

CASE REPORT

EUS-FNA Contribution in the Identification of Autoimmune Pancreatitis: A Case Report

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ABSTRACT

Context Autoimmune pancreatitis is a benign inflammatory disease of the pancreas which mimics pancreatic malignancy both clinically and radiologically. Autoimmune pancreatitis is presented as a diffuse enlargement of the pancreas and as a diffuse irregular narrowing of the main pancreatic duct.

Case report We report the endoscopic-ultrasound-guided (EUS-guided) fine needle aspiration (FNA) cytology features of a case with autoimmune pancreatitis. A 24-year-old woman with diabetes mellitus was admitted to our hospital after having painless jaundice for 15 days. She denied any alcohol consumption. The biochemical profile showed a marked elevation of bilirubin and hyperglycemia while gamma-GT and CA 19-9 levels were increased fivefold. The immunologic profile of the patient was negative. EUS revealed diffuse hypoechoic pancreatic enlargement (sausage-like appearance of the pancreas). EUS-FNA was performed and the smears were rich in inflammatory cells (mainly lymphoplasmacytes) with sparse epithelial cells lacking atypia, elements which show a strong correlation between the histopathological and cytological findings. The patient underwent steroid therapy which led to resolution of the clinical symptoms and imaging abnormalities within a month.

Conclusion The FNA-cytology findings in conjunction with clinical and EUS findings could potentially establish a diagnosis of autoimmune pancreatitis and exclude carcinoma, thus preventing pancreatic resection.

INTRODUCTION

Autoimmune pancreatitis is a chronic fibroinflammatory condition primarily affecting the pancreas [1]. The original description is attributed to Sarles *et al.* [2, 3] who reported several cases of chronic pancreatitis in patients with hypergammaglobulinemia in the 1960s. The diagnostic challenge is of relevance because steroid therapy usually provides resolution of the majority of symptoms, shrinkage of the inflammatory mass (when present) and can avoid unnecessary pancreatectomies [4, 5]. Although first reported in Japan, cases are now reported worldwide [6]. The various clinical manifestations and natural history of this condition have led to a plethora of synonyms, such as sclerosing pancreatitis [7], primary inflammatory pancreatitis [2, 3], lymphoplasmacytic sclerosing pancreatitis [8], autoimmune pancreatitis [9, 10] and sclerosing pancreatocholangitis [11].

Autoimmune pancreatitis is characterized by:
1) increased levels of serum gammaglobulins

or IgG and IgG4; 2) the presence of autoantibodies; 3) diffuse enlargement of the pancreas; 4) diffusely irregular narrowing of the main pancreatic duct and occasional stenosis of the intrapancreatic bile duct on ERCP images; 5) mild symptoms; 6) occasional association with other autoimmune diseases; and 7) effective steroid therapy [12]. Pancreatic endoscopic ultrasound-guided (EUS) fine needle aspiration (FNA) cytology is a widely used technique for evaluating pancreatic masses [13]. The overall accuracy of EUS is superior to CT scans and magnetic resonance imaging (MRI) for detecting pancreatic lesions. Despite the highly effective role of EUS for detecting and staging pancreatic lesions, the cytologic findings of autoimmune pancreatitis have not been well-studied. To our knowledge, the most comprehensive analysis of the cytologic features of this condition with EUS-FNA is the study of Deshpande *et al.* [14]. We report a case of autoimmune pancreatitis with emphasis on EUS-FNA findings and diagnostic dilemmas.

CASE REPORT

A 24-year-old woman with diabetes mellitus was admitted to our hospital with painless jaundice (of 15 days duration), mild abdominal pain and nausea. She denied any alcohol consumption. The biochemical profile showed a marked elevation in total (26 mg/dL; reference range: 0.1-1.0 mg/dL) and direct (14 mg/dL; reference range: 0.01-0.30 mg/dL) bilirubin and marked hyperglycemia (180 mg/dL; reference range: 70-110 mg/dL) with normal pH in arterial blood. Amylase, lipase, calcium, and triglycerides were normal. AST, ALT and ALP were elevated to twice the upper limit of the reference range while gamma-GT and CA 19-9 were increased five times. Anti-HAV, anti-HCV, anti-HIV, HBs Ag, IgM anti-EBV, and CMV were negative, as were ANAs, SMAs, AMAs, p-ANCA, c-ANCA and ENAs. Rheumatoid factor, gammaglobulins and IgG were not elevated and alpha1-antitrypsin levels and ceruloplasmin were in the normal range. IgG4, anti-carbonic anhydrase type II and

anti-lactoferrin antibodies were not determined. EUS was performed by using an echoendoscope (EG 3630UR, Pentax, Tokyo, Japan) connected to a monitoring device (6000 Victor, Hitachi, Tokyo, Japan) and the EUS-guided FNA was performed using 22-gauge needles (22G, Medi-Globe GmbH, Achenmühle, Germany) via a transgastric approach. Smears were made at bedside in the endoscopy suite of the hospital. The aspirated material was smeared onto glass slides, air-dried and immediately stained with rapid hemocolor stain for specimen adequacy assessment and preliminary diagnostic interpretation. Other smears were fixed immediately in 95% alcohol for subsequent Papanicolaou staining. Additional aspirated material was fixed in formalin, embedded in paraffin and processed for routine histologic examination using standard techniques. The upper abdominal ultrasound examination showed a normal appearing liver with an

