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Case Report

Diagnostic Dilemma in Pancreatic Lymphoma

Case Report and Review

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Summary

Non-Hodgkin's lymphoma predominantly involving the pancreas is a rare tumor of the gastrointestinal tract. Diagnosis can be difficult, since lymphoma may mimic carcinoma or pancreatitis. Lymphoproliferative diseases induced by immunosuppressive therapy frequently occur in the gastrointestinal tract of posttransplant patients. However, pancreatic involvement of posttransplant lymphoma is an exceptional condition. We present the case of a cyclosporin-treated renal transplant recipient with pancreatic lymphoma mimicking carcinomatous or inflammatory tumors. The diagnostic difficulties and treatment options of pancreatic lymphoma as well as lymphoproliferative disorders in immunosuppressed renal recipients are discussed in light of the current literature.

Key Words: Pancreas; lymphoma; immunosuppression; renal transplantation.

Introduction

Pancreatic non-Hodgkin's lymphoma is a rare tumor of the gastrointestinal tract, and constitutes far less than 5% of pancreatic malignancies *(1)*. Baylor et al. *(2)* reported pancreatic lymphoma comprising even <1% of all pancreatic malignancies. The risk of lymphoma arising *de novo* in immunosuppressed renal transplant recipients is known to be increased *(3)*, but pancreatic infiltration appears to be a very unusual situation.

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Case Report

Because of progressive renal insufficiency as a result of hydronephrosis and kidney agenesis, a 54-yr-old white female underwent uncomplicated cadaveric renal transplantation 4 yr earlier. Since then, immunosuppression therapy continuously consisted of cyclosporine in combination with prednisone as well as intermittent azathioprine. On her current admission to the hospital, she complained of acute dyspnea, dry cough, bilateral inspiratory pain associated with nausea, loss of appetite, epigastric pain, and pultaceous stool.

Physical examination was unimpressive. Enlarged lymph nodes were absent. Initial pathological serum laboratory findings indicated the following: hemoglobin 6.2 g/dL, white blood cell count 4000/μL, platelets 125,000/μL, ESR 90/102 mm, CRP 57 mg/L, creatinine 3.5 mg/dL, total serum protein 52 g/L, albumin 40.6%, γ-globulin 30.3% (polyclonal), amy-

lase 210 U/L (urine: 108 U/L), lipase 1200 U/L, and Quick's test 70%. Increased specific CMV-IgM implied an acute reinfection. Additionally, there was no evidence of raised tumor markers.

X-ray films of the chest revealed diffuse, reticular bihilary infiltrations associated with small pleural effusions, which were interpreted as signs of acute CMV pneumonia. Enlarged mediastinal lymph nodes were not evident. Without evidence of an acute pancreatitis, ultrasound examination (Fig. 1) disclosed two isolated round pancreatic lesions of low echogenicity within the gland (caput: 4 × 3 cm and corpus: 2.4 × 1.5 cm in diameter). Both foci were confined within the pancreas, and were suspicious of inflammatory or carcinomatous origin. There was no enlargement of lymph nodes. However, abdominal computed tomography (CT) scan did not confirm the presence of the two pancreatic foci, but rather diagnosed acute edematous pancreatitis. Thoracic CT examination was performed, but was unrevealing.

Because of progressive development of thrombocytopenia (WHO III°–IV°), anemia (WHO III°), and rapid deterioration of the plasmatic coagulation (no DIC), other diagnostic explorations (such as invasive endoscopic procedures, ultrasound-guided, fine-needle biopsy of the pancreatic foci, or staging laparotomy) could not be used. A bone marrow aspiration was performed, but yielded a nonspecific result. Various approaches of treatment, including different combinations of antibiotics and antimycotics (without evidence of any pathogenic organism by bronchoscopical lavage or blood cultures), discontinuation of azathioprine (which was questionably thought to induce the pancreatitis), and intermittent withholding of almost all drugs (since a toxic bone marrow depression was also discussed) proved to be unsuccessful. Furthermore, short-term progression of renal failure (increase of serum creatinine, advanced edema, oliguria, ascites) initiated hemodialysis, which subsequently led to a circulatory breakdown and ICU treatment requiring mechanical ventilation. Despite all efforts, cardiopulmonary failure rapidly progressed, and the patient died 27 d after clinical admission. An autopsy was obtained. Histopathological evaluation (Fig. 2A,B) revealed a high-grade, large-cell, not further classified, non-Hodgkin's lymphoma of the pancreas without evidence of infiltrating the retroperitoneal or peripancreatic lymph nodes. Similar microscopic lymphoid infiltrations were found in both lungs, stomach, cecum, liver, and peritoneal lymph nodes.

