American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2024; 25: e944286
DOI: 10.12659/AJCR.944286

Received: 2024.02.27
Accepted: 2024.07.09
Available online: 2024.08.05
Published: 2024.09.16

Focal Autoimmune Pancreatitis Morphologically Mimicking Pancreatic Cancer: A Case Report and Literature Review

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ADEF 1 Daniel Paramythiotis
ABCDEF 2,3 Eleni Karlafti
BCDE 1 Krystallenia Siniosoglou
E 1 Dimitrios Tsavdaris
BDE 4 Ioanna Abba Deka
DE 4 Georgia Raptou
BD 5 Xanthippi G. Mavropoulou
BD 5 Elizabeth Psoma
BD 1 Stavros Panidis
ABD 1 Antonios Michalopoulos

1 1st Propaedeutic Surgery Department, University General Hospital of Thessaloniki AHEPA, Aristotle University of Thessaloniki, Thessaloniki, Greece
2 Department of Emergency, University General Hospital of Thessaloniki AHEPA, Aristotle University of Thessaloniki, Thessaloniki, Greece
3 1st Propaedeutic Department of Internal Medicine, University General Hospital of Thessaloniki AHEPA, Aristotle University of Thessaloniki, Thessaloniki, Greece
4 Department of Pathology, University General Hospital of Thessaloniki AHEPA, Aristotle University of Thessaloniki, Thessaloniki, Greece
5 Department of Clinical Radiology, University General Hospital of Thessaloniki AHEPA, Aristotle University of Thessaloniki, Thessaloniki, Greece

Corresponding Author: Eleni Karlafti, e-mail: linakarlafti@hotmail.com
Financial support: None declared
Conflict of interest: None declared

Patient: Male, 58-year-old
Final Diagnosis: Focal autoimmune pancreatitis
Symptoms: Painless obstructive jaundice
Clinical Procedure: —
Specialty: Surgery
Objective: Challenging differential diagnosis
Background: Autoimmune pancreatitis (AIP) is identified as an outlier in the clinical practice of chronic pancreatitis caused by autoimmune system dysfunction. AIP is classified into 3 subtypes: AIP type 1 and AIP type 2, which are both sensitive to corticosteroids, and the recently introduced AIP type 3.
Case Report: We present a case of a patient who presented with painless obstructive jaundice. Computed tomography (CT) revealed hyperdense gallbladder material, further dilatation of intrahepatic bile ducts, and distention of the bile duct (15 mm). Based on the available clinical data, which were strongly compatible with pancreatic cancer, Whipple surgery was selected as the treatment for this case. The consequent histopathological report revealed areas of pancreatic parenchyma with fibrous connective tissue development and dense inflammatory cell infiltration with lymphocytes and plasmacytes, which showcased IgG4 positivity. The clinical results suggested a diagnosis of AIP type 1, and the patient was referred to his treating physician for further treatment of AIP. Preoperative histological examination of the pancreas, along with evaluation of the radiological and serological features, could have aided in determining the diagnosis of AIP type 1 pancreatitis despite the unique abnormality of this particular case.
Conclusions: Given the aforementioned conditions, AIP, even as a rare clinical entity, emerges as a canonical ailment and should be considered a viable possibility in clinical practice since it can exclude the patient from an unnecessary surgery.
Keywords: Autoimmune Pancreatitis • Jaundice, Obstructive • Pancreatic Neoplasms
Abbreviations: **AIP** – autoimmune pancreatitis; **CT** – computed tomography; **PTC** – percutaneous transhepatic cholangiography; **ERCP** – endoscopic retrograde cholangiopancreatography; **MRCP** – magnetic resonance cholangiopancreatography; **EUS-FNA** – endoscopic ultrasound-guided fine-needle aspiration; **MRI** – magnetic resonance imaging
Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/944286

3074 1 3 52

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Introduction

Autoimmune pancreatitis (AIP) is a rare form of chronic pancreatitis that occurs due to dysfunction in the immune system. In 1995 Yoshida et al first proposed the term, reporting a case of chronic pancreatitis responding to steroid therapy [1]. Based on the international consensus diagnostic criteria (ICDC), AIP is classified into 3 subtypes: AIP type 1, AIP type 2, and the recently introduced AIP type 3. Diagnosis relies on a combination of serological, histological, radiological findings, involvement of a non-pancreatic organ, and sensitivity to corticosteroids [2,3].

AIP type 1, also known as lymphoplasmacytic sclerosing pancreatitis (LPSP), is an IgG4-related disease characterized by high serum IgG4 levels and both pancreatic and extrapancreatic symptoms. Histologically, it is characterized by IgG4 cell infiltration in affected organs [2,4]. AIP type 2, also known as idiopathic duct-centric pancreatitis (IDCP), is usually a pancreas-centric disease and not associated with IgG4 levels. It is often associated with inflammatory bowel disease, with the same prevalence to males and females, and with low relapse rates. Due to the lack of an appropriate biomarker, histological examination is necessary for diagnosis [2,4]. Type 3 autoimmune pancreatitis (AIP) is a recently identified subtype linked to immune checkpoint inhibitor (ICI) therapy used in cancer treatment. Most patients have elevated pancreatic enzymes without symptoms, but symptoms can resemble acute pancreatitis or type 1 diabetes mellitus [5-7].

The clinical manifestations of AIP types 2 and 3 vary regionally [4]. Obstructive jaundice, with or without a pancreatic mass, is the most common symptom [3]. In type 1 AIP jaundice is typically painless, while in type 2 it coexists with abdominal pain and pancreatitis. Type 1 is divided into active and late phases. Symptoms of chronic anodyne pancreatitis atrophy of the pancreatic parenchyma, calcification, and ductal dilation may emerge later in patients with a typical rapidly evolving clinical picture, along with diabetes and steatorrhea due to endocrine and exocrine dysfunction [8]. Jaundice, weight loss, and abdominal pain may suggest a pancreatic tumor. A focal pancreatic mass or swelling can also mislead clinicians. However, pancreatic cancer, which is more common than AIP, must be excluded. Fluctuating jaundice symptoms, elevated serum IgG4 levels above 280 mg/dL (present in only 1% of pancreatic cancer patients), and involvement of other organs are factors that favor AIP over pancreatic malignancy [3,4,8,9].