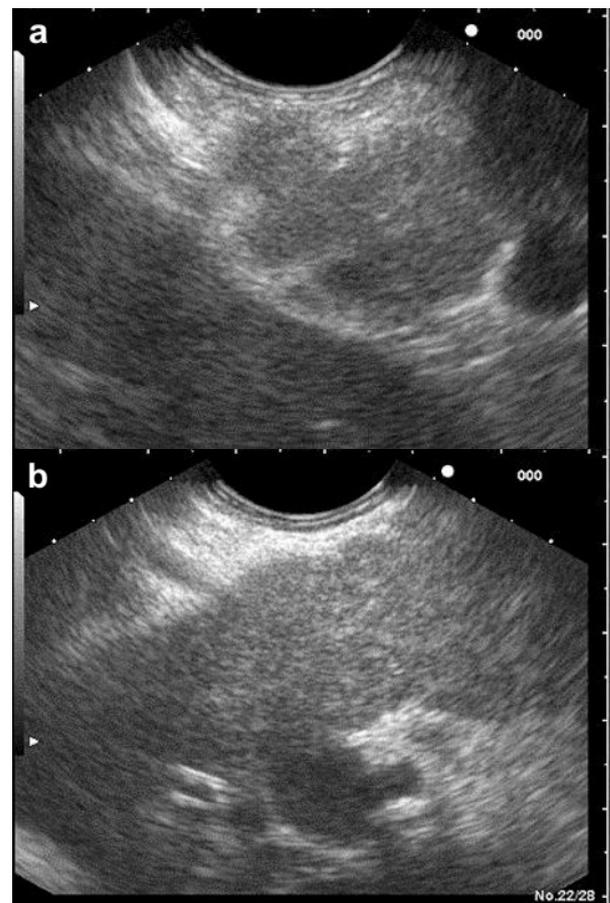


Figure 1. EUS imaging reveals a diffuse hypoechoic pancreatic enlargement.

intact gallbladder, dilated intrahepatic bile ducts with a 12 mm common bile duct and a diffusely enlarged hypoechoic pancreas.

The CT findings revealed a diffusely enlarged isodense pancreas with a suspected 1.5 cm isodense focal mass at the tail of the organ and a second possible 0.9 cm isodense lesion by the intrapancreatic portion of the dilated common bile duct at the head. The liver did not show any focal masses and had a normal morphology except for the dilated intrahepatic bile ducts.

ERCP confirmed the diffuse narrowing of the main pancreatic duct and the narrowed intrapancreatic portion of the common bile duct with an upstream dilation extending intrahepatically. The biliary obstruction was alleviated by inserting a plastic stent following a sphincterotomy

EUS revealed diffuse hypoechoic pancreatic enlargement (sausage-like appearance of the pancreas; Figure 1). Smears were rich in inflammatory cells, mainly lymphoplasmacytes, fragments of fibrous tissue and occasionally spindled cells (fibroblasts) (Figure 2). A monotonous population of sparse epithelial cells was also observed. These cells were round to oval, with moderate cytoplasm, single small but visible nucleoli lacking atypia. We identified them as ductular or pancreatic centroacinar cells. The histopathologic examination revealed a dense lymphoplasmacytic infiltrate around both small and large interlobular ducts (collar inflammation), and significant replacement of pancreatic parenchyma by stromal fibroblastic proliferation. The cytological and histopathological findings were strongly correlated. No immunohistochemical staining was used (e.g. IgG4 stain). On the basis of the above-mentioned clinical, imaging and cytological findings, a diagnosis of autoimmune pancreatitis was made.

