

Pancreatic T/histiocyte-rich large B-cell lymphoma: A case report and review of literature

Shu-Mei Zheng, De-Jiang Zhou, Yi-Hua Chen, Rui Jiang, Yun-Xia Wang, Yong Zhang, Hong-Li Xue, Hai-Qiong Wang, Dong Mou, Wei-Zheng Zeng

Shu-Mei Zheng, De-Jiang Zhou, Yun-Xia Wang, Yong Zhang, Hong-Li Xue, Hai-Qiong Wang, Dong Mou, Wei-Zheng Zeng, Department of Gastroenterology and Hepatology, Chengdu Military General Hospital, Chengdu 610083, Sichuan Province, China

Yi-Hua Chen, Department of Pathology, Chengdu Military General Hospital, Chengdu 610083, Sichuan Province, China

Rui Jiang, Department of Radiology, Chengdu Military General Hospital, Chengdu 610083, Sichuan Province, China

Author contributions: Zheng SM and Zhou DJ contributed equally to this work; Zheng SM and Zeng WZ designed the report; Wang YX, Zhang Y, Xue HL, Wang HQ and Mou D collected the patient's clinical data; Chen YH provided and analyzed the microscopy images; Jiang R provided and analyzed the CT scan images; Zheng SM and Zhou DJ wrote the paper; all authors have read and approved the final version to be published.

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Correspondence to: Wei-Zheng Zeng, MD, Director, Department of Gastroenterology and Hepatology, Chengdu

Military General Hospital, 270 Rongdu Road, Chengdu 610083, Sichuan Province, China. zengweizheng@163.com
Telephone: +86-28-86571145

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Abstract

Primary pancreatic lymphoma (PPL) is an extremely rare form of extranodal malignant lymphoma. The most common histological subtype of PPL is diffuse large B cell lymphoma (DLBCL). In rare cases, PPL can also present as follicular lymphoma, small lymphocytic lymphoma, and T cell lymphoma either of non-Hodgkin's lymphoma or of Hodgkin's lymphoma. T-cell/histiocyte-rich large B-cell lymphoma (T/HRBCL) is an uncommon morphologic variant of DLBCL with aggressive clinical course, it is predominantly a nodal disease, but extranodal sites such as bone marrow, liver, and spleen can be involved. Pancreatic involvement of T/HRBCL was not presented before. Herein, we report a 48-year-old male who was hospitalized with complaints of jaundice, dark brown urine, pale stools, and nausea. The radiological evaluation revealed a pancreatic head mass and, following operative biopsy, the tumor was diagnosed as T/HRBCL. The patient achieved remission after six cycles of CHOP chemotherapy. Therefore, T/HRBCL can be treated similarly to the stage-matched DLBCL and both of them get equivalent outcomes after chemotherapy.

Key words: Non-Hodgkin's lymphoma; T-cell/histiocyte-rich large B-cell lymphoma; Immunohistochemistry; Primary pancreatic lymphoma; Diagnosis

Core tip: T-cell/histiocyte-rich large B-cell lymphoma (T/HRBCL) is an uncommon morphologic variant of diffuse large B cell lymphoma. Pancreatic T/HRBCL has not been reported to date. Here, we present the first case of a patient diagnosed with pancreatic T/HRBCL who was successfully treated with systemic chemotherapy.

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INTRODUCTION

Two main types of lymphoma have been described to date, namely lymphoma (HL) and non-Hodgkin's lymphoma (NHL). HLs are nodular lesions that rarely disseminate to the extralymphatic organs, while NHLs often invade extralymphatic organs and do not spread in a contiguous fashion. The primary sites most frequently affected are head-neck area and the gastrointestinal (GI) tract (in ascending order). At the level of the oral cavity, the most affected sites are tonsils (55% of oral cases), palate (30% of cases), and genial mucosa (2% of cases). There are, instead, sporadic manifestations affecting the tongue (2% of cases), the buccal floor (2% of cases), and the retromolar trigone (2% of cases)^[1]. In Western series, GI lymphoma occurs principally in the stomach, followed by the small bowel and the colon^[2].

Primary pancreatic lymphoma (PPL) is a rare form of extranodal malignant lymphoma. Approximately 0.1% of all malignant lymphomas, fewer than 2% of extranodal malignant lymphomas, and 0.5% of all pancreatic masses constitute PPLs^[2-5]. Volmar *et al.*^[6] evaluated the pathological results of 1050 fine needle aspiration (FNA) biopsies of pancreatic lesions and reported that only 14 (1.3%) cases were pancreatic lymphomas. PPL represents a diagnostic and therapeutic challenge due to its rarity, difficult anatomic location to access, nonspecific clinical presentation that can mimic pancreatic adenocarcinoma, and variety of its histological subtypes. Histological subtype is a major prognostic factor in nodal and extranodal lymphomas.

