

First report of primary pancreatic natural killer/T-cell nasal type lymphoma

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Abstract. – **BACKGROUND:** Primary pancreatic lymphoma (PPL) is an extremely rare form of extranodal malignant lymphoma and pancreatic tumour. Natural killer/T-cell lymphoma is an aggressive rare form extranodal lymphoma with a predilection for the nasal cavity/nasopharynx, it can arise in other organs such as skin, testicles, spleen, adrenal, or GI tract, but the initial presentation of our patient in the pancreas is unreported.

CASE PRESENTATION: We present a case of primary pancreatic natural killer/T-cell nasal type lymphoma in a 62-year-old man. The presenting symptoms were non-specific only for upper abdominal pain and weight loss. Imaging techniques showed the lesion was located in the head of pancreas. Computed tomography (CT) scanning and otorhinolaryngology examination were negative for nasopharyngeal lymphoma. The initial concern was for pancreatic tumor and the patient underwent pancreaticoduodenectomy. The diagnosis of primary pancreatic natural killer/T-cell nasal type lymphoma was established as the combination of NK-lineage antigens (TIA-1, granzyme B, CD56) with EBV-expression.

CONCLUSIONS: This is the first case of primary pancreatic natural killer (NK)/T-cell nasal type lymphoma. PPL, although a rare pathologic entity, should be considered in the differential diagnosis for a large homogeneous mass with extrapancreatic extension in the head especially in those of normal serum CA 19-9 level.

Key Words:

Extranodal lymphoma, Natural killer (NK)/T-cell lymphoma, Nasopharynx, Primary pancreatic lymphoma, Epstein Barr virus.

Introduction

Primary pancreatic lymphoma (PPL) is an extremely rare disease, comprising fewer than 2% of extranodal malignant lymphoma and less than 0.5% of pancreatic tumours¹, and large-scale studies are rarely performed even in Western countries, in which the vast majority of the reported PPL cases were of B-cell type. In Japan

the incidence of T-cell type PPL was a little higher, and as a consequence, the prognosis in Japan was poorer than in Western countries². PPL can be difficult to differentiate from pancreatic adenocarcinoma without definitive pathological diagnosis³, and correct diagnosis is crucial given that PPL has different management and prognosis. Optimal treatment of PPL remains controversial, particularly the role of surgery and radiotherapy⁴.

To our knowledge, this is the first reported case of a primary pancreatic NK/T-cell nasal type lymphoma. NK/T-cell lymphoma is an aggressive, rare form of lymphoma that is associated with Epstein Barr virus (EBV)⁵. It usually originates in the nasal cavity/nasopharynx and invades the surrounding tissues; less often, it can arise in other organs including the skin, testicles, spleen, adrenal, or GI tract.

Case Presentation

A 62 year-old man presented with upper abdominal pain for two months. The patient had no B symptoms of fever, chills, or night sweats; however, he had lost 15 kg during the two months. Physical examination was no jaundice, no peripheral lymphadenopathy, no abnormal oral, oropharyngeal, or anterior nasal lesions, no palpable abdominal mass.

Haematological and biochemical analyses including haemoglobin level, platelets count, total and differential white blood cell count, erythrocyte sedimentation rate (ESR), serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), lactate dehydrogenase (LDH), total and direct bilirubin, alkaline phosphatase (ALP), serum protein electrophoresis, serum amylase, anti hepatitis C virus antibody (anti HCV-Ab) and hepatitis B virus surface antigen (HBs Ag) were all available in our patient which were all in normal levels. Serum CA 19-9 tumor marker assay was 22.9 IU/L (normal range 0~40IU/L).

Additional studies included: negative HIV, TP-PA and hepatitis panels. Past medical history was only significant for hypertension. Family history was negative for lymphoma and pancreatic tumor.

At initial evaluation at the Surgical Department of Shanghai Renji Hospital in July 2011, a computed tomography (CT) scanning of abdomen and pelvis revealed a 44 mm mass in the head of the pancreas with mild dilatation of the main pancreatic duct, but no dilatation of common bile duct and intrahepatic bile ducts, there was no evidence of liver metastasis, regional adenopathy, or other primary tumors (Figure 1, Figure 2). There was no abnormal find in chest CT. Because of a concern for a primary pancreatic malignancy, he underwent pancreaticoduodenectomy in August.

cellular antigen-1 (TIA-1) and granzyme B with strong uniform granular perinuclear positivity (cytotoxic granules); CD3 with dim heterogeneous cytoplasmic positivity; The following markers were dim positivity on immunohistochemical stains: CD20 and CD79, cellular antigen-1 (TIA-1) and granzyme B with strong uniform granular perinuclear positivity (cytotoxic granules); CD3 with dim heterogeneous cytoplasmic positivity; The following markers were dim positivity on immunohistochemical stains: CD20 and CD79, CD4, CD43, CD8, bcl-2, bcl-6, cytokeratin and LCA. Epstein Barr virus (EBV)-encoded RNA (EBER) staining by chromogenic in situ hybridization showed strong and uniform nuclear



Figure 1. A large localized, well-circumscribed and homogeneous mass in head of the pancreas, less dense than muscle, about 44 mm, without associated retroperitoneal and mesenteric lymphadenopathy, neither calcification nor necrosis within the mass.



