Review Article

Pancreatic Tuberculosis. A Surprise for a Surgeon

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Abstract **Pancreatic tuberculosis (TB) is a relatively rare disease that can mimic carcinoma, metastatic carcinoma, cystic neoplasia, retroperitoneal tumors, pancreatic abscess, pancreatic pseudocyst or pancreatitis. In general the correct diagnosis is not established before surgery unless there are detectable foci of TB somewhere else or a relevant clinical history. Review of the clinical presentations, radiographic investigations, laboratory findings, criteria and clues for diagnosis as well as management of pancreatic TB were summarized to emphasize the significance of this rare disease in the differential diagnosis of a pancreatic mass and the necessity of pathological and microbiological diagnosis by fine-needle aspiration.**

Key words: **pancreas, tuberculosis, pancreatic abscess, pancreatic pseudocyst, fine-needle aspiration**

INTRODUCTION

The abdomen is an ordinary site of extra-pulmonary involvement of tuberculosis (TB). The intra-abdominal sites frequently involved are the mesenteric and peripancreatic lymph nodes, peritoneum, ileo-cecum, liver, and spleen[1,2]. Pancreatic TB is considered to be rare [0.75% of all TB (21/ 2,808)][3], especially with isolated involvement or primary pancreatic TB. It is usually associated with miliary TB or immunodeficiency condition[4]. Only two cases of pancreatic TB have been reported from Thailand[5,6]. In 1992, Watanapa and Vathanopas published a case of 26-year-old man presented with the painless obstructive jaundice and finally diagnosed with pancreatic TB by histopathological examination of pancreaticoduo-dectomy specimen.

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Epidemiology

Pancreatic TB is extremely uncommon, even in countries where TB is highly prevalent. Pancreatic TB most often occurs as a complication of miliary TB. The incidence of TB of the pancreas in patients with miliary TB is 2.1-4.7%[4,7]. There is a history of TB in 19-44% of the cases with pancreatic TB[8,9]. Primary or isolated pancreatic TB is exceedingly rare; less than 100 cases of them have been published[10]. The low frequency of pancreatic TB may be partly due to the biological resistance of the pancreas to tubercular infection. Pancreatic enzymes, including lipases and deoxy-ribonucleases, have antimycobacterial effects[11]. However, the incidence of pancreatic TB has recently increased. In India, Bhansali did not discover a single case of pancreatic TB in a review of 300 cases of abdominal TB in 1977[1], but the recent study of collective data from 1999-2004 from the same endemic area detected pancreatic TB in 8.3% of the 384 patients who were diagnosed with abdominal TB[9]. The human immunodeficiency virus (HIV) pandemic and the worldwide resurrection of *M. tuberculosis* are all responsible for the increasing incidence[10]. Seven percent of patients with acquired immune deficiency syndrome (AIDS) and disseminated mycobacterial infection are affected by pancreatic TB[12]. Pancreatic TB typically presents in the following patient types: in patients who reside in endemic tuberculous zones, sporadically in no-risk healthy patients, and in patients who are immunocompromised[13].

Etiopathogenesis

It is hypothesized that TB can affect the pancreas either; firstly by adjacent spread from peripancreatic lymph nodes, secondly by hematogenous spread from an occult primary in the lung[11,14], thirdly by reactivation of latent occult TB in an immunocompromised host (such as alcoholism, steroid dependent, HIV-infected person, or surgical patient)[14,15], fourthly by ingestion of infectious material from an active pulmonary focus[15], and lastly by toxic-allergic reaction of the pancreas in response to generalized TB, indicating a nonspecific inflammatory host response to mycobacterial antigens rather than an infection and so called "concomitant pancreatitis" by Stock et al[16]. The incidence of pancreatic TB is dissimilar between sexes and depends on series, occurring at the mean age of around 40 years (peak of incidence is highest in the 4th decade of life)[3,6,9,10,17]. The most common topographic location is the pancreatic head (71.4-86.1%), followed by the body and tail of the pancreas (28.6%)[3,6], likely because of the richer vascularization and lymphatic drainage[18-20].