The most common histological subtype of PPL is diffuse large B cell lymphoma (DLBCL). T-cell/histiocyte-rich large B-cell lymphoma (T/HRBCL) is an uncommon morphologic variant of DLBCL, accounting for approximately 1% to 3% of all DLBCL^[7-11]. Nearly one half of patients with T/HRBCL present with liver, bone marrow, and/or spleen involvement^[12]. Pancreatic involvement of T/HRBCL has not been reported previously. We hereby

present the first case of T/HRBCL arising from pancreas.

CASE REPORT

A 48-year-old man was admitted to our hospital with 1-wk history of jaundice, dark brown urine, pale stools, and nausea. His medical history and physical exam were unremarkable. Laboratory workup revealed hepatic panel in cholestatic pattern with total bilirubin of 117 $\mu\text{mol/L}$, conjugated bilirubin of 66.8 $\mu\text{mol/L}$, alkaline phosphatase of 173 IU/L, γ -Glutamyltransferase (γ -GT) of 380 IU/L, and Alanine transaminase of 468 IU/L. Carbohydrate antigen 19-9 (CA19-9) was 11783 IU/mL. Lactate dehydrogenase (LDH) and β 2-microglobulin were normal. Abdominal computed tomography (CT) with contrast revealed a 4.2 cm \times 4.1 cm hypodense mass within the pancreatic head and enlargement of several mesenteric and retroperitoneal lymph nodes (Figure 1). Endoscopic retrograde cholangiopancreatography suggested an extrinsic compression of distal common bile duct with intrahepatic biliary dilation. He was clinically diagnosed as pancreatic tumor. During the surgery, a 4 cm \times 3 cm \times 4 cm mass was identified within the head of the pancreas, with several enlarged lymph nodes around the head of the pancreas and in the mesentery of the small intestine. The intraoperative frozen section of pancreatic head revealed chronic inflammation with atypical cells that were concerning for nonepithelial malignancy, thus the diagnosis of malignant lymphoma was suspected. Based on these findings, diagnostic biopsy of pancreatic mass, Roux-en-Y choledochojejunostomy, and Billroth II gastrojejunostomy were performed.

Postoperative histology of the pancreatic mass and mesenteric lymph node biopsies showed entirely effaced architecture by predominantly small lymphocytes and less often histiocytes. In addition, a limited number of scattered large atypical cells with pleomorphic vesicular nuclei and prominent nucleoli were embedded in the background (Figure 2). Immunohistochemical examination showed that the interspersed large atypical lymphoid cells were positive for pan-B cell markers CD20 (Figure 3A), PAX-5, CD21, CD43 and CD45RO. Most of the small lymphoid cells were CD3 positive T cells (Figure 3B). The histiocytes expressed CD68 (Figure 3C). Immunostaining for Ki-67 revealed a proliferation fraction of 30% among large atypical lymphoid cells (Figure 3D). Based on these histological features and immunophenotype, a diagnosis of pancreatic T/HRBCL was established.

One month after the operation, the patient was treated with 4 cycles of CHOP (cyclophosphamide, oncovin, adriamycin, and prednisone) regimen. He had significant improvement in radiological findings at the end of the 4th cycle. Two more CHOP regimens were completed to totally 6 cycles. A repeated CT scan one month after the last CHOP chemotherapy showed a complete remission. The patient was eventful and had no signs of recurrence in the 5 years since the last chemotherapy.



Figure 1 Abdominal computed tomography scan findings. A 4.2 cm × 4.1 cm hypodense mass within the head of the pancreas.

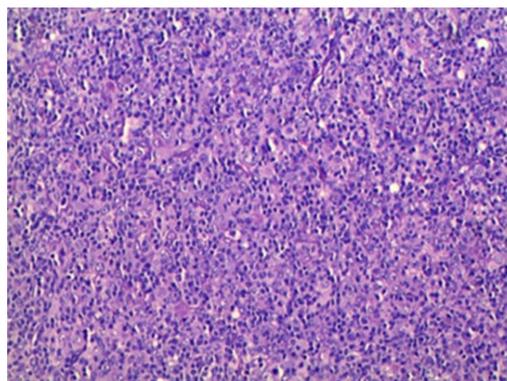


Figure 2 Histopathological examination. Large atypical lymphoid cells were scattered among small reactive lymphocytes and less often histiocytes (HE, × 20).