The decision was to treat the patient with prednisolone (40 mg daily for a month) and with short-acting insulin injections on demand. During re-examination one month later, a second EUS was done and the findings were almost normal. The pancreatic gland was slightly enlarged and the peripancreatic

mass had disappeared. The patient was euglycemic most of the time and remained

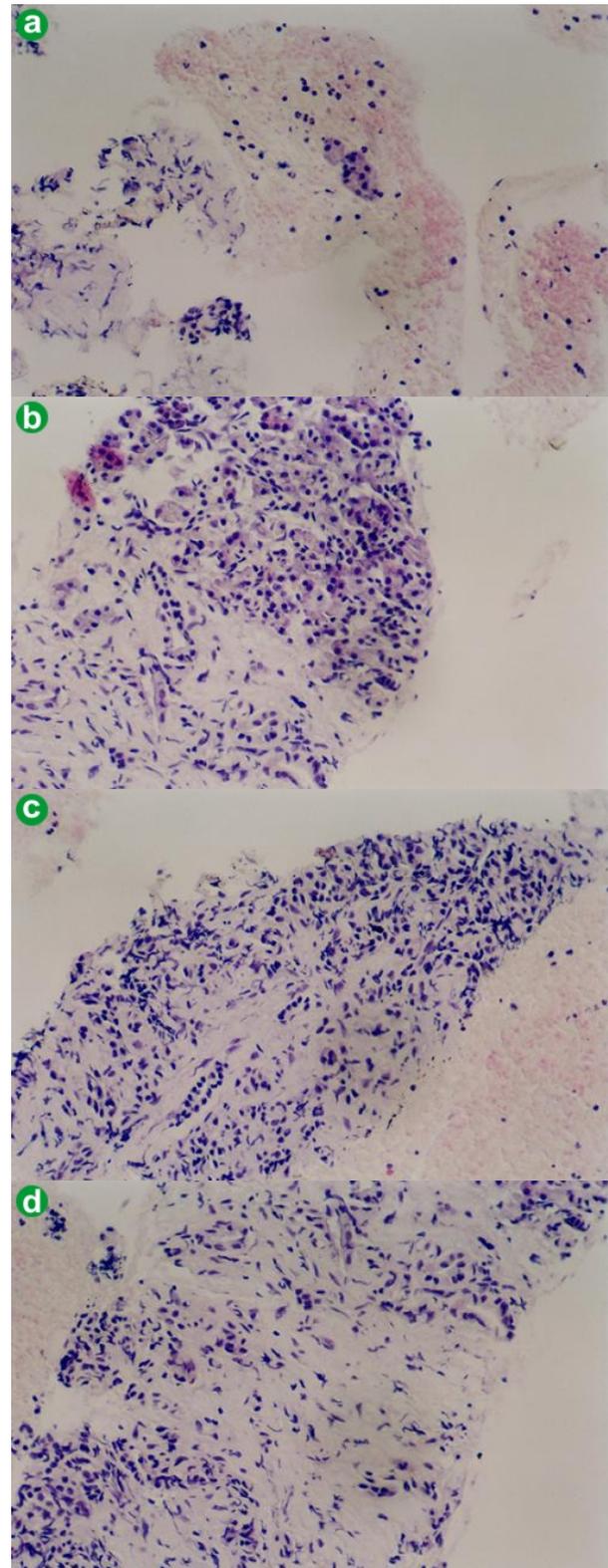


Figure 2. Cell block of autoimmune pancreatitis with cellular stromal fragments, spindled cells (fibroblasts), lymphocytes (with periductular cuffing), occasional plasmacytes, and epithelial cells (centroacinar type) forming small ducts without atypia. (H&E x100).

anicteric. She was dismissed and ordered to continue prednisolone at a dose of 5 mg daily for the next two months, until her next admission in order to remove the biliary stent.

DISCUSSION

In recent years, autoimmune pancreatitis has been established as a special type of chronic pancreatitis. Given that autoimmune pancreatitis is a steroid-responsive disease, it has become of paramount importance to achieve a preoperative diagnosis in order to avoid surgery. Needle/wedge biopsies of the pancreas were reported to be useful in diagnosing autoimmune pancreatitis in more than 50% of cases in one series [15], although other authors are less optimistic about the role of core biopsies in autoimmune pancreatitis [16]. Moreover, this procedure is more invasive than EUS-guided FNA cytology. Our case report shows that, in the appropriate clinical context, EUS-guided FNA cytology can yield morphologic features which could support a diagnosis of autoimmune pancreatitis.

Advances in technology have permitted the use of FNA biopsy under EUS guidance. The ability to obtain cytologic material under direct visualization adds a new dimension to the diagnostic usefulness of this technique because it offers an opportunity for prompt and accurate diagnosis. The overall accuracy of EUS is superior to a CT scan and magnetic resonance imaging (MRI) for detecting pancreatic lesions, especially for the diagnosis of malignant neoplasms. However, in benign lesions, an accurate diagnosis is very difficult in many cases. Recent attention has been drawn to the radiological features of autoimmune pancreatitis. On ERCP [5], the main pancreatic duct typically shows irregular narrowing without upstream dilatation. A segmental narrowing is most likely to mimic cancer as it is accompanied by segmental enlargement of the pancreas in the same area [5]. On helical CT, the pancreas may be diffusely enlarged or could show a focal mass. Seven out of 25 cases in one series showed focal enlargement having a mass-like effect [17]. EUS can be similarly deceptive,

with 43% of one series revealing a focal irregular hypoechoic mass [18]. In our case, EUS revealed diffuse hypoechoic pancreatic enlargement (sausage-like appearance), which was strongly suggestive of pancreatic cancer. Therefore, EUS-FNA was performed. In these instances, only cytology could provide an accurate diagnosis and the needed documentation for unresectable or metastatic malignant neoplasms, or evidence of a benign lesion which does not need further surgical intervention. Furthermore, a biopsy will confirm the cytologic diagnosis.