Preoperative histological examination of the pancreas, along with radiological and serological assessments, aids in the differential diagnosis of AIP type 1. This diagnosis includes both benign and malignant conditions such as pancreatic cancer, AIP types 2 and 3, chronic pancreatitis, pancreatic neuroendocrine tumors, pancreatic cysts, pseudocysts, and other rare pancreatic pathologies [2,4].The similarity in clinical and radiological features among these conditions can pose significant diagnostic challenges, as seen in this case. This was also evident in this case, where the distinctive abnormality presented a challenge in the diagnostic process. Immediate diagnosis is crucial to determine optimal treatment, as management differs between pancreatic cancer and AIP. Surgical treatment is typically the first option for pancreatic cancer, with AIP often diagnosed postoperatively. Despite advancements in understanding AIP, differentiation still poses a diagnostic challenge [8,10].

Case Report

A 58-years-old man presented to the hospital with the diagnosis of pancreatic head cancer based on his radiological report. The patient also reported 2 days of painless obstructive jaundice. His personal history revealed dyslipidemia and episodes of glucose metabolism disorder (prediabetes diagnosed 8 months prior) adjusted with diet alterations. Physical examination revealed a mild productive morning cough. Laboratory findings showed carcinoembryonic antigen (CEA) 3.02 ng/ml, cancer antigen (CA) 19-9 1.87 U/ml, CA 15-3 20.99 U/ml, CA 125 20.04 U/ml, serum glutamic-oxaloacetic transaminase (SGOT) 46 U/l, serum glutamic pyruvic transaminase (SGPT) 92 U/l, γ-GT 557U/l, total bilirubin 15,8 mg/dl, direct 13.29 mg/dl, indirect 2.5 1 mg/dl, serum amylase 155 U/l, and erythrocyte sedimentation rate (ESR) 46.

Contrast-enhanced computed tomography (CECT) of the abdomen revealed a diffuse enlargement of the pancreatic parenchyma, especially of the head of the pancreas, with an ill-defined hypodense border and hyperdense content in the gallbladder. Pancreatic and peripancreatic inflammation and dilatation of intrahepatic bile ducts and the main bile duct were present (**Figure 1**).

Magnetic resonance imaging (MRI) confirmed the acute inflammation of the head of the pancreas (**Figure 2A-2C**). Magnetic resonance cholangiopancreatography (MRCP) showed a focal lesion at the lower limit of the head of the pancreas, with low signal on T1 sequences, hypovascular with restricted diffusion. The results were considered suspicious for malignancy. Dilation of the pancreatic duct was also noted. Lymph nodes appeared to be normal in the examined abdominal area (**Figure 2D**). Due to obstruction in the pancreatic duct, leading to obstructive jaundice and multiple technical challenges, a percutaneous transhepatic cholangiography (PTC) procedure was carried out as an effective alternative, resulting in successful stent placement. PCT revealed dilatation of the biliary tract due to a stricture in the lower common hepatic duct (**Figure 2E**). The patient responded well to postoperative treatment, with a decrease in bilirubin levels.