DISCUSSION

PPL, a lymphoma localized to the pancreas with or without peripancreatic nodal involvement, is an exceedingly rare entity. Two main criteria have been used to define PPL^[13,14]. However, there is now a standardized definition within the current World Health Organization framework of primary extranodal lymphomas, which facilitates uniformity and precision^[15]. PPL is generally defined when the bulk of the disease is localized to the pancreas. Adjacent lymph node involvement and distant spread may exist but the primary clinical presentation is in the pancreas and therapy is targeted to this location. Our case demonstrates all the above criteria.

The most common histological subtype of PPL is DLBCL, accounting for 77% to 80% of all patients^[3,16,17]. PPL can also present as follicular lymphoma, small lymphocytic lymphoma, Burkitt's lymphoma, and T cell lymphoma^[17-19]. T/HRBCL is a nodal disease, but extranodal sites, such as spleen, liver and bone marrow can be involved^[10-12,20,21]. In recent reports, primary cutaneous^[22], thyroid^[23], thymus^[24], and gastrointestinal presentations^[25,26] of T/HRBCL were also described. To date, pancreatic involvement of T/HRBCL has not been reported.

T/HRBCL is an uncommon morphological variant of DLBCL, but one with many distinctive clinical features^[7,8]. T/HRBCL tends to present in a relatively younger age group with a median age in the fourth decade and demonstrates male predominance, while DLBCL usually occurs in the fifth or sixth decade of life. T/HRBCL mostly presents in more advanced stages and has an aggressive clinical course^[11,20]. It is crucial to differentiate PPL including T/HRBCL from those of occupying lesions, such as pancreatic adenocarcinoma, and inflammatory ones, including acute or chronic pancreatitis, autoimmune diseases, or pancreatic tuberculosis, since their treatment and prognosis may differ considerably. Both pancreatic adenocarcinoma and PPL are diagnosed at a similar age and can present with nonspecific clinical presentations and radiographic findings. Percutaneous ultrasound, endoscopic ultrasound (EUS), CT, and magnetic resonance imaging are well-

established procedures to evaluate pancreatic lesions. Two different morphological patterns of pancreatic involvement are observed, namely a localized, well-circumscribed tumor pattern, as in the present case, and a diffuse enlargement pattern, infiltrating or replacing the majority of the pancreatic gland^[27]. The combination of a bulky head of pancreas tumor without dilatation of main pancreatic duct and with significant lymphadenopathy below the level of renal veins points to the diagnosis of PPL, while the presence of calcification or necrosis rules out lymphoma. Positron emission tomography scan is generally helpful in the staging of lymphoma, particularly in differentiating malignant lesion from benign ones. Although imaging techniques may suggest PPL, they are unable to distinguish between PPL and other pancreatic lesions. Therefore, the definitive diagnosis of PPL is based on the histopathological and cytopathological examinations. For a definitive diagnosis, CT-, or EUS-guided FNA biopsy is the optimal approach, as it is highly accurate. Alternatively, a laparoscopy or laparotomy may be performed to conduct a biopsy of the pancreatic mass or lymph nodes when the FNA biopsy is nondiagnostic or inadequate. In addition, submitting the specimen to flow cytometry is a valuable method for the diagnosis of PPL to individualize the appropriate therapy^[27]. The laboratory tests are nonspecific for PPL. Sadot *et al.*^[17] reported that serum LDH level was elevated in 55% of the PPL cases, while CA19-9 was increased in 25% of PPL patients. In our case, the serum CA19-9 level was significantly increased, but his LDH and β 2-microglobulin levels were normal.

Due to its rarity, nonspecific clinical manifestations, and variety of histological subtypes, final diagnosis and classification of PPL subtypes are often very difficult tasks without the aid of a cytopathological and immunopathological evaluation. The cells in T/HRBCL have a wide cytological spectrum characterized by fewer than 10% large neoplastic B cells (CD20, CD21, PAX-5, CD43 or CD45RO positive) amid a prominent inflammatory infiltrates, the majority of which are small polyclonal T cells with or without the presence of histiocytes. Despite a rich T cell background, well-formed T cell rosettes are