Figure 2. Mild dilatation of Wirsung's duct, but no dilatation of common bile duct and intrahepatic bile ducts.

positivity in the neoplastic population (Figure 4). T-cell receptor and immunoglobulin clonality studies were not performed, as the combination of NK-lineage antigens (TIA-1, granzyme B, CD56) with EBV-expression was diagnostic of extranodal NK/T-cell lymphoma. After the operation, additional skull-neck thin-layer CT scanning and otorhinolaryngology examination were negative for nasopharyngeal lymphoma. The operation was successful and the patient was well recovered. The patient was advised the adjuvant chemotherapy and radiation but he refused further treatment due to his poor financial status. He expired 6 months after surgery.

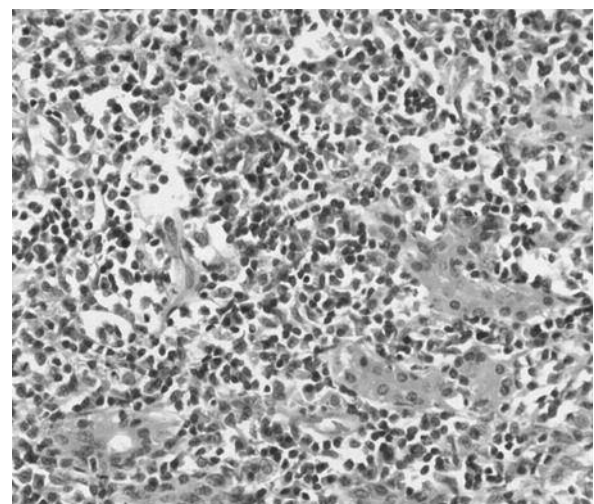


Figure 3. Extranodal natural killer T cell lymphoma, nasal type. Hematoxylin and eosin staining, $\times 200$. Population of relatively uniform and small mononuclear cells infiltrating and replacing pancreatic gland.

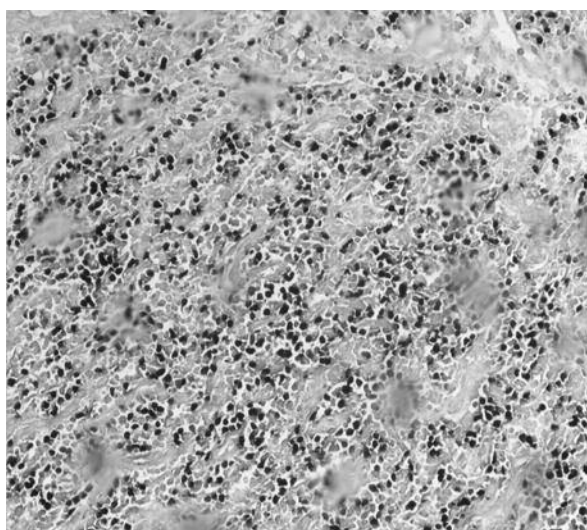


Figure 4. Epstein Barr virus-encoded RNA (EBER) staining was strongly and uniformly positive by chromogenic in situ hybridization in the neoplastic population, HE×100.

Discussion

Primary pancreatic lymphoma (PPL) is an extremely rare disease that may be confused with the more common pancreatic adenocarcinoma, it representing fewer than 2% of extranodal malignant lymphomas and less than 0.5% of all pancreatic tumours. The largest single study in Western countries involved 14 patients⁶, while 19 cases were described by a Japanese study², the most reports described isolated cases. Similar to previous literature⁷, the mean age in PPL apparently older than in pancreatic adenocarcinoma, the presenting symptoms and signs were nonspecific, elevation of aminotransferases, alkaline phosphatase and direct bilirubin were the common findings, elevation of CA19-9 is not common.

PPL can present as an isolated lesion mimicking pancreatic carcinoma¹. Fewer than 150 cases of PPL have been reported in English literature but no one about primary pancreatic NK/T-cell lymphoma⁸. All cases of PPL reported to date in Western countries are of the B-cell type, but some cases of T-cell pancreatic lymphoma have been reported in Japanese series². Most reported PPLs are intermediate or high-grade NHL, with diffuse large cell lymphoma being the predominant histotype². Instead of being primary in the pancreas, pancreatic lymphoma may also occur by direct extension from adjacent peripancreatic lymphadenopathy (it was called secondary pan-

creatic lymphoma). To distinguish PPL from secondary pancreatic lymphoma, Behrn's clinical and diagnostic criteria of PPL include the following: mass predominantly within the pancreas with grossly involved lymph nodes confined to the peripancreatic region; no palpable superficially lymphadenopathy; no hepatic or splenic involvement; no enlargement of mediastinal lymph nodes; and a normal leukocyte count⁹. Although the pancreatic gland is involved secondarily in more than 30% of patients with non-Hodgkin's lymphoma, primary manifestation is extremely rare.