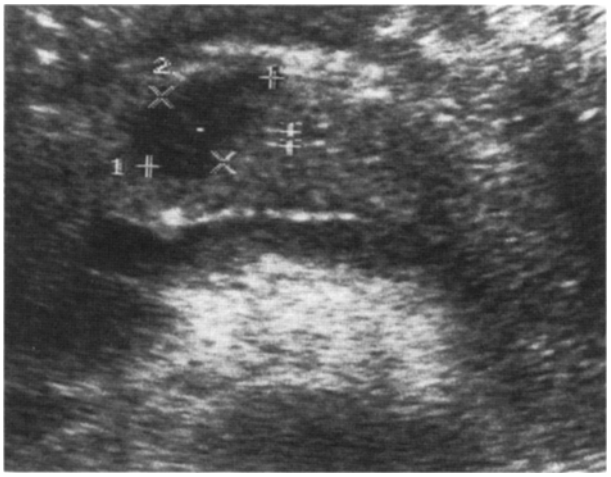

Fig. 1. Ultrasound showed an isolated round pancreatic lesion of low echogenicity within the corpus of the gland (1: 2.4 cm; 2: 1.5 cm).

Discussion

Approximately 25% of malignant tumors arising *de novo* in immunosuppressed renal recipients are lymphomas, which is in contrast to the incidence in the general population (2–4%) *(4,5)*. Since the beginning of the 1970s we noticed a yearly lymphoma incidence of 1.5% in renal transplant recipients (total of approx 3000 renal transplantations) at the University Hospital of Essen, which is similar to reported data *(6)*. Pancreatic infiltration of posttransplant lymphoma generally seems to be a very uncommon condition, although pancreatic lymphoma—usually as part of a disseminated process—is not rare in other immunosuppressed, e.g., HIV-infected *(7,8)*, patients. To the best of our knowledge, a comparable case of a posttransplant lymphoma predominantly involving the pancreas without evident infiltration of the nearest surrounding or retroperitoneal lymph nodes has not been reported previously.

Problems encountered in establishing diagnosis of pancreatic lymphoma, which may mimic carcinoma or vice versa, are well known *(9)*. Lymphoma primarily presenting itself as pancreatitis or lymphoma-associated pancreatitis has been reported before *(10,11)*.