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

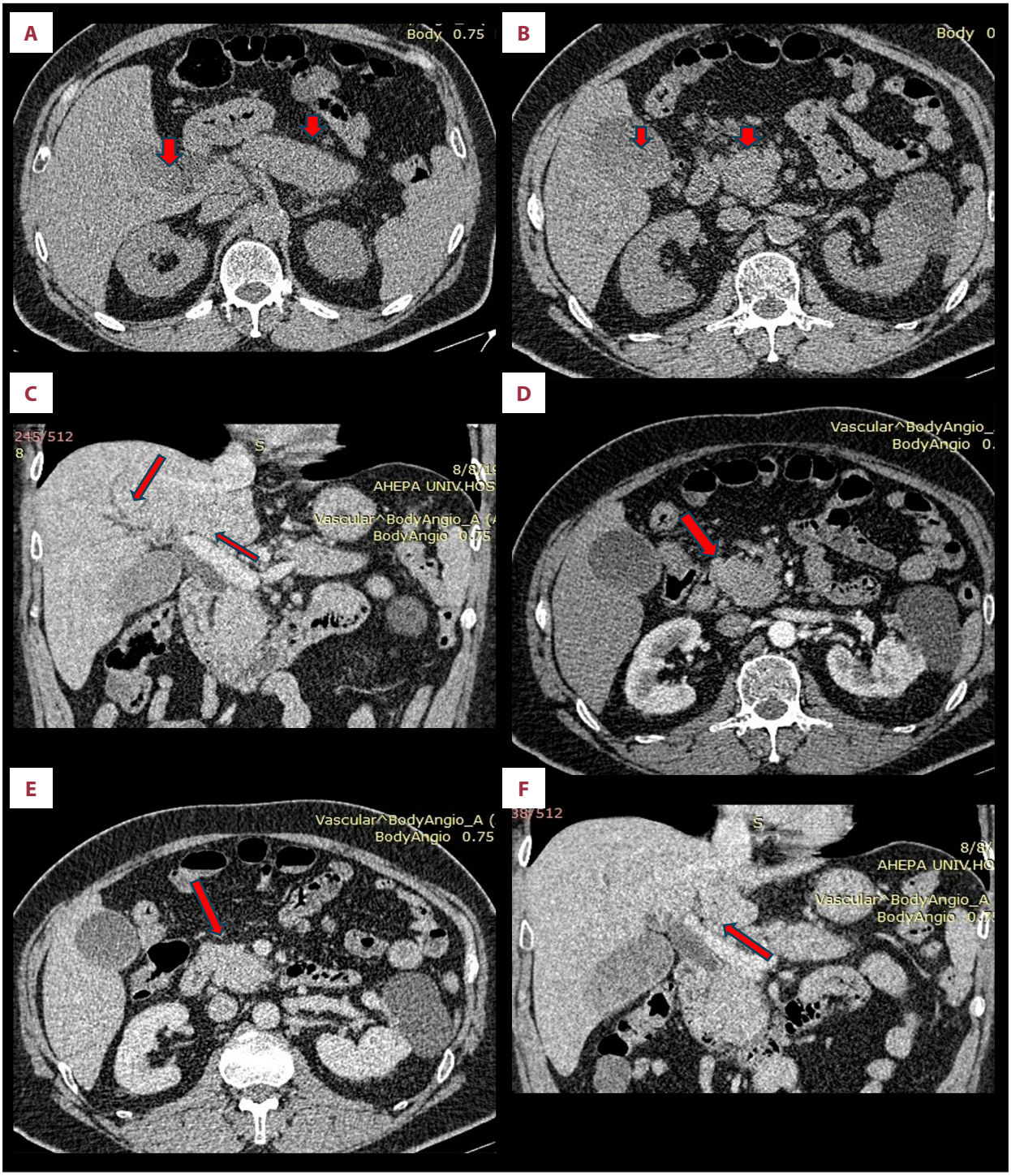


Figure 1. Detailed CT scan imaging characteristics of pancreatic enlargement and inflammation. (**A, B**) NECT axial images: Diffuse enlargement of the pancreas, especially of the head, with poorly-defined borders. Hyperdense content in the gallbladder. (**C, D**) CECT late arterial/portal venous phase; axial images: Heterogeneous attenuation of the head of the pancreas. Pancreatic inflammation is mainly localized to the area adjacent to the duodenum. Peripancreatic inflammation with surrounding fat stranding. (**E, F**) coronal and axial MPR images respectively: Pancreatic inflammation causing dilatation of the common bile duct and intrahepatic bile ducts. Arrows in the images point to the regions of inflammation and areas with ill-defined borders. NECT – non-enhanced computed tomography; CECT – contrast-enhanced computed tomography; MPR – multiplanar reconstruction.

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

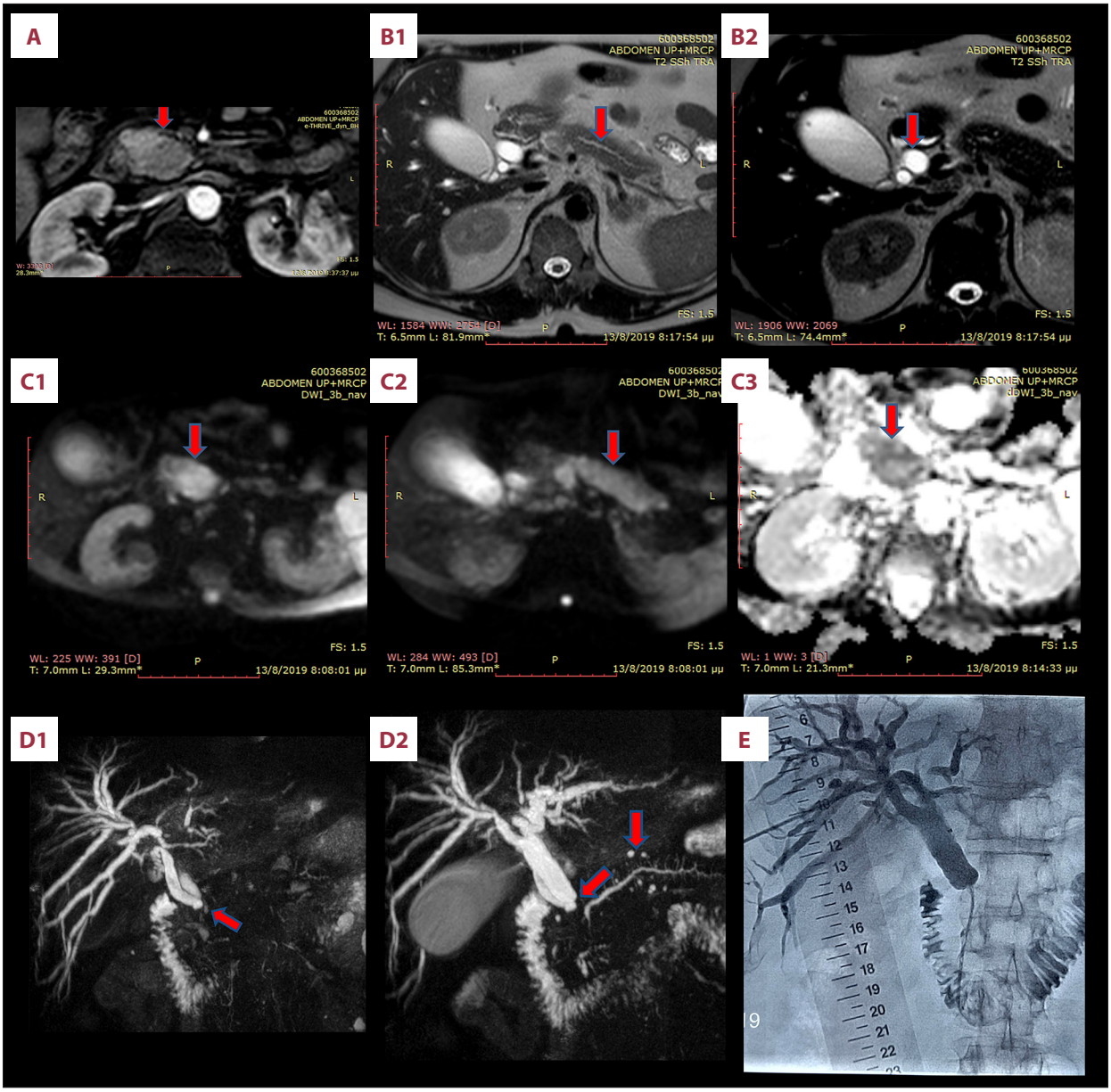
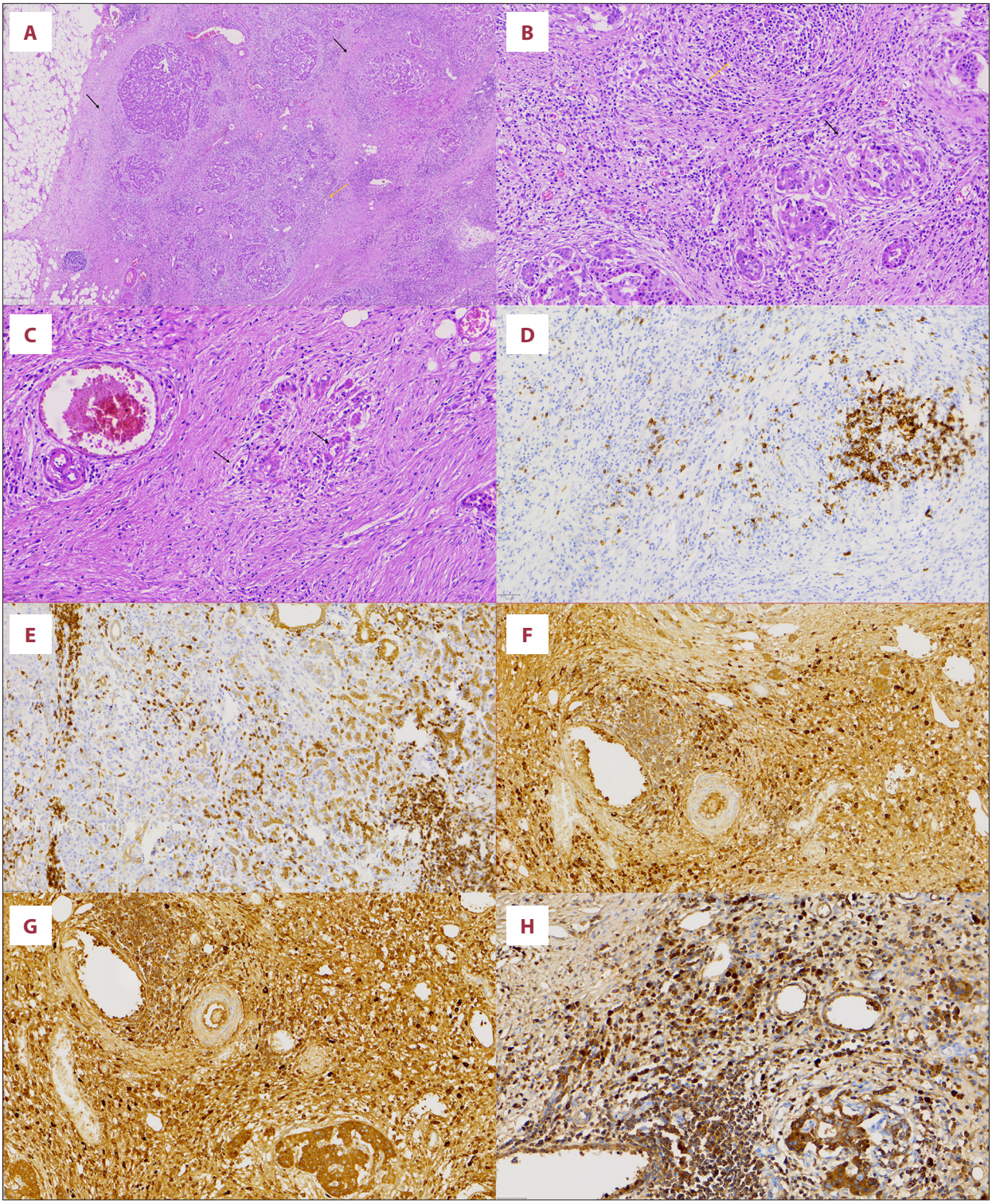