Presenting symptoms of PPL are nonspecific, typically including abdominal pain, weight loss, vomiting, nausea and a palpable mass⁹, but also jaundice, acute pancreatitis, and small bowel obstruction³. Systemic symptoms such as fever, chills and night sweats are uncommon.

PPL is often¹⁰ described as a large homogeneous mass at imaging techniques, frequently infiltrating extra-pancreatic surrounding tissue, with or without associated retroperitoneal and/or mesenteric lymphadenopathy. In most cases the lesion is located in head of the gland, less common presentations are masses in the body or tail, diffuse pancreatic involvement is really uncommon that may mimic the imaging findings of acute pancreatitis with gland enlargement and irregular infiltration of the peripancreatic fat. Merkle et al¹¹ described imaging findings in PPL and they concluded that on CT two different morphologic patterns of pancreatic involvement can be seen: a localized, well-circumscribed tumoral form and a diffuse enlargement infiltrating or replacing most of the pancreatic gland. Also some imaging findings have been reported to differentiate PPL from pancreatic adenocarcinoma: the combination of a bulky localized tumor in the pancreatic head without significant dilatation of the main pancreatic duct strengthens the diagnosis of PPL over adenocarcinoma; enlarged lymph nodes below the level of renal vein and invasive tumour growth not respecting anatomic boundaries and infiltrating retroperitoneal or upper abdominal organs and the gastrointestinal tract are additional reliable signs for PPL. Neither calcification nor necrosis within the mass have been described in any case of untreated PPL¹¹. Clinically, the differential diagnosis of PPL from pancreatic adenocarcinoma is often extremely difficult, particularly when these masses are associated with an elevated CA 19-9 level¹². Only the clinical presentation of abdominal pain and a palpable

mass without jaundice was valuable in attempting to distinguish most patients with pancreatic adenocarcinoma from those in the minority with PPL. It can be difficult to differentiate from pancreatic adenocarcinoma without definitive pathological diagnosis³.

Percutaneous ultrasound (US), endoscopic US and computed tomography (CT) scan are well-established procedures to evaluate pancreatic mass; however, these methods alone cannot allow a pathologic diagnosis. Imaging techniques can only suggest the suspicion of PPL but are unable to distinguish PPL from pancreatic adenocarcinoma¹³. A cyto-histological examination is mandatory for diagnosis and treatment planning of patient with suspicious PPL. A cyto-histological diagnosis of pancreatic mass can be performed by CT or US guided fine-needle aspiration biopsy (FNAB) and tissue core fine-needle biopsy (FNB)^{14,15}. The vast majority of reported PPL cases are B-cell type lymphoma. This is the first report of primary pancreatic natural killer (NK)/T-cell nasal type lymphoma.

NK/T-cell lymphoma is an aggressive rare form extranodal lymphoma with a predilection for the nasal cavity/nasopharynx and invades the surrounding tissues, less often, it can arise in other organs including the skin, testicles, spleen, adrenal, or the GI tract. The initial presentation of our patient in the pancreas is unreported. Often these tumors present in patients who are immunosuppressed or who have had solid organ transplantation, there is no history in this case of either. The prevalence increases to 5% in HIV patients because the gastrointestinal tract is the most commonly affected extranodal site in AIDS-related non-Hodgkin's lymphoma¹⁶. NK/T-cell lymphoma is strongly associated with Epstein Barr virus (EBV)⁵, suggesting a pathogenic role for this virus^{17,18}. Our patient's pancreas was positive for EBV. Unfortunately, this disease pursues an aggressive course and many of the patients succumb to disseminated disease.

The optimal treatment is not established¹⁹. Novel therapies in NK/T-cell lymphomas have been reviewed²⁰. Li et al²¹ reported a 5 year overall survival of 36% in 77 patients with NK/T-cell sinonasal lymphoma. They found combined chemotherapy and radiation to be beneficial. Kim et al²⁰ reviewed their retrospective experience with CEOP-B (cyclophosphamide, epirubicin, vincristine, prednisolone, bleomycin) chemotherapy in 43 newly diagnosed extranodal NK/T-cell lymphoma patients. The CR/unconfirmed-CR

rate was 44% and overall response rate was 67%. The median overall survival was 27.9 months and the median disease-free survival was 15.3 months. No clinical or laboratory factors were predictive of survival, except age. Radiation did not show a definite survival benefit. Lee et al²² recently proposed an extranodal NK/T-cell, nasal type lymphoma prognostic model from a multicenter retrospective study of 262 patients. Prognostic factors included B symptoms, stage, LDH level, and regional lymph node involvement.

Conclusions

The presenting symptoms of PPL are non-specific, so when we find a mass located in the head of pancreas in imaging techniques, the diagnosis of PPL should be considered. A cyto-histological examination is mandatory for diagnosis and treatment planning of patient with suspicious PPL, US or CT guided biopsy techniques can provide sufficient diagnosis tissue. The limited number of PPL can not permit a comparison between the outcome of surgical and non-surgical therapy. Larger series of patients are needed to evaluate if chemotherapy, eventually followed by involved field radiation therapy, is the best treatment of choice of PPL. Data should be collected in a large cooperative setting.

Competing Interests

The Authors declare that they have no competing interests.

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