CASE REPORT

Nodular Lymphoid Hyperplasia Masquerading as Neoplasia of the Bile Duct and Pancreas

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ABSTRACT

Context Nodular lymphoid hyperplasia is a disease may that occur in multiple locations including the gastrointestinal tract. Few reports exist on the occurrence in the hepatopancreaticobiliary system, and yet this has not been reported in the bile duct. **Case report** A fifty-seven-year-old male presented with painless jaundice, intra-hepatic biliary dilatation and a lesion in the distal pancreas (as shown in the computed tomography scan). The endoscopic retrograde cholangiopancreatogram findings were consistent with Bismuth II Klatskin type tumor. The patient underwent surgical resection of both lesions. The pathological analysis demonstrated reactive nodular hyperplasia in both the pancreas and bile duct. **Conclusion** Nodular lymphoid hyperplasia is a rare, benign disease of the hepatopancreaticobiliary tree and is most often diagnosed at the time of surgical resection, secondary to an inability to exclude neoplasia. Awareness regarding this rare disease entity may change patient management.

INTRODUCTION

Nodular lymphoid hyperplasia, also known as reactive nodular hyperplasia or pseudolymphoma, is a rare hepatopancreaticobiliary disease that has been reported in multiple locations including the orbit, lung, skin, breast, and gastrointestinal tract [1]. These benign lesions are marked by proliferation of polyclonal lymphocytes in follicles with germinal centers. In the case of the gastrointestinal tract, it has been reported in the stomach, esophagus, small bowel, gallbladder, pancreas, liver, and large intestine [2, 3]. The stomach is the most common gastrointestinal site and in this location nodular lymphoid hyperplasia can progress to mucosa-associated lymphoid tissue (MALT) lymphoma. In other gastrointestinal locations, nodular lymphoid hyperplasia is considered to be a benign disease with no malignant potential [3, 4].

When nodular lymphoid hyperplasia is HPB in origin, it is mostly diagnosed at the time of surgical resection for a presumed malignancy. The liver is the most commonly reported HPB location [5]; however, fewer than 50 cases of hepatic nodular lymphoid hyperplasia have been reported so far [5, 6]. In most cases, this disease has been identified incidentally, and the diagnosis is confirmed on resection for the presumed hepatocellular carcinoma [5]. In 1991, the first case of nodular lymphoid hyperplasia in the pancreas was reported by Nakashiro et al. [7] To our knowledge there have been no previous reports of combined biliary and pancreatic involvement or nodular lymphoid hyperplasia arising in the biliary tree. Given the benign nature of the disease and reports of spontaneous regression in the lungs, liver, and pancreas, the recognition of this rare condition and differentiation from malignancy is of paramount importance [1, 8].

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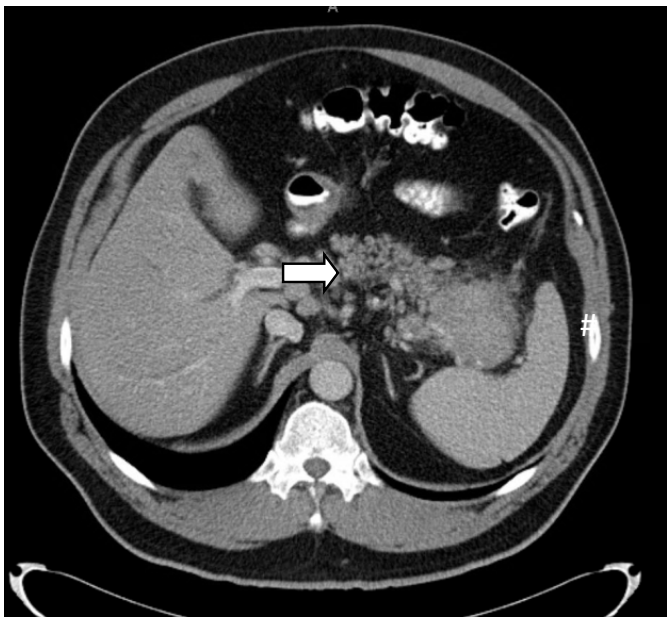
CASE REPORT