Figure 2. Detailed MRI and MRCP imaging characteristics of pancreatic pathologies. (**A-C**) MRI: (**A**) Low-intensity area in the pancreatic head. (**B**) Dilatation of the pancreatic (**B1**) and the common bile duct (**B2**). Sediment–fluid level in the gallbladder. (**C**) Diffusion restriction in the pancreatic head (**C1**) in comparison to the rest of the body and tail (**C2**). Low signal on the ADC map (**C3**). (**D**) MRCP: abrupt ending of the common bile duct (there is no icicle sign) (**D1**). Multiple cystic lesions in the periphery of the pancreas (dilatation of the pancreatic duct brunches?) (**D2**). (B) PTC showing abrupt ending of the common bile duct. Arrows in the images point out the areas of interest, such as regions of low intensity, dilatation, sediment–fluid levels, diffusion restrictions, and abrupt endings. MRI – magnetic resonance imaging; MRCP – magnetic resonance cholangiopancreatography; PTC – percutaneous transhepatic cholangiography.

Considering the imaging methods, as well as the clinical and laboratory findings, the patient underwent a Whipple operation on suspicion of malignancy. The surgery was completed without complications and the patient was admitted to The Intensive Care Unit (ICU) for postoperative follow-up. He was extubated without complications and then transferred to the clinic for further recovery. The tissue removed during the procedure, including of the head of pancreas, the gallbladder and cystic duct, part of the duodenum and lymph nodes (mesenteric, hepatoduodenal and celiac artery lymph nodes), underwent histopathological examination for further evaluation of the carcinoma's stage.

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]



Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

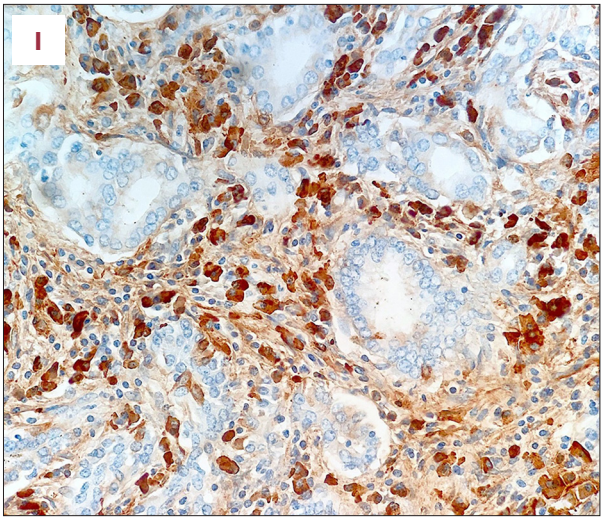


Figure 3. Histopathological and Immunohistochemical Analysis of Pancreatic Tissue. (**A-C**) H&E: (**A**) Pancreatic parenchyma with destruction of normal architecture, extended storiform fibrosis (black indication) and presence of lymphoplasmacytic infiltrate (yellow indication). (**B**) Pancreatic parenchyma with acinar atrophy and degeneration (black indication). Dense lymphoplasmacytic infiltrate is visible (yellow indication), (**C**) On the right side of the image obliteration of the vein with the presence of recanalization (black indication) is seen. (**D**) CD20: CD20+ lymphocytes form a secondary lymphoid follicle, (**E**) CD3: CD3+ lymphocytes are abundant, forming clusters and are mostly arranged around blood vessels. (**F, G**) KAPPA&LAMBDA: The increased number of polyclonal plasmacytes are highlighted by the Kappa and Lambda immunohistochemical stains. (**F**) KAPPA, (**G**) LAMBDA. (**H**) IgG: Clusters of IgG positive plasmacytes, seen in pancreatic parenchyma and surrounding pancreatic acini. (**I**) IgG4: The majority of IgG positive plasmacytes surrounding atrophic pancreatic acini are IgG4. Darkly stained cells are considered positive. Arrows and annotations in the images point to regions of fibrosis, lymphoplasmacytic infiltrate, acinar atrophy, vein obliteration, secondary lymphoid follicles, clusters of lymphocytes, and plasmacytes. H&E – hematoxylin and eosin staining. CD20 and CD3 – immunohistochemical markers for lymphocytes. Kappa and Lambda – immunohistochemical markers for polyclonal plasmacytes. IgG and IgG4 – immunohistochemical markers for IgG- and IgG4-positive plasmacytes; Staining method – hematoxylin and eosin; CD20, CD3, Kappa, Lambda, IgG, and IgG4 immunohistochemical stains.

During gross examination of the pancreas, a poorly-defined white area was recognized macroscopically. This diffuse area was primarily located in the head of the pancreas and was firmer than the rest of the pancreatic tissue. We obtained multiple tissue samples from this area. There, the pancreatic parenchyma showed disruption of its internal architecture with destruction of the normal lobular architecture and development of dense, fibrous connective tissue with diffuse inflammatory cell infiltration mainly composed of clusters of lymphocytes (CD20 and CD3) and plasmacytes (polyclonal in kappa and lambda light chains) (**Figure 3A-3C**).

The clusters of plasmacytes showed expression of IgG and IgG4 (**Figure 3H, 3I**). No neoplastic cells were present in any of the sections obtained. The lymphoplasmacytic infiltrations were mainly located around atrophic acini. Vessel obliteration was noted as well. The duodenal mucosa also showed epithelial apoptosis and inflammatory cell infiltration. Reactive lesions were observed in the lymph nodes, without any sign of malignancy. Pancreatic ducts were dilated, with areas of pancreatic intraepithelial neoplasia (PANIN I). Areas of ulceration, fibrous connective tissue development, and dense inflammatory cell infiltration with lymphocytes and plasmatocytes were also observed at the operative border of the cystic duct. These findings suggested a diagnosis of AIP type 1. The patient received instructions to contact his treating physician to proceed with further treatment regarding his AIP condition.

Discussion

AIP is a rare condition, with a prevalence of less than 1 person/100 000 [11]. Since the evolution of diagnostic means (radiological, histological, and serological), the number of patients diagnosed with AIP, an uncommon autoimmune disease in clinical practice, has increased. In the past few years, 27% of patients suspected of having pancreatic adenocarcinoma who underwent the Whipple procedure were ultimately diagnosed with AIP [12]. This is a significant percentage that should not be overlooked, as surgery is not a simple and safe clinical procedure, but carries risk of many postoperative complications and risks for the patient. Through this case, the need for a comprehensive differential diagnosis becomes easily understandable, as it could potentially avert surgical intervention. Specifically, if the patient's clinical presentation (lack of pain) and the absence of cancer markers had raised our suspicion of IgG4-related disease, the patient may have avoided undergoing extensive surgeries like the Whipple procedure.

According to the ICDC, AIP is diagnosed by a combination of clinical and histological features: lymphoplasmacytic infiltration and fibrosis on histological examination, along with characteristic imaging findings, elevated serum IgG4 levels, and response to steroid therapy as clinical criteria [13]

The patient's presentation with a scheduled operation for suspected pancreatic head cancer underscores the initial diagnostic

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

challenge, particularly given the radiological findings suggestive of malignancy. The manifestation of painless obstructive jaundice is another obstacle to the smooth implementation of the diagnostic approach. Specifically, painless obstructive jaundice is a common manifestation of both diseases [2,4]. However, the absence of significant elevation in CA19-9 levels warrants consideration of alternative diagnoses, including autoimmune pancreatitis. Furthermore, an elevated serum amylase level is consistent with pancreatic involvement, although it lacks specificity for distinguishing between different etiologies of pancreatitis. The presence of elevated inflammatory markers underscores the inflammatory nature of the condition and supports the diagnosis of autoimmune pancreatitis, which is characterized by a significant inflammatory component [3-5,9,10]. The patient's personal history suggested a predisposition to autoimmune diseases, as indicated by dyslipidemia and the recent diagnosis of prediabetes.

The CT findings (**Figure 1**) show diffuse enlargement of the pancreas with inflammation mainly in the pancreatic head. Peripancreatic inflammation and dilation of the biliary tract were also observed, consistent with a suspicion of pancreatic problems, potentially autoimmune pancreatitis. MRI results (**Figure 2**) confirmed significant pathology in the pancreatic head, including a low-intensity area, suggesting inflammation. Additionally, the images show dilatation of the pancreatic and common bile ducts, suggesting ductal obstruction, which is often found in AIP. Furthermore, diffusion restriction within the pancreatic head, as evidenced by low signal on the ADC map, showed inflammation, which is characteristic of AIP. MRCP and PTC provide additional information, revealing biliary tract involvement, further supporting the diagnosis. Histopathological examination (**Figure 3**) confirmed autoimmune pancreatitis, displaying characteristic features like storiform fibrosis, lymphoplasmacytic infiltrate, and obliterative phlebitis. The presence of IgG4-positive plasma cells supports the diagnosis of IgG4-related autoimmune pancreatitis, a subtype associated with elevated serum IgG4 levels and systemic involvement of multiple organs.

CECT and MRI confirmed pancreatic inflammation, especially regarding in the head of the pancreas, as well as biliary tract involvement, consistent with the initial suspicion of pancreatic cancer. MRCP findings also raise suspicion of malignancy. However, the finding of diffuse pancreatic enlargement without a discrete mass suggested a diagnosis of AIP type 3 pancreatitis.