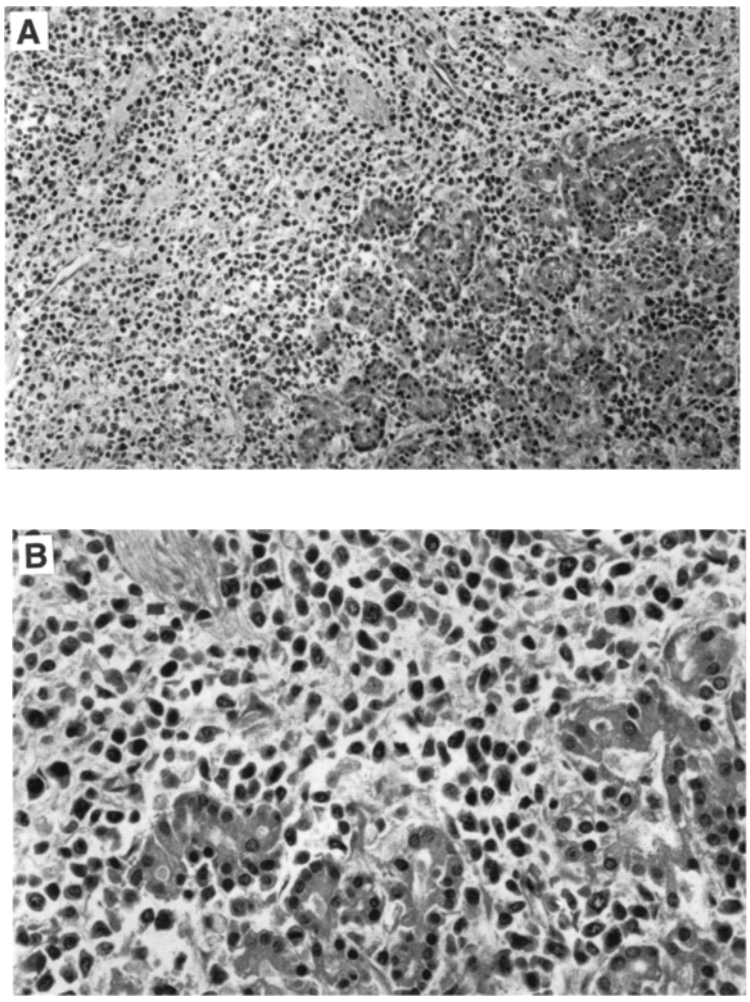

Fig. 2. (**A**) Pancreatic tissue, infiltrated by a high-grade, large-cell, not further classified non-Hodgkin's lymphoma (H&E, 140×). (**B**) Detail of (A) (H&E, 350×).

Pancreatic lymphoma may be evident by CT scan as a pancreatic mass, peripancreatic lymphadenopathy, and invasion of the near surroundings, as well as obstruction of the pancreatic and common bile ducts and subsequent dilatation of intrahepatic and extrahepatic bile ducts *(12)*. Usually in nonimmunosuppressed patients, CT scans of the abdomen may show enlarged lesions of the pancreas (>5 cm) at the initial examination *(12–17)*. In a common sense, characteristic but nonspecific radiologic features of primary or secondary pancreatic non-Hodgkin's lymphoma may include the following: large size of tumor (>6–7 cm), hypoechogenic, blurred margins, constant homogenity, diffuse, invasive infiltration of other organs, and retroperitoneal and/or mesenteric lymphadenopathy *(1,18)*. Inhomogenous contrasting of pancreatic lymphomas by CT scan has also been demonstrated *(16,19,20)*. Pre- and postcontrast CT scans may demonstrate "contrast inversion," i.e., the pancreatic lesions are of higher density than the normal parenchyma on unenhanced scans and of lower density after iv contrast enhancement *(21)*. Presence of biliary dilatation and/or rich vascularization, such as observed in other cases *(1,12,14,19)*, does not permit, by itself, the diagnosis of lymphoma.

In a comprehensive review, Dodd et al. *(22)* stated that posttransplant lymphoproliferative disorders involving abdominal solid organs appear similar regardless of the organ involved. Most masses are of low attenuation, and are nonenhancing on CT scans

and hypoechoic with variable transmission. Moreover, the masses tend to be well defined and spherical, although poorly marginated. On the other hand, Tubman et al. *(6)* have shown that posttransplant lymphomas compared to those in the general population are often characterized by atypical growth patterns and radiographic appearances. Single or multiple masses, particularly if centrally lucent, should suggest posttransplantation lymphoma, but as demonstrated in the present case, this central lucency, which seems to correlate with necrosis seen at histologic examination, is not an obligatory finding.