In this report, we present the case of a fifty-seven-year-old white male with nodular lymphoid hyperplasia of the bile duct and pancreas. The patient reported no prior medical history, received no medications on a regular basis, and reported no prior surgery when he presented with painless jaundice. The patient was noted to have a weight loss of 30 pounds over several months. He denied having any weakness or fatigue prior to the presentation. A computed tomography (CT) scan with intravenous contrast of the abdomen and pelvis demonstrated mild intrahepatic duct dilation and a 6 by 4.5 cm mass in the tail of the pancreas (**Figure 1**). The patient underwent an endoscopic retrograde cholangiopancreatogram (ERCP) with brushings that demonstrated a Bismuth II Klatskin type biliary stricture with moderate stenosis of the left and right hepatic ducts. Although coated metal biliary stent was placed only into the obstructed common bile duct, the patient had temporary relief from jaundice. Serological tests showed normal levels of IgG4 and anti-nuclear antibody (ANA). The endoscopic ultrasound (EUS) demonstrated a mass in the pancreatic tail described as "heterogeneous and mixed, solid and cystic". The appearance of the mass was described as "atypical for malignancy" although malignancy remained in the differential.

The final pathology report from the common bile duct (CBD) brushings demonstrated malignant cells suspicious of adenocarcinoma and the distal pancreatic mass biopsies were indeterminate with "fragments of fibrotic



S # pancreatic mass
Mild bile duct dilatation

Figure 1. Computed tomography of the patient with nodular lymphoid hyperplasia of the bile duct and pancreas

pancreatic tissue and chronic inflammation." Malignancy could not be definitively ruled out. Of note, the flow cytometric test demonstrated the absence of monoclonal B-cell population (**Figure 2**). The patient subsequently underwent a resection of the right and left extra-hepatic bile ducts, common bile duct, cholecystectomy, Roux-en-Y hepaticojejunostomy, along with a distal pancreatectomy and splenectomy. The pathological analysis of the resection specimen demonstrated biliary duct nodular lymphoid hyperplasia, pancreatic nodular lymphoid hyperplasia, and nodular hyperplasia involving the cystic duct (**Figures 3 and 4**).

DISCUSSION

Nodular lymphoid hyperplasia is a benign entity that can arise in multiple organs [3, 5]. HPB cases have been reported in the pancreas and liver [3]. When nodular lymphoid hyperplasia is hepatic or pancreatic in origin it may present as multiple synchronous lesions [1, 5, 9]. Amer et al reported a patient with synchronous liver and pancreas nodular hyperplasia [10]. However, no cases of this disease in the bile duct have been reported up to date. In this study, we describe a patient who presented with concomitant pancreatic and bile duct nodular lymphoid hyperplasia that was resected because of concern for malignancy.

Nodular lymphoid hyperplasia is a propagation of lymphatic and follicular components without cytological atypia but with complex-reactive germinal centers [5]. This lesion differs from lymphoma because of its polyclonal and immunophenotypical characteristics that are inconsistent with lymphoma [3, 11]. Apart from the association with MALT lymphoma in the stomach, the disease exhibits no malignant potential [1, 3, 9]. Surgical resection is not mandatory and spontaneous regression has been reported in the lung, liver, and pancreas [8].

HPB nodular lymphoid hyperplasia is a rare condition mostly found in the liver; however, fewer than 50 cases have been reported so far [5, 6]. Preoperative diagnosis of hepatic-nodular lymphoid hyperplasia seems to be difficult [6, 11, 12]. Biopsies are often negative for malignancy, and typical radiographic distinction from hepatocellular carcinoma is nearly impossible [12]. Its presentation in the pancreas is less common than in the liver, with less than 10 such cases reported in the literature [1]. In 1991, Nadashiro et al reported the first case of nodular lymphoid hyperplasia of the pancreas in a 57-year-old woman with jaundice who underwent a pancreatoduodenectomy [7]. Similarly to hepatic nodular lymphoid hyperplasia, these tumors are resected because malignancy cannot be excluded. Two cases of patients with multiple pancreatic lesions have also been reported [1, 8].