A review of 18 surgical studies [14-31] published in the past 11 years clearly shows the difficulty of AIP diagnosis (**Table 1**). In a 2019 study by Dickerson et al, which included 45 cases with a confirmed AIP diagnosis, 26 were operated on under suspicion of pancreatic cancer, of which 3 cases also had a positive biopsy for pancreatic cancer [21]. A study by Detlefsen in 2012, which included 114 European patients undergoing surgical treatment and concluded in a postoperative AIP diagnosis, suggested that most patients could be excluded from surgery based on clinical, serological, and histopathological features [20]. Nevertheless, cancer is a more common disease and a leading cause of death, but it has a better prognosis if treated promptly. Thus, the possibility of malignancy should be excluded, as it can coexist with autoimmune pancreatitis, occur during the onset of the disease, or develop afterward [22].

Laboratory findings can provide significant guidance for diagnosis in cases like this and can also indicate the likely direction of the diagnosis. Specifically, IgG4 serum level, although it is commonly elevated in most AIP type 1 cases, usually cannot on its own confirm the diagnosis of AIP. A 2001 report by Hamano et al suggested that an IgG4 serum level of 135 mg/dL has an accuracy of 97%, a sensitivity of 95%, and specificity of 97%. Similarly, a study conducted by the Mayo clinic in 2007 found an IgG4 level of 140 mg/dL has sensitivity of 93% and specificity of 36% [32,33].

Recent studies have assessed the diagnostic value of CA19-9 levels in differentiating between AIP and pancreatic cancer. High levels of CA19-9 are common in patients with pancreatic cancer, yet they can also be elevated in some AIP cases [34]. For example, van Heerde et al (2014) reported that low CA19-9 levels suggest an AIP diagnosis over malignancy [35]. Serum IgG4 and CA19-9 levels are factors of limited significance individually in the differential diagnosis of these 2 diseases. However, it has been reported that when they are used jointly, their sensitivity and specificity have clinical utility [35,36]. Antinuclear antibodies, antilactoferrin, and rheumatoid factor may also present elevated levels in AIP cases [37].

Imaging plays a crucial role in diagnosing AIP and distinguishing it from pancreatic cancer. CT and MRI are particularly useful for identifying key features of AIP, such as diffuse or focal enlargement of the pancreas and associated biliary tract abnormalities [38]. The diffuse type may present with an enlarged 'sausage-like' pancreas with an atrophic pancreatic duct. A hypodense capsule-like border surrounds the pancreatic parenchyma, possibly because of inflammation and fibrosis of nearby tissue. The focal type is more difficult to differentiate from cancer due to the existence of tumor-like masses, followed by partial duct stenosis. Lymph node alteration of shape and structure is also a radiological similarity of both, which can be misleading. MRI has an advantage over CT in identifying focal AIP from ductal adenocarcinoma [39].

Magnetic resonance cholangiopancreatography (MRCP) can provide useful information regarding the biliary tree and ductal abnormalities due to inflammation. On MRCP, it is possible to depict the extended obstruction of the pancreatic duct, the

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Table 1. Review of 18 studies published in the last 11 years on postoperative cases with autoimmune pancreatitis.

Study (study period) [Ref]	Study cohort	AIP type	Symptoms	Weight loss	IgG4
Detlefsen, 2012 (1987-2010) [20]	114 patients with AIP	Type 1: 63 (55.3%) Type 2: 51 (44.7%)	UN	UN	Available in 29 patients (25.4%) (+) type 1 (Postoperative): 12/18 (66.7%) type 2: 1/11 (9.1%)
van Heerde, 2012 (2000-2009) [15]	7 patients with AIP among 274 PDs (2.6%)	type 1: 2 (28,5%) type 2: 4 (57.2%)	Jaundice (86%), weight loss, Pain moderate/severe (29%), Recent onset diabetes (29%)	Mean weight loss 2.7 kg	(+) 1/3 (preoperational)
Yurci, 2013 (1990-2012) [16]	47 patients with AIP, 24 underwent surgery	type 1: 29 (74.3%) type 2: 7 (17.9%)	Abdominal pain 29 (61.7%), Acute pancreatitis 19 (40.4%), Weight loss 28 (59.6%)	UN	Available in 21 patients, 0-139: 10 patients (47.6%), 140-279: 4 patients (19.0%), ≥280: 7 patients (33.3%)
Miura, 2013 (1990-2010) [14]	13 patients with AIP in comparison to 29 patients with CP	type 1 (100%)	Abdominal pain (46%), Jaundice (23%)	UN	(+) in $^{1}/_{3}$ (Preoperational), (+) in $^{2}/_{3}$ (Post Operational)
Vitali, 2014 (2005-2011) [17]	11 patients with AIP among 373 surgical operations for pancreatic cancer	type 1: 8 type 2: 3	Abdominal pain (64%), Weight loss (64%), Jaundice (36%), Acute pancreatitis (27%)	59%, (range 13.7-9.4 kg)	UN
Macinga, 2017 (2000-2013) [18]	15 patients with AIP among 295 patients who underwent surgery	type 1: 6 type 2: 9	Weight loss (80%), Jaundice (47%), Diabetes (33%)	AIP: 8,5kg (range 3-12), AIP +PC: 15.5 (range 8-50)	Normal range (preoperative): 100% (from the total 3 patients with available results)
Dickerson, 2019 (1997-2016) [21]	45 patients with AIP, 27 underwent surgery	type 1: 16 type 2: 9	UN	UN	(+) 2/11
Seki, 2023 (1979-2018) [19]	19 patients with AIP	type 1: 18 type 2: 1	Epigastralgia (n=4, 21%), Jaundice (n=3, 15,7%), Backache (n=2, 10,5%)	UN	Measured in 5 patients, (+) in 3 patients

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Table 1 continued. Review of 18 studies published in the last 11 years on postoperative cases with autoimmune pancreatitis.