Endoscopic ultrasonography may be more helpful in revealing small pancreatic tumors (< 2.5 cm) and lymph nodes than CT scan or ultrasonography, yet differentiation between adenocarcinoma and pseudotumerous pancreatitis is almost impossible *(23)*. Ultrasound-guided, fine-needle pancreatic biopsy has been described to yield accurate results (overall accuracy 85%; false-negative results in approx 10%) *(24)*. Dinkel et al. *(25)* demonstrated a sensitivity of CT-guided, fine-needle biopsy for malignant pancreatic tumors of 87% and a specifity of 100%. Thus, needle biopsy of a pancreatic mass can be diagnostic of a malignant lymphoma *(1,17)*. However, differentiation of anaplastic carcinoma and lymphoma may be very difficult—even by wedge biopsy *(9)*. Since it is often impossible to establish the diagnosis of lymphoma with cytologic features *(13–15,26–28)*, the application of gene arrangements to aspirated material may be the choice *(29)*. In addition, the absence of elevated carcinoembryonic antigen assay in fine-needle aspirates of pancreatic tissue may be seen as a hint of lymphoma, but also of benign disorders or metastatic lung carcinoma *(30)*.

Endoscopic retrograde cholangiopancreatography might contribute to, e.g., demonstrating stenosis or displacement of the pancreatic and/or bile ducts with dilatation above the narrowed areas when other methods have previously not been successful *(16,31)*. However, ERCP often appears to be normal or unsuccessful *(26,27,32,33)*.

Several authors failed to diagnose pancreatic lymphoma preoperatively by various imaging techniques with or without needle biopsy, but reached the right diagnosis by explorative laparotomy *(9,12,26,31,34)* or as in this case, by postmortem autopsy *(9)*.

Webb et al. *(1)* showed that complete remission can be achieved by chemotherapy (CHOP, CAMEL, or MACOP-B) with or without surgery. However, conflicting results have been reported for long-term survivial rates in patients with unresected pancreatic lymphoma treated with chemotherapy with or without radiotherapy *(15,31,35)*. Taken together, surgical resection, if possible, is strongly recommended. Reduction or discontinuation of immunosuppression therapy should be considered and may subsequently lead to regression of the so-called posttransplant lymphomas *(36)*.

References

1 Webb TH, Lillemoe KD, Pitt HA, et al. Pancreatic lymphoma: is surgery mandatory for diagnosis and treatment? *Ann Surg* 1989; 209: 25–30.

2 Baylor SM, Berg JW. Cross-classification of survival characteristics of 5,000 cases of cancer of the pancreas. *J Surg Oncol* 1973; 5: 335–358.

3 Penn I, Starzl TE. Malignant tumors arising de novo in immunosuppressed organ transplant recipients. *Transplantation* 1972; 14: 407–417.

4 Cockburn I. Assessment of the risks of malignancy and lymphomas developing in patients using sandimmune. *Transplant Proc* 1987; 19: 1804–1807.

5 Penn I. Malignant lymphomas in organ transplant recipients. *Transplant Proc* 1981; 13: 736–738.

6 Tubman DE, Frick MP, Hanto DW. Lymphoma after organ transplantation: radiologic manifestations in the central nervous system, thorax and abdomen. *Radiology* 1983; 149: 625–631.

7 Bonacini M. Pancreatic involvement in human immunodeficiency virus infection. *J Clin Gastroenterol* 1991; 13: 58–64.

8 Radin DR, Esplin JA, Levine AM, et al. Aids-related non-Hodgkin's lymphoma: abdominal CT findings in 112 patients. *AJR* 1993; 160: 1133–1139.

9 Ackerman NB, Aust JC, Bredenberg CE, et al. Problems in differentiating between pancreatic lymphoma and anaplastic carcinoma and their management. *Ann Surg* 1976; 184: 705–708.

10 Safadi R, Or R, Bar Ziv J, et al. Lymphoma-associated pancreatitis as a presenting manifestation of immunoblastic lymphoma. *Leuk Lymph* 1994; 12: 317–319.

11 Kotwall CA, Brow JR, Keith RG. Lymphoma pancreatitis: a real entity. *Can J Surg* 1989; 32: 375–377.

12 Cappell MS, Yao F, Cho KC, et al. Lymphoma predominantly involving the pancreas. *Dig Dis Sci* 1989; 34: 942–947.

13 Tuchek JM, De Jong SA, Pickleman J. Diagnosis, surgical intervention, and prognosis of primary pancreatic lymphoma. *Am Surg* 1993; 59: 513–518.