Clinical manifestations

The symptomatology is nonspecific and various. The commonest is abdominal pain (90.6%), followed by nausea associated with vomiting (87.50%), fever (81.25%), weight loss (53.12%), palpable mass (28.12%) (Figure 1), and jaundice (9.37%)[9]. The mean duration of symptoms prior to presentation is 2.6-6 months (range 5 days to 11 months)[9,17]. The manifestation of the disease is usually that of a pancreatic mass and/or peripancreatic mass mimicking carcinoma, metastatic carcinoma, cystic neoplasm or retroperitoneal tumor but it can also occur as a pancreatic abscess or pseudocyst, acute pancreatitis, chronic pancreatitis, gastrointestinal bleeding, portal venous thrombosis and even colonic perforation[5,6,9,10,14-25].

In cases of AIDS, the most common presentation is tuberculous pancreatic abscess (70.0%)[6]. In addition, 71.1% of the cases have no previous serological evidence of HIV infection and most of the HIV-infected patients (90.5%) have a CD4 cell count ≤190/mm^3). Because of the virulence of TB, its symptoms tend to manifest at an early stage of HIV infection.

Pancreatic TB should be considered in the differential diagnosis of pancreatic masses in patients with the following conditions: 1) reside in or travel to areas in which TB is active[5,9,10,14,16-18,20-26]; 2) a past history of contact to TB (presence in 22.41-43.75% of the patients)[3,9,17]; 3) young people (in contrast to beyond 6th decade in pancreatic carcinoma)[3,5,9,10,14,15,17,18,20,21,23-27];

Figure 1 A pancreatic mass at epigastrum.

4) presence of active extra-abdominal TB e.g. lung, vertebra and adjacent paraspinal soft tissue, cervical lymph nodes, and skin[3,9,18,23,25,27,28]; 5) clinical signs of abdominal pain, fever, and weight loss[3,10,14,17,21,25,27]; 6) HIV-infected patients (50% of cases are seropositive for HIV infection) or other immunocompromised host[6,9,10,27]; 7) diagnose of solitary pancreatic cystic lesions[14,18]; 8) atypical pancreatitis[23,24]; and 9) diagnose of pancreatic ductal adenocarcinoma with non-dilated pancreatic duct[8,29].

Hematology and biochemistry

Hematologic and biochemical abnormalities may be found in decreasing order as follows: elevated erythrocyte sedimentation rate (>20 mm) (81.25%), leukocytosis (white blood count >15,000/mm^3) (78.12%), anemia (hemoglobin <11 g%) (56.25%), leucopenia (white blood count <4,000/mm^3) (21.87%), elevated pancreatic enzyme (lipase or amylase) (15.62%) and abnormal liver function test (12.50%)[9]. Tuberculin skin test is positive in over 70% of the cases[10].

Diagnostic studies

Diagnosing pancreatic TB is challenging. Mostly, the correct diagnosis is established postoperatively when the excised pancreaticoduodectomy or distal pancreatectomy specimen came back as a pathological surprise. Report from China showed that 35 patients and 5 patients out of 58 cases of TB of the pancreas were firstly impressed by pancreatic tumor and retroperitoneal tumor, respectively. Seventy one percent of patients diagnosed with pancreatic TB underwent laparotomy or pancreaticoduodenectomy[17]. In Korea, all of patients (11 cases) were initially misled by pancreatic cancer and 73% of them underwent laparotomy[18].

Radiographic findings

Pancreatic TB can be classified radiologically into three forms, a more common mass-forming form (94.4%), a less frequent diffuse form and a small nodular form[6,30]. Most of clinical and radiological reviews of literature underscore a focal form due to high frequency.

