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Primary pancreatic lymphoma

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ABSTRACT

Aims and backgrounds. Primary pancreatic lymphoma is non-Hodgkin lymphoma primarily involving the pancreas, which is rare in pancreatic diseases. The aim of this work is to summarize the diagnostic and therapeutic experience of primary pancreatic lymphoma.

Methods. We retrospectively reviewed the clinical data of 7 cases of primary pancreatic lymphoma admitted to Huashan Hospital in the past 3 years. Available English literature was also reviewed using the following terms: primary pancreatic lymphoma and pancreatic lymphoma.

Results. The literature review identified 157 additional cases, and a total of 164 cases had been analyzed. In this series, only 30% had a successful non-operative diagnosis. The curative rate of the surgery-adjuvant chemotherapy group was higher than that of the chemotherapy alone group.

Conclusions. Obtaining specimens through surgery is an effective diagnostic tool. Surgical resection in combination with postoperative chemotherapy plays a therapeutic role.

Introduction

About 30% of non-Hodgkin lymphomas involves the pancreas[1]. It may also be primary involvement of the pancreas, which is called primary pancreatic lymphoma (PPL). PPL is rare and represents less than 1% of extranodal lymphomas and 0.7% of all pancreatic malignancies[2,3]. Symptoms of PPL may mimic pancreatic adenocarcinoma, but PPL is more amenable to treatment. Most PPL are the low-grade B-cell type. It is difficult but important to distinguish PPL from pancreatic adenocarcinoma because of the dramatic difference in the prognosis and treatment of the two diseases. We reviewed 164 cases of PPL and herein discuss its diagnostic and therapeutic perplexities.

Patients and methods

We retrospectively reviewed the clinical data of 7 cases admitted in Huashan Hospital, Fudan University, Shanghai, China, during a 3-year period from October 2003 to August 2006, which accounted for 2.5% of a total of 282 pancreatic tumor cases during this period. The available English literature was also reviewed using the following terms: primary pancreatic lymphoma and pancreatic lymphoma. The clinical and diagnostic criteria of Behrns *et al.*[4] for PPL include the following: mass predominantly within the pancreas with grossly involved lymph nodes confined to the peripancreatic region, no palpable superficial lymphadenopathy, no hepatic or splenic involvement, no mediastinal nodal enlargement on chest radiograph, and normal white cell count. Staging was assigned by the modified Ann Arbor classification[5]. In the classification, stage I tumors are confined to the gastrointestinal tract, whereas stage II neoplasms involve regional lymph nodes. Statistical analyses included descriptive statistical analysis and chi-squared analysis.

Key words: diagnosis, non-Hodgkin lymphoma, pancreatic neoplasm, primary pancreatic lymphoma, treatment.

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Results

Seven cases of PPL were identified and treated in Huashan Hospital. The clinical characteristics of all the patients were consistent with the criteria for the diagnosis of PPL defined by Behrns *et al.*[4] According to the modified Ann Arbor classification[5], 1 case belonged to stage IIE and the remaining cases to stage IE. The patients included 6 males and 1 female, who ranged in age from 25 to 73 years (median, 56), and duration of symptoms ranged from 1 day to 1 year. The primary clinical manifestations were abdominal pain, jaundice, nausea and vomiting, back pain, epigastric mass, and weight loss.

Computerized tomography scan showed 5 cases with tumors in the head of the pancreas, 1 case in the tail and 1 case that involved the whole pancreas. The tumors varied in size from 4 to 11 cm (mean, 6.4). All tumors had heterogeneous density with unclear margins and heterogeneous enhancement without peripancreatic intumesce lymphaden (Figures 1 and 2). Four cases had dilation of the common bile duct, intrahepatic bile duct and pancreatic duct, with elevated serum levels of total bilirubin and direct bilirubin and slightly high serum levels of CA19-9. Endoscopic retrograde cholangiopancreatography in one case revealed that the common bile duct and pancreatic duct at the head were dilated, and a plastic biliary tract stent was inserted.

One case had elevation of serum amylase. One case was tested for serum LDH level and 2 were tested for serum beta2-microglobulin level, both of which were elevated. WBC count was within the normal range in all cases. The specimens were obtained from surgical resection in 5 cases. Ultrasound-guided endoscopic fine needle biopsy was performed in the remaining 2 cases.

Histological categorization was according to the Revised European American Lymphoma classification. All the cases had a B cell origin, including 6 cases of diffuse large B cell lymphoma and 1 case of small B cell lymphoma. Four cases accepted pancreaticoduodenectomy and chemotherapy, 2 underwent only chemotherapy, and 1 did not have any treatment. The chemotherapy regimen for all patients was CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) plus rituximab. All the patients were followed, and the survival was 2, 12, 15, 15, 16, 27 and 30 months. Three cases are still being followed.