14 Shtamler B, Bickel A, Manor E, et al. Primary lymphoma of the head of the pancreas. *J Surg Oncol* 1988; 38: 48–51.

15 Behrns KE, Sarr MG, Strickler JG. Pancreatic lymphoma: is it a surgical disease? *Pancreas* 1994; 9: 662–667.

16 Borrowdale R, Strong RW. Primary lymphoma of the pancreas. *Aust NZ J Surg* 1994; 64: 444–446.

17 Scully RE, Mark EJ, McNeely BU. Case records of the Massachusetts General Hospital. Weekly Clinicopathological Exercises. Case 11-85. *N Engl J Med* 1985; 312: 706–711.
18 Prayer L, Schurawitzki H, Mallek R, et al. CT in pancreatic involvement of non-Hodgkin lymphoma. *Acta Radiol* 1992; 33: 123–127.
19 Joly I, David A, Payan MJ, et al. A case of primary non-Hodgkin lymphoma of the pancreas. *Pancreas* 1992; 7: 118–120.
20 Teefey SA, Stephens DH, Sheedy PF. CT appearance of primary pancreatic lymphoma. *Gastrointest Radiol* 1986; 11: 41–43.
21 Ng YY, Healy JC, Vincent JM, et al. The radiology of non-Hodgkin's lymphoma in childhood: a review of 80 cases. *Clin Radiol* 1994; 49: 594–600.
22 Dodd GD III, Greenler DP, Confer SR. Thoracic and abdominal manifestations of lymphoma occuring in the immunocompromised patient. *Radiol Clin North Am* 1992; 30: 597–610.
23 Palazzo L, Rouseau G, Gayet B, et al. Endoscopic ultrasonography in the diagnosis and staging of pancreatic adenocarcinoma. *Endoscopy* 1993; 25: 143–150.
24 Tikkakoski T, Siniluoto T, Päiivänsalo M, et al. Diagnostic accuracy of ultrasound-guided fine-needle pancreatic biopsy. *Fortschr. Röntgenstr* 1992; 156: 178–181.
25 Dinkel E, Helwig A, Jäger B, et al. Computer tomography-guided fine-needle biopsy of the pancreas for histological purposes. *Radiologe* 1990; 30: 420–424.
26 Brown PC, Hart MJ, White TT. Pancreatic lymphoma, diagnosis and management. *Int J Pancreatol* 1987; 2: 93–100.
27 Fischer MG, Kabakow B. Lymphoma of the pancreas. *Mt Sinai J Med* 1987; 54: 423–426.
28 Rodriguez J, Kasberg C, Nipper M, et al. CT-guided needle biopsy of the pancreas: a retrospective analysis of diagnostic accuracy. *Am J Gastroenterol* 1992; 87: 1610–1613.
29 Hu E, Horning S, Flynn S, et al. Diagnosis of B cell lymphoma by analysis of immunoglobulin gene rearrangements in biopsy specimens obtained by fine needle aspiration. *J Clin Oncol* 1986; 4: 278–283.
30 Pinto MM, Levine RH. Carcinoembryonic antigen assay in fine needle aspirate of pancreas: a diagnostic adjunct to cytology. *Am J Gastroenterol* 1992; 87: 530–533.
31 Hart MJ, White TT, Brown PC, et al. Potentially curable masses in the pancreas. *Am J Surg* 1987; 154: 134–136.
32 Pasanen PA, Eskelinen M, Vornanen M, et al. Pancreatic lymphoma. *Ann Chir Gynaecol* 1993; 82: 207–209.
33 Gawdat K, Howe K. Pancreatic lymphoma. *J Clin Gastroenterol* 1993; 16: 258–260.
34 Yusuf SW, Harrison JD, Manhire AR, et al. Primary B-cell immunoblastic lymphoma of pancreas. *Eur J Surg Oncol* 1991; 17: 555–557.
35 Summary of Pancreas Club Meeting. *Am J Surg* 1992; 164: 311–315.
36 Starzl TE, Porter KA, Iwatsuki S, et al. Reversibility of lymphomas and lymphoproliferative lesions developing under cyclosporin-steroid therapy. *Lancet* 1984; I: 583–587.