The vast majority of patients with HPB nodular lymphoid hyperplasia are diagnosed after surgical resection [8]. This is classically seen in middle-aged women co-

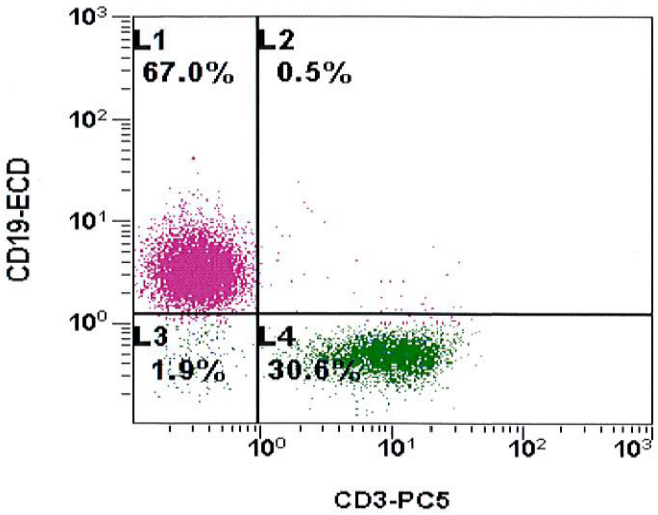


Figure 2. Flow cytometry demonstrated a mixed population of CD3 positive T-lymphocytes and CD19 positive B-cells

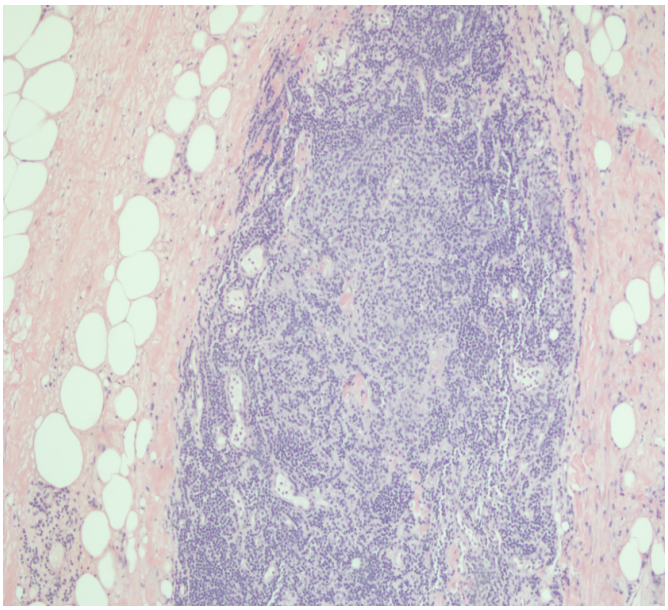


Figure 3. Medium power view demonstrating loose lymphoid aggregate of small polymorphic lymphocytes with germinal center

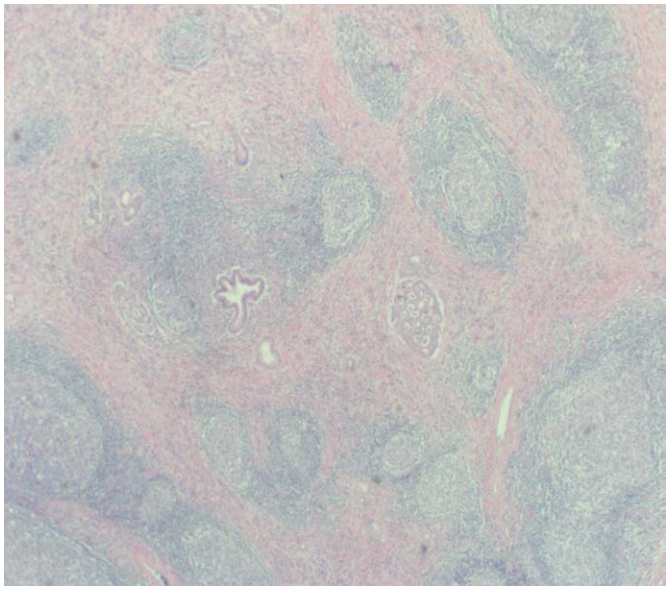


Figure 4. View of pancreas involved by nodular lymphoid infiltrate with admixed/entrapped ductal structures seen in middle

diagnosed with autoimmune disease [1, 5]. In a report of 13 patients with hepatic nodular lymphoid hyperplasia, the majority of patients were found to be women, and almost half had a documented autoimmune disorder [5]. Although preoperative biopsies do not show any evidence of malignancy, it is often difficult to exclude neoplasia or lymphoma. Kim et al reviewed the imaging characteristics of patients suffering from pancreatic nodular lymphoid hyperplasia [9] and reported that the CT scan with IV contrast of these patients exhibited localized tumors with sharp demarcation, the differential diagnosis of which included neuroendocrine tumor, lymphoma, and pseudotumor. However, in contrast to the classic presentation of neuroendocrine tumors in NLH there was a delayed enhancement on CT scan with IV contrast.