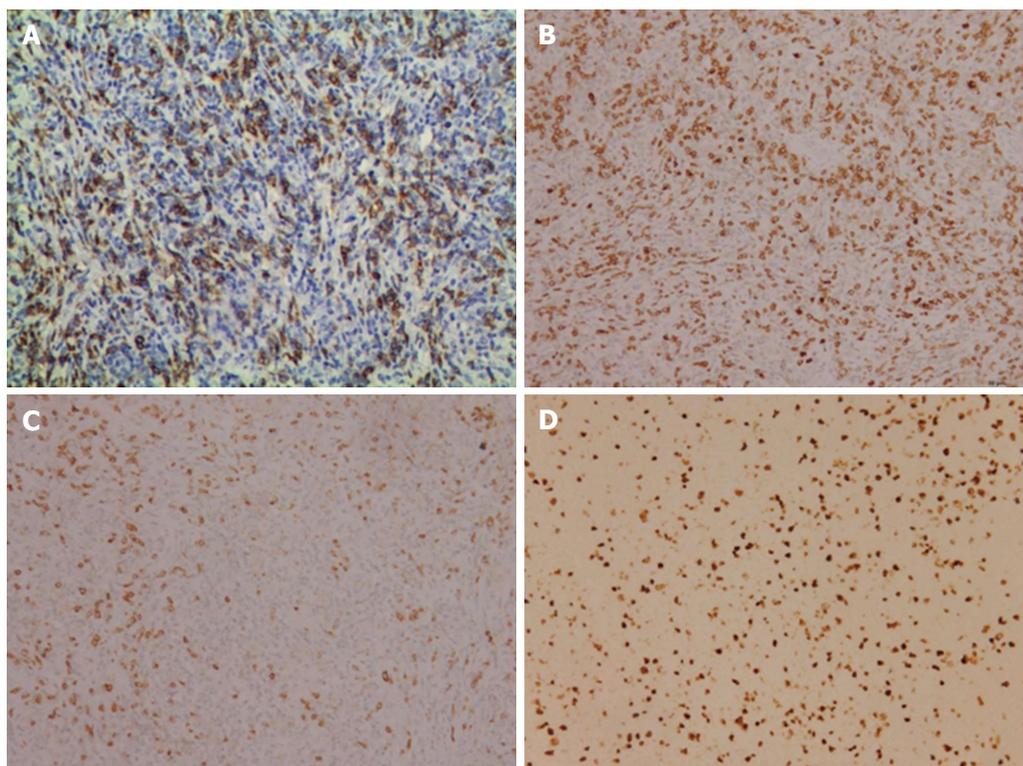


Figure 3 Immunohistochemistry studies. A: The dispersed CD20 positive large B cells ($\times 20$); B: Numerous CD3 positive small T cells in the background ($\times 20$); C: CD68 positive histiocytes in the background ($\times 20$); D: Ki-67 expression of neoplastic cells ($\times 20$).

usually absent in T/HRBCL. T/HRBCL shares several morphologic and immunophenotypic similarities with nodular lymphocyte predominant Hodgkin's lymphoma (NLPHL), posing a great diagnostic challenge in some cases^[28]. The histological distinction between T/HRBCL and NLPHL largely relies on immunohistochemical analysis of the background population. Features that favor T/HRBCL usually include the absence of background small B cells. NLPHL shows nodules containing numerous small lymphocytes and a variable number of variant Hodgkin's cells (popcorn cells) which are usually positive for CD45 and CD20 but negative for CD15 and CD30. However, the surrounding small lymphocytes in NLPHL are usually a mixture of B cells (predominately) and T cells (though rich T cells can be seen in late stage of NLPHL), and CD57 or PD-1 positive T cells rosette around the large neoplastic B cells^[29]. In the present case, the small lymphocytes in the background were predominantly CD3 positive T cells with no T cell rosettes, suggesting a T/HRBCL.

Regarding treatment, T/HRBCL patients are generally treated similarly to the stage-matched DLBCL^[30]. When patients are well matched according to the IPI and the treatment is adapted to the disease stage and risk, T/HRBCL and conventional DLBCL have similar outcomes after chemotherapy^[11]. Anthracycline-based CHOP regimen is recommended as the standard treatment for T/HRBCL. A series of early studies related to the treatment of T/HRBCL demonstrated that the complete response (CR) rate of T/HRBCL to