Study (study period) [Ref]	Study cohort	AIP type	Symptoms	Weight loss	IgG4
Ikeura et al, 2014 [26]	30 patients with AIP	Type 1: 23 Type 2: 7	Jaundice 17 Abdominal pain 11 Weight loss 10	UN	17% >2× upper limit of normal value 39% 1-2× upper limit of normal value
Wojcicki et al, 2015 [27]	9 patients with AIP among 469 patients who underwent surgery	Type 1: 8 Type 2: 1	Jaundice 16 (47.06%), Pain 18 (52.94%), Weight loss 16 (47.06%)	UN	UN
Kimura et al, 2014 [25]	6 patients with AIP type 1, underwent surgery	100% AIP type 1	3 Epigastralgia 2 Jaundice	UN	4 patients had an elevated level, 0-139: 0 patients, 140-279: 3 patients, ≥280: 1 patient
Zhang et al, 2015 (2003-2012) [23]	16 patients with AIP among 271 patients who underwent surgery	Type 1: 12	6 Emaciation 7 Jaundice 7 Abdominal pain	UN	12 patients had an elevated level
Clark et al, 2013 (1986-2011) [31]	74 patients with AIP who underwent surgery	type 1: 34 type 2: 29	25 Pancreatitis 34 Jaundice 33 Weight loss	UN	Median serum IgG4 of 64 mg/d for 10 patients
Ünalp et al, 2012 (2001-2010) [28]	10 patients with AIP type 1, underwent surgery	100% AIP type 1	7 Jaundice 1 Abdominal pain	UN	Not examined
Zhang et al, 2013 (1990-2010) [24]	10 patients with AIP among 105 patients who underwent surgery	type 1: 7 type 2: 3	UN	UN	7 patients had an elevated level
Nikolic et al, 2022 (2001-2020) [22]	35 patients with AIP who underwent surgery	type 1: 28 type 2: 7	15 Jaundice 17 Weight loss 17 Abdominal pain	UN	7 patients had an elevated level
Vujasinovic et al, 2018 (2004-2018) [29]	71 patients with AIP, 20 underwent surgery	type 1: 62 type 2: 9	25 Jaundice 28 Weight loss and Abdominal pain	UN	27 patients had an elevated level
Tran et al, 2012 (2000-2010) [30]	6 patients with AIP among 65 patients who underwent PD	100% AIP type 1	6 Jaundice 5 Weight loss 4 Abdominal pain	15 kg: 2 patients 25 kg: 2 patients 30 kg: 1 patient	6 patients had an elevated level

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Table 1 continued. Review of 18 studies published in the last 11 years on postoperative cases with autoimmune pancreatitis.

Study (study period) [Ref]	CA 19-9	Imaging	Steroid trial	Preoperative biopsy	Concurrent malignancy
Detlefsen, 2012 (1987-2010) [20]	UN	UN	UN	UN	None
van Heerde, 2012 (2000-2009) [15]	(+) 3/7 (preoperational)	Non-typical	None	EUS-FNA performed in 1 patient	UN
Yurci, 2013 (1990-2012) [16]	Available in 30 patients, >150 IU/ml: 6 patients(20.0%)	Based on History classification, strongly signifying AIP: 10 patients, supportive of AIP: 6 patients, strongly signifying cancer: 7 patients	none before resection	7 pts Cytology was negative in 6 cases and showed atypical ductal cells in 1 case	UN
Miura, 2013 (1990-2010) [14]	UN	Stenosis of the MPD: 10 patients (70%), Expansion of the MPD: 6 patients (46%), Pancreatic parenchymal expansion: Focal: 5 patients, Diffuse: 3 patients	UN	UN	None
Vitali, 2014 (2005-2011) [17]	UN	UN	UN	UN	None
Macinga, 2017 (2000-2013) [18]	Patients with AIP: 35.2 kU/L (median), patients with AIP + PC: 89.8 kU/L (median)	CT: Atypical imaging: 9 patients, Level 2 evidence based on ICDC: 6 patients	UN	EUS-FNA in 11 patients, AIP + PC: 3 positive, 1 inconclusive,AIP: 4 true negative, 2 false positive, 1 inconclusive	Type 1: 2 type 2: 4
Dickerson, 2019 (1997-2016) [21]	(+) 12/26	Stenosis of the MPD: 5 patients (20%), Expansion of the MPD: 3 patients (12%), Pancreatic parenchymal expansion: focal: 6 patients (24%), diffuse: 14 patients (56%), Tumor-like mass: 4 patients (16%), Double duct sign: 3 patients (12%)	UN	the EUS-FNA performed was negative for AIP	3 patients

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Table 1 continued. Review of 18 studies published in the last 11 years on postoperative cases with autoimmune pancreatitis.

Study (study period) [Ref]	CA 19-9	Imaging	Steroid trial	Preoperative biopsy	Concurrent malignancy
Seki, 2023 (1979-2018) [19]	UN	Abnormality at the MPD or/ and the common bile duct(n=9), incasement of the large vessels(n=4)	UN	EUS was performed for 3 patients, 1 diagnosed with TFCP	UN
Ikeura et al, 2014 [26]	UN	CT or MRI revealed focal enlargement of the pancreas in 19 patients (63%) and pancreatic mass in 11 patients (37%). Delayed enhancement of the lesion was observed in 6 of 9 patients who underwent dynamic CT or MRI.	30% of the patients	UN	UN
Wojcicki et al, 2015 [27]	Available in 28 out of the 34 patients with levels >37 U/ml present only in 8	Mass could be identified in 3 patients, biliary and pancreatic duct dilatation was present in 15 and 5 cases respectively and enlarged lymph nodes in 12.	UN	EUS-FNA samples have been obtained for 5 (4 – benign, 1- 'atypical cells').	UN
Kimura et al, 2014 [25]	0 patients had an elevated level	UN	UN	2 Pancreatic specimens taken by US-guided percutaneous needle biopsy, EUS-FNAC	UN
Zhang et al, 2015 (2003-2012) [23]	9 patients had an elevated level	11 exhibited diffuse pancreatic enlargement and focal pancreatic enlargement in the head of the pancreas, 4, 'sausage-like' pancreatic changes, 3, pancreatic duct expansion and 5, 'halo' sign pancreatic changes	UN	UN	UN
Clark et al, 2013 (1986-2011) [31]	UN	24 Main pancreatic duct dilation 8 Pancreatic cyst 52 Focal mass 14 Diffuse gland enlargement	UN	UN	UN

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Table 1 continued. Review of 18 studies published in the last 11 years on postoperative cases with autoimmune pancreatitis.

