



Autoimmune Pancreatitis and Pancreatic Cancer. Is there a Relationship between these Conditions? About a Case and Review of the Literature

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ABSTRACT

Introduction: Chronic pancreatitis is a risk factor for pancreatic cancer, but the association with autoimmune pancreatitis (AIP) is less clear. AIP is a rare disease with a challenging diagnosis. Two types of AIP are presented: type 1 and type 2. **Case Presentation:** A 35-year-old female with a history of pancreatitis and subsequent diagnosis of pancreatic cancer. **Discussion:** AIP can be difficult to diagnose because it shares characteristics with pancreatic cancer. IgG4 levels can help diagnose AIP, but they are not always elevated. There is a possible association between AIP and pancreatic cancer, especially in type 1 AIP. Treatment of AIP with steroids can improve symptoms. **Conclusions:** AIP should be considered in the differential diagnosis of patients with obstructive jaundice and pancreatic lesions. Pancreatic biopsy is necessary for a definitive diagnosis of AIP.

Keywords: Autoimmune pancreatitis, AIP, Pancreatic cancer, IgG4, Pancreatoduodenectomy.

INTRODUCTION

Chronic pancreatitis is a well-known risk factor for pancreatic cancer, whereas the association with autoimmune pancreatitis remains debated [1]. Autoimmune pancreatitis (AIP) is a rare condition with an annual incidence of 1.4 per 100,000 inhabitants and a prevalence of 4.6 per 100,000 inhabitants [2]. Diagnosis is challenging and requires a comprehensive evaluation involving clinical, radiological, serological, and histopathological findings. Two types of

autoimmune pancreatitis have been described: type 1, considered a pancreatic manifestation of a multiorgan disease related to IgG4, and type 2, a pancreas-specific pathology unrelated to IgG4 [3]. It is sometimes associated with pancreatic lesions that mimic cancer on imaging, presenting clinically as acute pancreatitis and progressive jaundice [4]

CASE PRESENTATION

A 35-year-old female from Puebla, with a history of hypertension treated pharmacologically for 6 months, occasional alcoholism, denied first-degree relatives with cancer history, previously hospitalized in October 2022 for acute pancreatitis seemingly of biliary origin, and resolved choledocholithiasis by endoscopic retrograde cholangiopancreatography (ERCP) with stone extraction, followed by laparoscopic cholecystectomy.



Figure 1: The double-duct sign (dilatation of the extrahepatic bile duct and pancreatic duct) is typically a sign of malignancy.

In May 2023, she presented with epigastric abdominal pain, scleral icterus, and acholia, prompting urgent medical evaluation. Clinical examination revealed obesity grade II, epigastric pain exacerbated by deep palpation, without signs of peritoneal irritation, and scleral icterus. Laboratory findings showed: RBC 13g/dL, WBC $6 \times 10^9/L$, creatinine 0.6mg/dL, ALT 149IU/L, AST 128IU/L, total bilirubin 5.37mg/dL, direct bilirubin 4.94mg/dL, ALP 614U/L, amylase 72U/L, carbohydrate antigen 19-9 (CA 19-9) 35U/mL. Imaging studies revealed a "double duct" pattern on abdominal computed tomography (Fig.-1). She underwent ERCP, reporting ampullary changes with hypertrophy, stent placement, and ampullary region biopsy showing: chronic and acute inflammation with superficial ulceration (Fig.-2).



Figure 2: The yellow arrow indicates inflammatory changes at the ampulla.

Magnetic resonance cholangiopancreatography showed a morphologically preserved pancreas without extrinsic lesion or dilation, but with main pancreatic duct dilation up to 5.5mm, biliary tract with presence of endoluminal prosthesis (Fig.-3).

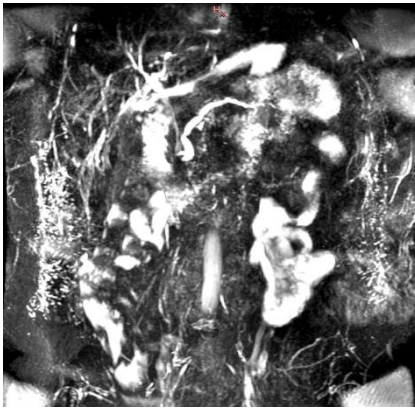


Figure 3: It shows dilation of the pancreatic duct and filling defect in the bile duct compatible with the stent.