Ultrasound (US) scans of the abdomen are simple, noninvasive, cost effective, and readily available; thus, they are usually used as an initial diagnostic tool and exhibit excellent sensitivity. In a clinical and imaging review of 32 cases, US scans can identify focal pancreatic lesions in up to 100%[9]. Furthermore, US scans can reveal an ascites (43.75%), a focal hypoechoic lesion (90.62%) or heterogeneously hypo-isoechoic lesion (9.37%) (Figure 2), multiloculated cystic lesions (primarily in the head of the pancreas), diffuse enlargement of the pancreas, enlarged peripancreatic (Figure 3A), retroperitoneal, para-aortic (Figure 3B), porta hepatic, periportal, mesenteric, celiac, or splenic hilum lymph nodes[6,9,17,23,27]. Occasionally, biliary dilatation results from the obstruction of the common bile duct[20-22,24], pancreatic duct dilatation, air bubble(s) within the mass, encasement of the celiac artery, or compression/thrombosis of portal vein with collaterals (Figure 4), and portal hypertension[6,22,25,26,28].

Computed tomography (CT) scans may demonstrate a focal, sharply delineated or ill-defined heterogeneously hypodense mass, cystic mass, small nodular lesions, and other signs corresponding to US scans[19]. Focal calcification can be seen in 56%[17]. An irregular, heterogeneous enhancing mass may be found in dynamic contrast-enhanced CT study. Ring enhancement and low density areas within enlarged lymph nodes suggest tuberculous lymphadenitis[2,12]. Peripancreatic nodule can be found in 38-91%[9,17]. Tubercular etiology should be suspected in the case of certain ancillary findings, including characteristic of hypodense lymph nodes, lesions in other solid viscera such as the liver, bile duct, kidney, or spleen; hepatomegaly; splenomegaly; splenic vein thrombosis; ascites; peritoneal nodularity; mural thickening in the ileocecal area; pulmonary TB; or pleural effusion[2,4,9,12,14,17,27].
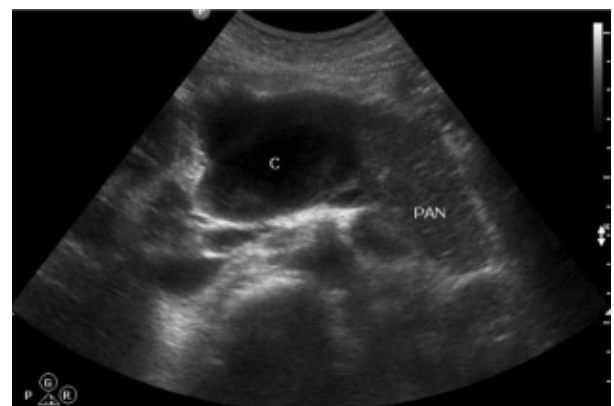
Figure 2 US demonstrates a well-defined lobulated cystic lesion (C) in the head of the pancreas.
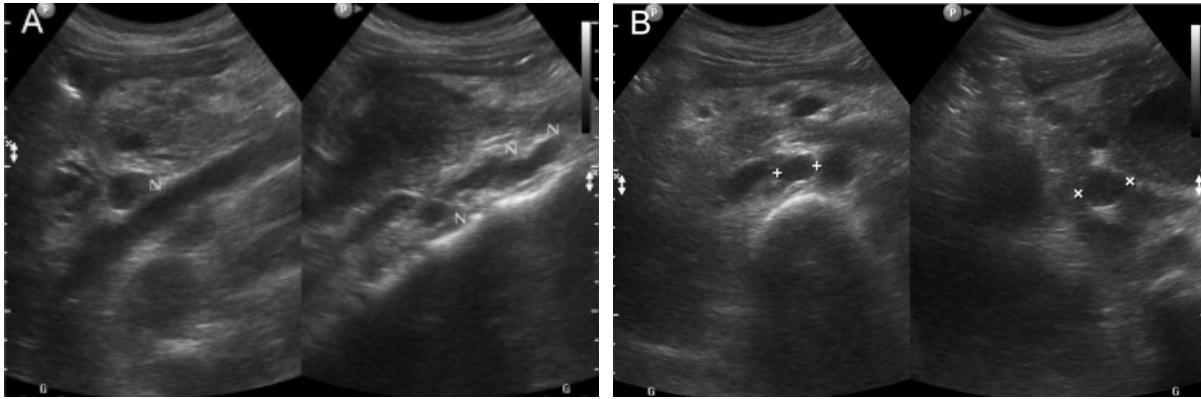
Figure 3 Multiple peripancreatic lymph nodes in A and para-aortic lymph nodes in B (N = lymph node).
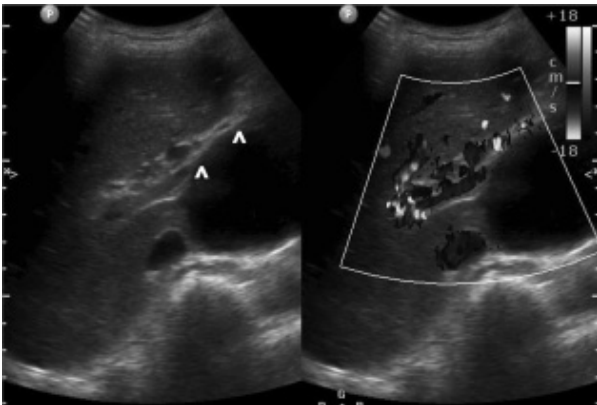
Figure 4 Portal vein compression (arrow head) and varices at porta hepatis.