Review of the literature identified 157 additional cases of PPL. Among the total 164 cases, the male to female ratio was 2.7:1, and mean age 59. Of note, 5 patients were under 20 years of age. The head of the pancreas was the most common location (76%), and the diameter of the tumors was more than 6 cm in 61% of cases. Epigastric pain (69%) was the most common presenting symptom, followed by jaundice (48%), weight loss (37%), vomiting and/or nausea (27%), anorexia (17%), back pain (7%) and fever (7%). Only 2% presented classical symptoms of fever and night sweats. About 8% of patients first appeared as acute pancreatitis and 26% had a palpable abdominal mass.

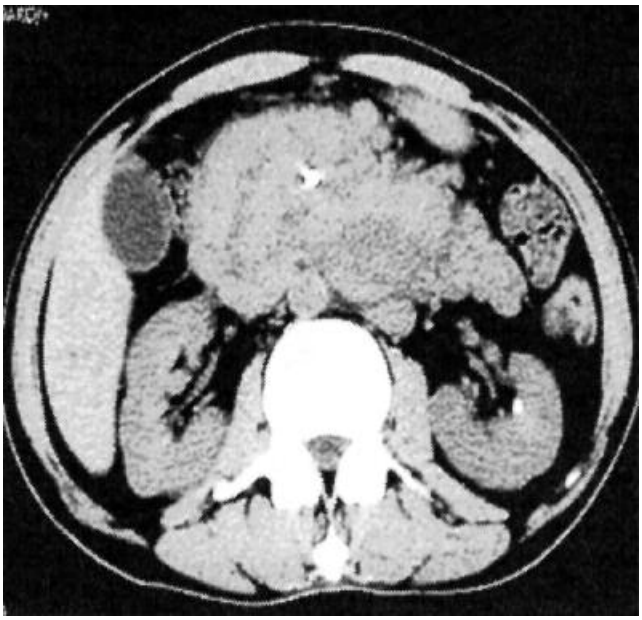

Figure 1 - CT scan showing a large mass in the head of the pancreas with heterogeneous density and involvement of abdominal vessels.

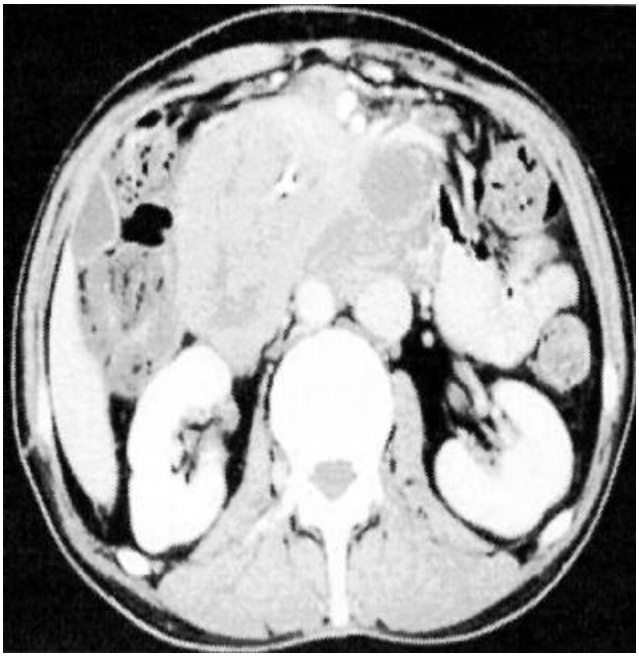

Figure 2 - Enhancement CT was heterogeneous (a stent insertion).

Among 53% of cases who had dilation of the common bile duct, only 5% had dilation of the pancreatic duct. Local lymph node intumesce was seen in 40% of cases. Only 1 case had mass necrosis. Among 27 cases mentioned, evaluation of CA199 showed 23 (85%) cases with

an elevated CA199 level and 14 (52%) cases accompanied by jaundice. Serum LDH level of 27 (64%) patients was elevated out of 41 cases who had the LDH test, and serum 2-microglobulin was elevated in all 5 (100%) cases evaluated. Four of 6 evaluated cases (67%) showed high CA125 levels. About 92% were B cell lymphoma, and diffuse large B cell lymphomas were the most common (55%). Only 29% had a histological diagnosis established by a non-operative biopsy. The misdiagnosis rate before definitive pathological diagnosis was high, to 87%. The curative rate of the surgery-adjuvant chemotherapy group (75%) was higher than that of the chemotherapy alone group (51%). Without any definitive treatment, results were uniformly poor with no patient free of disease and poor long-tem survival.