chemotherapy was 48% to 85%, and the 3-year and 5-year overall survival (OS) rate were 50% to 64% and 46% to 58%, respectively^[11,30,31]. The matched-control analysis showed a trend toward a better response to chemotherapy for patients with DLBCL than T/HRBCL, whereas no difference was observed in OS between the two groups^[11]. Recently, CHOP chemotherapy in combination with rituximab (R-CHOP) is used in T/HRBCL as it is used in all CD20 positive nodal and extranodal lymphomas^[11,32]. Kim *et al.*^[33] reported that there was no significant difference in the CR rate to R-CHOP between T/HRBCL (91%) and DLBCL (97%). The 3-year OS rates were 75% for T/HRBCL and 81% for DLBCL, respectively ($P = 0.719$). The addition of rituximab to CHOP seems to be helpful for the management of T/HRBCL, as it is for DLBCL. Chemotherapy combined with radiotherapy may be useful for the treatment. Behrns *et al.*^[13] reported that the median survival time for single chemotherapy and radiotherapy-treated PPL patients was 13 and 22 mo, respectively, whereas it could be improved to 26 mo with combined chemoradiotherapy. The role of surgery should be reserved for diagnostic or palliative intent. Lin *et al.*^[3] reported that patients with biliary tract or gastrointestinal obstruction should receive biliary or gastric bypass. After surgery, the systemic chemotherapy should be initiated for long-term remission. It is, therefore, important to choose the appropriate treatment depending on disease progression and condition of patients. In our case, the

patient was not diagnosed with PPL preoperatively, and there was obstruction of the biliary tract, so gastrointestinal and biliary bypass was performed to alleviate symptoms for subsequent therapy. The present case showed a good clinical course; however, prolonged follow-up is recommended to monitor disease relapse at both the primary and distant sites.

Although patients with malignant lymphoma benefit from the traditional treatments, the prognosis of the entity is poor due to the high relapse of the disease and the toxicity of these therapies. Besides the present chemotherapy, developing safer agents is an important project. A recent study described that the antioxidant and antitumor activity of the bioactive polyphenolic fraction isolated from the beer brewing process may be helpful for antitumor therapy, which throws a new light on treatment of lymphomas^[34].

In summary, pancreatic H/TRBCL is an aggressive disease that often presents with adverse prognostic factors. However, when treatment is adapted to the disease risk, outcome is equivalent to patients with DLBCL. Systemic chemotherapy should be the initial therapy when the diagnosis is established. Chemotherapy combined with radiotherapy may be useful for the treatment. Surgery should be reserved for diagnostic and non-curative intent. Prolonged follow-up is recommended to detect relapse. Further innovative researches on antitumor therapies should be undertaken to make new possibilities for improvement of the poor prognosis of malignant lymphoma.

COMMENTS

Case characteristics

A 48-year-old man was referred to our hospital with 1-wk history of jaundice, dark brown urine, pale stools, and nausea.

Clinical diagnosis

A 4-cm-diameter mass located in the pancreatic head, along with enlarged mesenteric and retroperitoneal lymph nodes.

Differential diagnosis

Pancreatic adenocarcinoma, chronic pancreatitis, peripheral T cell lymphoma, or nodular lymphocyte predominant Hodgkin's lymphoma.

Imaging diagnosis

The abdominal computed tomography scan showed a 4-cm-diameter tumor located in the pancreatic head and enlargement of several mesenteric and retroperitoneal lymph nodes.

Laboratory diagnosis

Laboratory workup revealed hepatic panel in cholestatic pattern with total bilirubin of 117 $\mu\text{mol/L}$, conjugated bilirubin of 66.8 $\mu\text{mol/L}$, alkaline phosphatase of 173 IU/L, and γ -Glutamyltransferase of 380 IU/L. Carbohydrate antigen 19-9 is 11783 IU/mL.

Pathological diagnosis

Primary pancreatic T-cell/histiocyte-rich large B-cell lymphoma (T/HRBCL).

Treatment

Surgical bypass followed by systemic chemotherapy was performed.

Related reports

Previously, cases of primary cutaneous, thyroid, thymus, and gastrointestinal T/HRBCL were reported.

Term explanation

Primary pancreatic lymphoma (PPL), a lymphoma localized to the pancreas with or without peripancreatic nodal involvement, is an exceedingly rare entity. The most common histological subtype of PPL is diffuse large B cell lymphoma (DLBCL). Pancreatic T/HRBCL is an uncommon morphologic variant of DLBCL arising from pancreas.

Experiences and lessons

Systemic therapy should be the initial therapy when the diagnosis of primary pancreatic T/HRBCL is established. Surgery should be reserved for diagnostic and non-curative intent. Prolonged follow-up is recommended to detect relapse.

Peer-review

Authors reported the first case of a patient diagnosed with pancreatic T/HRBCL who was successfully treated with systemic chemotherapy. Novelty of the case is that lymphoma in pancreas otherwise diagnosis and management are same.

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