In the present case, the patient presented with painless jaundice, a suspicious lesion in the bile duct, and brushings consistent with adenocarcinoma. The CT imaging report revealed the presence of synchronous lesion in the tail of the pancreas that was heterogeneous with a mixture of cystic and solid components. The malignant potential of the pancreatic mass was unclear. The patient underwent a resection of the extra-hepatic and common bile duct with reconstruction and distal pancreatectomy with splenectomy. To the best of our knowledge, this is the first description of a patient with biliary nodular lymphoid hyperplasia.

The differential diagnosis of nodular lymphoid hyperplasia includes benign and malignant tumors that may present similarly. These include neoplastic (adenocarcinoma, neuroendocrine tumors, metastasis, and lymphoma) and non-neoplastic inflammatory or immune conditions. Cytologic and/or histologic sampling of lesions with basic immunohistochemical studies should readily distinguish solid epithelial tumors. Gastrointestinal lymphomas are more commonly observed as secondary extranodal involvement and suspicion should be higher in patients with underlying immune deficiency. The distribution, morphology, and cytologic characteristics of the lymphoid population, flow cytometry and/or immunohistochemistry will most often establish the diagnosis of neoplastic lymphoid disease. Molecular analysis with immunoglobin (IgH) heavy chain gene rearrangement or TcR gene rearrangement studies can establish clonality in lymphoma. Non-neoplastic conditions in the differential for the bile duct include primary biliary cirrhosis, primary sclerosing cholangitis, inflammatory stricture from stone disease, and acute or chronic pancreatitis.

Two benign conditions that should be considered for the pancreatic mass in this situation include autoimmune pancreatitis and follicular cholangitis and pancreatitis. Autoimmune pancreatitis can be primary or secondary (associated with an autoimmune condition such as Sjögren's syndrome, or inflammatory bowel disease). Primary forms of disease are uncommon and have been described as subcategories. For example, when found with associated sclerosing changes of intrapancreatic bile ducts this has been described as lymphoplasmacytic sclerosing pancreatitis [13]. Laboratory studies may reveal the presence of autoantibodies such as antinuclear antibody (ANA) or rheumatoid factor (RF). Gross pathologic findings are variable. Often a diffuse, ill-defined mass or firm pancreatic tissue is described. A variably dense lymphoplasmacytic rich infiltrate is suggestive of an autoimmune component. However, pathologic features of autoimmune pancreatitis and other causes of chronic pancreatitis often overlap; therefore, appropriate correlation with other clinical features such as radiographic findings and laboratory data is essential. Follicular cholangitis and pancreatitis is a unique clinicopathological entity [14].

Histology will demonstrate lymphoplasmacytic inflammation around the large bile or pancreatic ducts.

Patients with pancreatic nodular lymphoid hyperplasia typically present an incidental finding on imaging [9]. This might lead to an increased incidence as the increased use of cross-sectional imaging has led to higher number of pancreatic incidentalomas discovery [15, 16]. These lesions tend to be less common, often benign pancreatic neoplasms [16, 17]. While evaluating asymptomatic pancreatic incidentalomas, surgeons need to be aware of the differential includes benign disease entities, such as nodular lymphoid hyperplasia.

CONCLUSION

Nodular lymphoid hyperplasia is a rare benign condition that has been described in multiple locations, including the gastrointestinal tract. When this disease entity presents in the HPB system, it is most often diagnosed at the time of surgical resection, secondary to an inability to be distinguished from malignancy on imaging. In the pancreas, imaging characteristics can be similar to neuroendocrine tumors; however, enhancement may be delayed. Thus, it is important for pancreaticobiliary and general surgeons to be aware of this clinical entity. A better understanding on this rare benign clinical entity and distinguishing it from a malignant neoplasm might allow patients to avoid resection.

Conflict of interest

The authors have no conflict of interest to declare.

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