Based on the 90.6% sensitivity, Nagar et al have recommended that TB of the pancreas should be a differential diagnosis for pancreatic masses associated with peripancreatic lymphadenopathy[9].

Magnetic resonance imaging of the local form shows hypointense on T1-weighted images and hypointense or heterogeneous mass with mixture of hypointense and hyperintense on T2-weighted images[15,31]. However, radiographic signs of pancreatic TB are neither specific nor pathognomonic, and most radiographic findings can be observed in pancreatitis of any cause or pancreatic carcinoma[17,19,23].

Gadolinium-enhanced T1-weighted images reveal peripheral enhancement with area of central enhancement[15]. Pancreatogram is varying including duct dilation, normal duct, and duct occlusion in descending order.[18] Positron emission tomography with 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (FDG) is useless because both pancreatic TB and malignancy have an increased uptake of the FDG metabolite[32].

Intra-operative findings

In intra-operative view, one may encounter an ascites in abdominal cavity as well as area of adhesion of pancreatic head and duodenum with multiple paraduodenal, peripancreatic, aortocaval, mesenteric, hepatoduodenal, hepatic hilum, and celiac lymph nodes (even small nodes can contain granulomatous lesions). The pancreatic head is hard and edematous with a mass of multicystic appearance and carrying thick, turbid, or milk-like fluid[14,23,31,33].

Histopathological and microbiological findings

A definitive diagnosis is usually based on a histopathological or microbigical examination of a specimen that is obtained from the pancreas or based on peripancreatic lymph nodes exhibiting chronic granulomatous inflammation with caseous necrosis and multinucleated giant cells. In addition, acid-fast bacilli using Ziehl-Neelsen or auramine staining can also be employed for this purpose (Figure 5). The success rate of fine-needle aspiration (FNA) in diagnosing pancreatic TB is 50.0-85.7% for percutaneously obtained specimens[6,34] and about 76.2% for endoscopic US-obtained specimens[3]. Endoscopic US-guided FNA is a low-complication diagnostic tool (1-2%) for pancreatic mass, recommended by American Joint Commission on Cancer[19]. In contrast to percutaneous route, endoscopic US-guided FNA is considered to be safer and with lower risk of needle tract seeding, therefore some authors have suggested it to differentiate between pancreatic/peripancreatic TB and cancer[3].