Discussion

PPL is a very rare neoplasm that may be confused with the more common pancreatic adenocarcinoma[4,6,7]. In a review of the literature, about 87% of patients were misdiagnosed before definitive pathological results. There is no important difference between PPL and pancreatic adenocarcinoma as regards age, sex or symptoms. Five cases of juvenile PPL were reported, which is less common than in pancreatic adenocarcinoma. The head of the pancreas is the most common location[8,9] and diffuse large B-cell lymphoma is the most common type. T-cell lymphomas, although very uncommon, often had a dismal prognosis[10]. Presenting symptoms are non-specific, and systemic B symptoms such as fever, chills and night sweats are uncommon[7-9]. Upper-gastric pain, unlike in pancreatic adenocarcinoma, rarely radiates to the back[7]. Interestingly, for 12% of PPL patients the diagnosis upon admission was acute pancreatitis[11-14]. Behrns *et al.*[4] reported that jaundice was an infrequent finding, despite large lymphomatous masses involving the pancreatic head. However, in our series, jaundice was not an uncommon presentation (more than 48%). About 26% of PPL showed an epigastric mass during physical examination; such a finding is less frequent in pancreatic adenocarcinoma.

Imaging results could suggest the suspicion of PPL but are unable to distinguish PPL from pancreatic adenocarcinoma[9,15]. CT is by far the most common imaging technique used in the detection and characterization of pancreatic tumors. The tumor is often described as a large homogeneous mass with extrapancreatic extension, with or without associated lymphadenopathy, with homogeneous enhancement with intravenous contrast[9,16]. However, heterogeneous areas within a large tumor mass and heterogeneous enhancement could also be seen in many cases in the series and therefore did not allow exclusion of PPL. Characteristic findings on CT scan include a bulky mass (often larger than 8 cm) invasively growing without respecting anatomic boundaries, without dilatation of main pancreatic ducts[7,9], without calcification or necrosis[7,9], but usually with surrounding extensive lymphadenopathy[15,17]. In the current literature, almost 53% of cases had dilation of the common bile duct, but only 5% had dilation of the pancreatic duct.

CA19-9 is usually normal and sometimes slightly elevated when biliary obstruction is present[18,19] for CA19-9 is produced by pancreatic and biliary duct cells. LDH and β2-microglobulin are both essential serum markers for the diagnosis and differential diagnosis of PPL and also have an important prognostic value[7,9,20]. CA125 seems to be a promising tumor marker in the assessment of prognosis and therapeutic response in non-Hodgkin lymphoma[21]. Serum sIL-2R values higher than 5000 U/mL may help the diagnosis of PPL in the presence of bulky pancreatic masses[22].

Guided core-needle biopsy, especially ultrasound-guided endoscopic fine-needle biopsy is considered as a safe, rapid, and easy procedure that can allow a histological diagnosis of PPL[7,8]. An accurate guided core-needle biopsy is critical for timely, nonsurgical management and obviates exploratory laparotomy. However, in this series, only about 30% had a successful non-operative diagnosis. This may be because percutaneous imaging-guided biopsy was not considered an accurate diagnostic tool in early reports[9]. We stress the need for experienced cytopathologists as well as advanced immunochemical assays to obtain a correct diagnosis on a small amount of tissue[6]. Laparotomy is usually required to make a definitive diagnosis[4,10]. Exploratory laparotomy also plays a important role in diagnosing, staging[23] and in performing biliary or gastric bypass to relieve the symptoms in patient with biliary or gastrointestinal obstruction.

Chemotherapy is the treatment of choice for most patients with PPL[9]. The role of surgery has been controversial for a long time[4,7,9]. Koniaris *et al.*[24] retrospectively reviewed 122 cases of pancreatic lymphoma in the English literature. Fifty-eight of these cases represented stage I or II lymphoma; they were treated without surgical resection and had a 46% curative rate. Fifteen patients who had surgical resection for localized disease had a 94% cure rate. In another report, 40% relapse-free survival was reported in 14 patients treated with chemotherapy and radiation[23]. In the series from the Mayo Clinic, 83% (10/12) of the patients treated with chemotherapy and/or radiation failed treatment[4]. In the current series, the curative rate of the surgery-adjuvant chemotherapy group (75%) was also higher than the chemotherapy-alone group (51%). In view of the poor response of PPL to chemotherapy, surgical resection combined with chemotherapy has a therapeutic role.

The role of radiation therapy in the management of PPL is also not yet defined for the limited cases. As one of the principal modalities of treatment of non-Hodgkin lymphoma for over 30 years, local radiotherapy as an

adjunct to chemotherapy could be used as consolidation[25,26]. However, a cooperative prospective study is needed to lead to further improvement in treatment outcomes.

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