The patient re-admitted in August 2023 with clinical presentation of abdominal pain, scleral icterus, and laboratory data reporting: ALP 768U/L, total bilirubin 8.31mg/dL, direct bilirubin 7.84mg/dL, indirect bilirubin 0.47mg/dL, RBC 12g/dL, WBC $10 \times 10^9/L$, repeat ERCP with difficulty in cannulation due to migrated prosthesis into intrahepatic biliary tract, with ampullary changes, and biopsies taken (Fig.-4).

Given the risk of cholangitis and with no pathology report, a percutaneous transhepatic catheter was temporarily placed for decompression. Subsequently, ampullary biopsy pathology reported: chronic enteritis with accentuated activity and epithelial atypia, ulcerated area. Due to the presence of a premalignant lesion associated with ampullary local changes, and candidate for surgical procedure, based on vascular relationships by contrasted tomography, the patient underwent Whipple procedure due to high suspicion of periampullary tumor, specifically a probable ampullary tumor vs pancreatic head tumor.

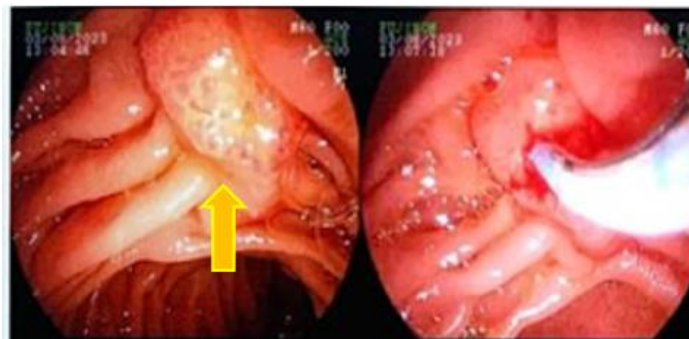


Figure 4: The yellow mark shows ampullary changes where the biopsy was taken.

Pancreatoduodenectomy was performed with intraoperative findings of a 3 cm pancreatic head tumor lesion, 11 mm biliary duct dilation, and 10 mm pancreatic duct dilation, and the specimen was sent for histopathological study which reported on histological sections identified malignant neoplasm of epithelial lineage with glandular growth pattern (Fig.-5).

Corresponding to ductal adenocarcinoma without further specification, tumor site: pancreatic head and tumor size: 2.5x2x2cm, involving ampulla, posterior surface of pancreas, duodenal muscle, and additional finding of non-neoplastic pancreatic parenchyma with abundant fibrosis areas delimiting some acinar groups, showing inflammatory infiltrate of mature lymphocytes and plasma cells, suggestive of autoimmune pancreatitis.

Following histopathological findings, a serum IgG4 measurement was requested, with the following result: Immunoglobulin IgG: 1263.35 mg/dL (reference: 552-1631), IgG Subclass 4: 39mg/dL (reference: 3.0-201.0). At the time of measurement, it was within normal range.

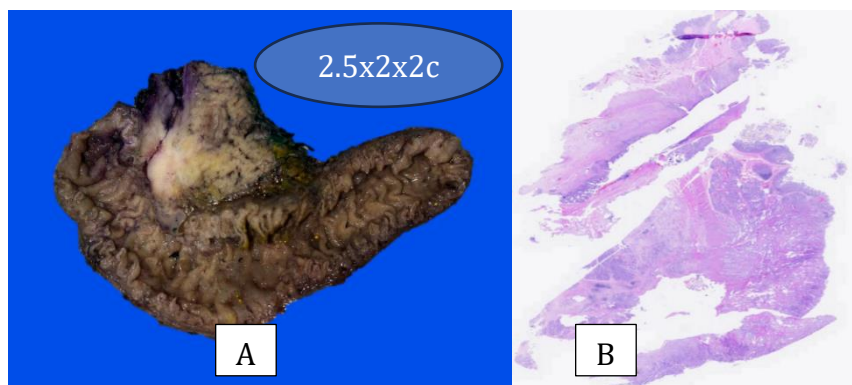


Figure 5: A - Shows the macroscopic lesion. B - Shows the microscopic pattern of the neoplasm.

DISCUSSION

AIP represents 5-10% of acute pancreatitis cases; however, its incidence is currently uncertain, as it is diagnosed in up to 2% of patients undergoing pancreatic surgery for suspected pancreatic cancer [1]. It is estimated that 5% of patients receive a pancreatic cancer diagnosis within two decades of chronic pancreatitis diagnosis [1].