In HIV-infected patients, the sensitivity of acid-fast stainings and mycobacterial cultures of the
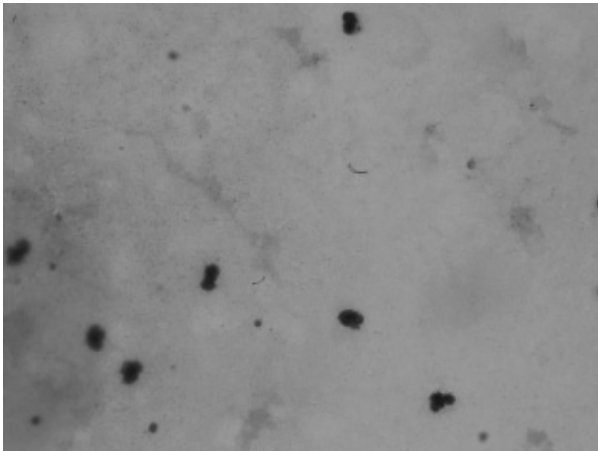
Figure 5 Acid fast bacilli and acute inflammatory cells in proteinaceous fluid (Ziehl-Neelsen staining, original magnification × 100).

specimens are 100.0% and 94.7%, respectively which are higher than those of immunocompetent patients (23-38% [11,35] and 37.5-77%[3,11], respectively) and indicates the much higher pathogen burden and lower immunological response in these immunocompromised hosts[6].

A polymerase-chain-reaction assay, when used to detect mycobacterial deoxyribonucleic acid, yields highly specific same-day results. Although its sensitivity to TB in FNA specimens has not yet been determined, the polymerase-chain-reaction assay is increasingly used as an adjunct to special staining techniques and mycobacterial cultures. It may yield positive results even when specimen cultures are negative[3]. However, laparotomy with intra-operative FNA or biopsies of pancreatic mass and/or lymph nodes is recommended in the inconclusive case because a more common pancreatic carcinoma cannot be excluded[23,33] and coexistence of peri-ampullary carcinoma with peri-pancreatic tuberculous lymphadenopathy has been reported[36].

In cases of AIDS with suspected pancreatic TB, mycobacterial smears and cultures from blood, sputum, brochoalveolar lavage, urine, stool, bone marrow, superficial lymph nodes, ascites, or pleural effusion specimens should be taken due to the augmented yield of these sites[6]. Furthermore, because cytomegalovirus, *Mycobacterium avium* complex, *Toxoplasma gondii*, and *Cyptococcus neoformans* infection are asymptomatic and not mass-forming lesions; limited availability of FNA; and an outstandingly treatable disease when compared

to non-Hodgkin's lymphoma and Kaposi's sarcoma that invaded the pancreas, Jaber and Gleckman have suggested empirical antituberculous drug (ATD) to HIV-infected patients who have no evidence of pancreatitis causing by alcoholism, biliary tract disease, surgery, or trauma and suffer abdominal pain from pancreatic mass lesions[27].

Treatment and outcomes

If left untreated, pancreatic TB is highly fatal, but it is highly responsive to standard ATD as well (90%)[6,34]. In most cases of pancreatic TB, medication is the preferred treatment; surgery and the drainage of fluid are not preferred[17,27]. A standard multiple ATD regimen with directly observed therapy for 6-12 months is usually effective[3,17,27,33]. The mean time of radiographic resolution is 132 days (range 78-186 days)[17].

However, if the tuberculous pancreatic mass is enlarged or causes symptoms even after the ATDs have been employed for a reasonable period, surgical resection is advocated by some authors[33]. In a minority of the cases with biliary or duodenal obstruction, surgical or endoscopic treatment may be helpful[17,20,22,25]. Although the prognosis for this disease is good in immunocompetent patients (only 1 out of 58 cases that were reported in the Chinese-language literature resulted in death[17]), the prognosis is grave in AIDS patients due to the underlying disease[6].

CONCLUSION

Pancreatic TB is extremely rare, has various clinical presentations, and tends to masquerade as a pancreatic malignancy, cystic tumor, abscess, or pseudocyst. In patients presenting with pancreatic masses and certain diagnostic clues, a differential diagnosis of pancreatic TB that is combined with a histopathological and microbiological diagnosis via FNA can often prevent unnecessary surgery.

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