the bile duct wall, stenosis, and intrahepatic bile duct dilatation. These patients may thus be misdiagnosed with HCCA and undergo surgery. IAC should be treated with steroids,[1] whereas the most effective treatment for PSC is liver transplantation, rather than surgical resection.[2] Unnecessary surgery may delay appropriate treatment in these patients and lead to deterioration of their condition. Many cases of misdiagnosis have been reported, all of whom received unnecessary operations.[3-12] Careful

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differentiation between benign and malignant lesions is thus important in patients with hilar bile duct stenosis. This study aimed to clarify the differences between benign and malignant hilar bile duct stenosis in terms of clinical history, serology, imaging, and liver pathology.

Patients and methods

Patients selection

We retrospectively collected data for patients with hilar bile duct stenosis according to imaging examinations from June 2010 to June 2015. The inclusion criteria were hilar bile duct stenosis on computed tomography (CT) or magnetic resonance cholangiopancreatography (MRCP). Patients with presence of hilar mass were excluded from this study.

A total of 81 patients with hilar bile duct stenosis were detected, and 28 patients (all HCCA) with presence of hilar mass on CT or MRCP were excluded. Finally, 53 patients were included in this study, including 41 HCCA in the malignant group and 12 SC (six PSC and six IAC) in the benign group. Radical surgery and pathologic diagnosis were conducted in 30 patients with HCCA. The remaining 11 HCCA patients were diagnosed according to their imaging results, only received biliary drainage because of poor physical performance, tumor progression, or patients' willingness. All the 11 HCCA patients without surgery were followed until death, and all died of tumor progression or metastasis with an average survival time of 3.3 mo (1-6 mo). Five of the patients in the benign group (three PSC and two IAC) were misdiagnosed as HCCA preoperatively and underwent surgery, but diagnoses of PSC and IAC were subsequently confirmed by pathology. The other seven patients (three PSC and four IAC) in the benign group all underwent liver biopsy. IAC was diagnosed according to the HISORt criteria,[13] and PSC was diagnosed on the basis of imaging results and liver pathology.

Methods

Data on patient age, symptoms, and medical history were collected. Laboratory tests included alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, γ-glutamyl transpeptidase, total bilirubin, conjugative bilirubin, carbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), antinuclear antibody, and serum IgG4 level. Laboratory results were either post-admission test results or results from frozen blood samples. All the blood samples were collected with the consents of the patients. CT and MRCP were conducted in all patients. The following imaging signs were recorded: hilar bile duct stenosis, bile duct wall thickening, multiple-segmental bile duct stenosis, and pancreas changes (pancreas swelling, pancreatic duct dilatation, or infiltration around the pancreas). All the imaging was reviewed by a radiologist who was not involved in the diagnosis or treatment of the patients.

Thirty patients in the malignant group underwent radical surgery (18 cases associated with left hemihepatectomy, nine cases associated with segment IVb and V resection, and three cases associated with extended left hemihepatectomy [including segment V]). Five patients in the benign group (three PSC and two IAC) who were preoperatively misdiagnosed with HCCA also underwent surgery (two cases associated with left hemihepatectomy, two cases associated with segment IVb and V resection, and one case associated with extended left hemihepatectomy [including segment V]).Liver biopsy was performed on the 35 surgically resected specimens with a 16-gauge needle. Percutaneous liver biopsy with ultrasound guidance was performed on the remaining seven patients (three PSC and four IAC) in the benign group with a 16-gauge needle. Liver pathology was analyzed by a pathologist who was not involved in the diagnosis or treatment of the patients. Liver pathologic features included: severity of periportal inflammation in noninvolved liver, fibrosis around bile duct, and the number of IgG4-positive plasma cells per high-power field (HPF). The severity of periportal inflammation in noninvolved liver was classified as mild, moderate, or severe; mild reflected a small amount of inflammatory cell infiltration in the periportal area, severe reflected massive and dense inflammatory cell infiltration, and moderate was intermediate between the two. Fibrosis around intrahepatic bile duct referred to significant fibrous tissue proliferation around the intrahepatic bile duct. The numbers of IgG4-positive plasma cells in three HPFs were counted, and the average value was taken as the result. This study was approved by the Institutional Review Board of China-Japan Friendship Hospital, and informed consent for all invasive procedures was obtained from all patients.

Statistical analysis

Statistical analysis was performed using SPSS 20.0 software. Qualitative data were expressed as number of cases and quantitative data as mean ± standard deviation. Intergroup comparisons of quantitative data were conducted using Mann–Whitney *U* test, and comparisons of qualitative data were made using Fisher's exact test. Corrected *P* values <0.05 were considered statistically significant.

Results

Clinical and serologic comparisons

There was no difference between the malignant and benign groups in terms of age, gender, body mass index, or clinical symptoms (Table 1). Two patients in the benign group had concurrent ulcerative colitis, three had a history of acute pancreatitis, and one had a history of parotitis. No patients in the HCCA group had such histories. The difference between the groups overall was significant ($P < 0.001$). No difference was detected on serum bilirubin and liver enzyme between the two groups (Table 2). Although serum CA19-9 and CEA levels were higher in the malignant group, the differences were not significant (Table 2). Three patients in each group were antinuclear antibody–positive with no difference ($P = 0.121$). Serum IgG4 levels were elevated in five (12.2%) malignant and eight (66.7%, six IAC and two PSC) benign cases respectively, with a significant difference between them ($P < 0.001$). Compared with the malignant group, serum IgG4