The association between pancreatic cancer and AIP is widely debated due to the low incidence and diagnostic challenge of the latter disorder. There are few clinical and epidemiological studies investigating the relationship between these two conditions. Beyond this, the relationship between AIP and pancreatic cancer cannot be completely ruled out. Even though AIP is a rare form of chronic pancreatitis, the risk is elevated in patients with type 1 AIP; all reported cases of AIP related to pancreatic cancer were described in patients with type 1 AIP [1].

The International Consensus Diagnostic Criteria for Autoimmune Pancreatitis was developed in 2011 [2]. AIP is defined as a specific form of pancreatitis characterized by obstructive jaundice with or without pancreatic lesions, lymphoplasmacytic infiltrate, and steroid responsiveness. It is subdivided into 2 types: type 1 as a pancreatic manifestation of an IgG4-related multiorgan disease, most commonly affecting the hepatopancreaticobiliary system; type 2 involves pancreatic pathology without systemic involvement, characterized by fibroinflammatory changes surrounding pancreatic ducts, with granulocytic epithelial lesions being pathognomonic [3].

The most common clinical presentation includes obstructive jaundice and abdominal discomfort or pain, rarely presenting as acute pancreatitis; there are also cases of completely asymptomatic autoimmune pancreatitis [5]. Contrary to typical forms of autoimmune pancreatitis, patients with atypical presentation and pancreatic cancer share similar clinical presentations, laboratory findings, and morphological characteristics on imaging studies [6]. IgG4 measurement has become a useful tool, albeit sometimes variable and imprecise due to lack of standardization in IgG4 subclass assessment [6]. Clinically, patients with AIP and those with pancreatic cancer share common characteristics such as painless jaundice, elevated tumor markers, or recent onset of diabetes mellitus. Key findings suggestive of AIP include fluctuating obstructive jaundice, elevated serum IgG4 levels, diffuse pancreatic enlargement, duct narrowing with dilation, systemic involvement, and response to steroids [6].

Histologically, AIP is characterized by T lymphocyte infiltration, storiform fibrosis, obliterative phlebitis, narrowed pancreatic ducts due to periductal fibrosis, and lymphoplasmacytic infiltrate [6]. The most important differential diagnosis from pancreatic cancer is chronic pancreatitis; unfortunately, differentiation can be challenging, and patients often undergo pancreaticoduodenectomy. Differential histological features of AIP include periductal plasma cell inflammation, fibroinflammatory stroma, and obliterative venulitis [7]. CA 19-9 is one of the most studied biomarkers in patients with pancreatic cancer. Generally, CA 19-9 levels are above the clinical threshold of 37 U/ml for malignant diseases, whereas most benign conditions have CA 19-9 levels below 37 U/ml [8]. Its nonspecific expression leads to false negatives in Lewis-negative genotypes and false positives in non-malignant biliary obstruction, limiting its universal application. CA 19-9 <100 U/ml likely indicates resectable disease, while values >100 U/ml may suggest unresectable or metastatic disease [9].

There is a proven association between pancreatic cancer and forms of chronic, sporadic, and hereditary pancreatitis [10]. Inflammation and metainflammation increase the risk of pancreatic cancer; however, pancreatic cancer induces an immunosuppressive response, and the balance between these influences elevates carcinogenesis [11].

The Whipple procedure is not indicated solely for malignant neoplastic processes but also for benign conditions aimed at treating cancer and symptomatic benign diseases. In surgery for precancerous lesions, it is understood that pancreatic cancer arises from a process of sequential steps with increasing dysplasia grade. Currently, there are no evaluation programs for non-hereditary forms of cancer, so risk factors such as recent-onset diabetes mellitus, obesity, smoking, and chronic pancreatitis should be considered and timely surgery offered [12].

CONCLUSIONS

As previously mentioned, AIP is an entity that can cause chronic pancreatitis, and there is a well-established relationship between the latter and pancreatic cancer. Likewise, there is a proven relationship between AIP and pancreatic cancer and with a stronger relationship with AIP type 1, in the present case, we wanted to demonstrate the possible relationship of AIP as a possible etiology of Pancreatic Cancer vs. the presence of two different etiologies which alone have low incidence and prevalence.

In our case, although there were suggestive data by imaging, such as dilation of the pancreatic duct, and subsequently by histopathology, peri-acinar fibrosis and lymphocytic infiltrate, there was also a negative IgG 4 measurement, at least at the time of the taking, after the surgical procedure, so in this context it possibly lacked validity.

Management with a multidisciplinary approach is required to complete study protocols and detect entities that may affect or favor the progression of potentially malignant pathologies that are in turn curable through timely treatments and/or procedures.

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