The cardinal features of autoimmune pancreatitis include a dense lymphoplasmacytic infiltrate of the pancreatic parenchyma with secondary fibrosis and the absence of changes associated with chronic alcoholic pancreatitis. A collar of inflammation around both the small and the large interlobular ducts is one of the key diagnostic features [8, 15]. One would think that a dense lymphoid background would be seen in a cytologic preparation. In our case, a significant lymphoplasmacytic background was shown. The lymphocytes are frequently trapped within stromal fragments. The lymphocyte population is predominantly composed of T lymphocytes, but B cells are consistently present. Most cells are positive for CD4 (55%), although others report a predominance of CD8-positive T cells [19, 20]. It has been suggested that cytokines released by T lymphocytes up-regulate the aberrant expression of HLA class II molecules by the duct epithelial cells [21].

Evaluation of the stromal fragments, which are seen in both adenocarcinoma and autoimmune pancreatitis, are cardinal to the cytologic diagnosis of this entity. Most importantly, malignant cells in carcinoma are usually seen lacing the edge of stromal fragments. In our case, stromal fragments were also observed. The cellularity of the stroma is also a characteristic feature of autoimmune pancreatitis. This cytologic feature has a firm histologic basis. An analysis of autoimmune pancreatitis cases [14] shows that the periductal and interlobular stroma is cellular and is composed of

fibroblasts and myofibroblast-like cells infiltrated by lymphocytes and plasma cells. Eventually, the myofibroblastic proliferation may evolve into a myofibroblastic tumor-like lesion [22]. Spindled stromal cells (fibroblasts) were focally observed (mixed with lymphocytes) in our case, which is important for the identification of this disease. Other morphological features, such as intraductal neutrophilic infiltration, epithelioid cell granulomas, periphlebitis and obliterative phlebitis were occasionally noticed [8, 15, 16, 23] and are useful in establishing a diagnosis of autoimmune pancreatitis.

The presence of sparse epithelial cells in aspiration smears of autoimmune pancreatitis frequently evokes diagnostic difficulties in the differentiation between autoimmune pancreatitis and pancreatic adenocarcinomas. Aspirates which demonstrate cellular dyshesion of ductal cells are highly suspicious for well-differentiated adenocarcinoma. Another potential pitfall is related to the significant centroacinar component sometimes seen in these aspirates. The presence of large numbers of oval monomorphic cells, lacking the typical cytoplasm of acinar cells can raise the differential diagnosis of acinar cell carcinoma versus pancreatic endocrine tumor versus solid-pseudopapillary tumor. However, acinar cell carcinomas usually display nuclear atypia and have large inclusion-like nucleoli [14], thus clearly distinguishing them from a benign acinar epithelium. In autoimmune pancreatitis, the lobular inflammation may cause acinar atrophy and "loosening" of the centroacinar cells which are more readily aspirated. [14]. Histologically, the loss of the acinar parenchyma frequently reflects both ductal obstruction and primary lobular involvement. In our smears, these epithelial cells were round to oval, with moderate cytoplasm, single small nucleoli lacking atypia, which excluded the adenocarcinoma diagnosis.

Often, the diagnosis of autoimmune pancreatitis can be difficult using cytology alone and requires a larger specimen obtained with EUS trucut biopsy [24].

According to a recent study [25], EUS-FNA molecular analysis is a new tool for the accurate differentiation between malignant and benign pancreatic masses. Khalid *et al.* [25] have described a method which detects key DNA abnormalities in EUS-guided FNA aspirate samples from pancreatic masses. A detailed molecular analysis utilizing microsatellite loss and *K-ras* point mutation is highly accurate in diagnosing pancreatic cancer and differentiates it from pancreatitis. Autoimmune pancreatitis is characterized by high levels of serum IgG4, and it has been reported that the serum IgG4 levels in patients with sclerosing pancreatitis are significantly higher than in patients with pancreatic cancer [4]. Others confirm that IgG4 serum levels are specifically elevated in autoimmune pancreatitis and are closely related to disease activity [20, 26].

In conclusion, we believe that EUS-FNA cytology findings, in addition to clinical, serological findings and responsiveness to steroid therapy, may suggest an accurate diagnosis of autoimmune pancreatitis.

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