Study (study period) [Ref]	CA 19-9	Imaging	Steroid trial	Preoperative biopsy	Concurrent malignancy
Ünalp et al, 2012 (2001-2010) [28]	8 patients had an elevated level	UN	UN	UN	UN
Zhang et al, 2013 (1990-2010) [24]	UN	UN	UN	UN	UN
Nikolic et al, 2022 (2001-2020) [22]	5 patients had an elevated level	UN	UN	UN	2 patients
Vujasinovic et al, 2018 (2004-2018) [29]	UN	54 focal pancreatic enlargement 19 diffuse enlargement 19 signs of acute pancreatitis	100% of the patients	UN	UN
Tran et al, 2012 (2000-2010) [30]	1 patient had an elevated level	3 distal bile duct strictures 5 pancreatic head masses 2 dilated bile duct	50% of the patients	3 EUS-FNA 1 major duodenal papilla core biopsy	UN

UN – unmentioned; PD – pancreatoduodenectomy; CP – chronic pancreatitis.

absence of upstream dilatation, numerous stenoses, and the existence of multiple obstructions leading to side branch dilation. The icicle sign, also known as the duct-penetrating sign, is the contraction of the main pancreatic duct without clear involvement of the lumen's wall strongly suggests AIP. In cases of pancreatic duct narrowing, post-obstruction expansion of the upper segment is more common in pancreatic cancer. A fully obstructed duct strongly indicates malignancy. Corticosteroid therapy can reverse AIP radiological findings, usually improving the appearance of the pancreatic duct as a treatment response sign [2,9,10,40,41]. Additionally, EUS-FNA aids in pancreatic cancer diagnosis but requires expertise. Therefore, core-needle biopsy is preferred to ensure adequate tissue sampling [42]. Lastly, Tru-cut biopsy enhances sensitivity [4].

Positron emission tomography/computed tomography (PET/CT), with both F-18 FDG and fibroblast activation protein inhibitor (FAPI) tracers, can be used to differentiate AIP from pancreatic cancer. Specifically, F-18 FDG PET/CT can detect differences between AIP and pancreatic cancer regarding the morphology, maximum standardized uptake value, primary tumor texture feature, and numbers and location of extrapancreatic foci. In addition, FAPI PET/CT will show a higher uptake of FAPI tracers in pancreatic cancer due to the existence of high levels of FAP expression, in contrast to AIP. PET/CT can non-invasively assess the response to steroid therapy, as it can track changes in metabolic activity. Finally, PET/CT can also help identify the optimal location for pancreatic biopsy [43-46].

Histological examination remains the criterion standard for diagnosing IgG4-related pancreatitis. The characteristic findings include dense storiform fibrosis, lymphoplasmacytic infiltrate, and obliterative phlebitis. Obliterative phlebitis refers to inflammation and destruction of the veins within the pancreatic parenchyma. It can be accompanied by fibrous wall obliteration, inflammatory cell infiltration, and luminal narrowing. Storiform fibrosis involves dense fibrosis disrupting normal pancreatic architecture and sometimes mimics pancreatic adenocarcinoma. These findings alone are not pathognomonic to IgG4-related disease and can also be observed in other conditions, such as other autoimmune pancreatic disorders. These histopathological features, along with immunohistochemical staining for IgG4, help in the differential diagnosis of possible diseases. Immunohistochemical staining for IgG4 indicates an increased number of IgG4-positive plasma cells within the affected tissue. Typically, the ratio of IgG4+ to IgG+ plasma cells is 40%, while in pancreatic surgical resection specimens 50% of IgG4+ plasma cells/high powered field are present [2,47,48].

In AIP type 3, imaging and pathology findings cannot lead to a diagnosis, as these features remain understudied to date. The

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

diagnosis of AIP type 3 is typically made by exclusion, with a common characteristic among these patients being the administration of immune checkpoint inhibitors, as this is due to the onset of AIP type 3.

Both type 1 and type 2 AIP are typically treated with corticosteroids, often showing a response within the first week. Prednisolone is orally taken for 2-4 weeks and gradually tapered by 5-10 mg every 1-2 weeks until reaching 20 mg/day, followed by a slower reduction of 5 mg every 2 weeks. Prolonged corticosteroid treatment at lower doses can decrease relapse rates, but can lead to complications [49]. In cases of relapse, corticosteroids may be readministered, and patients may even need longer-term low-dose treatment. If there is a moderate response or no response to therapy, surgical intervention should be considered, as it can indicate malignancy or another clinical condition [50]. The use of corticosteroids can be misleading for confirming an AIP diagnosis since they can initially improve the clinical picture of pancreatic cancer [41]. Recently, besides steroids, immunosuppressive agents and biologics have been considered for treating AIP type 1. Azathioprine combined with steroids is being investigated, along with other immunosuppressants. Rituximab is primarily studied as a second-line option, but further exploration is needed to ascertain its benefits and broader application [51,52]. Management of AIP type 3, in contrast to types 1 and 2, is typically conservative, including IV fluid hydration, pain control, and stopping the inciting medication. The benefit of corticosteroids is unclear. Although generally mild, it can lead to rapid organ volume loss [5-7].

Conclusions

In conclusion, AIP is an uncommon disease in clinical practice, but is important because it can manifest with symptoms similar to those of pancreatic cancer, a common malignancy with high mortality. Nonetheless, AIP responds well to steroid treatment, while pancreatic cancer demands a risky and technically difficult surgery. This case report underscores the diagnostic challenges posed by autoimmune pancreatitis (AIP) masquerading as pancreatic cancer. Despite the initial suspicion based on imaging and laboratory findings suggestive of malignancy, histopathological examination revealed classic features of AIP, including lymphoplasmacytic infiltration and obliterative phlebitis. Distinction between the 2 entities appears to be of importance as it contributes to higher survival rates and avoids postoperative risks for the patient. Even with the progress made in differentiation of the 2 entities, distinguishing AIP from pancreatic cancer, as in our case, can be challenging. Assessment of basic AIP biomarkers in the diagnostic algorithm of pancreatic cancer could aid in recognizing more AIP cases. It seems that above all, awareness regarding AIP should be raised for patients with suspicion of pancreatic cancer as a possible diagnosis.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References:

1. Yoshida K, Toki F, Takeuchi T, et al. Chronic pancreatitis caused by an autoimmune abnormality. Proposal of the concept of autoimmune pancreatitis. Dig Dis Sci. 1995;40(7):1561-68
2. Cai O, Tan S. From pathogenesis, clinical manifestation, and diagnosis to treatment: An overview on autoimmune pancreatitis. Gastroenterol Res Pract. 2017;2017:3246459
3. Shimosegawa T, Chari ST, Frulloni L, et al. International consensus diagnostic criteria for autoimmune pancreatitis: Guidelines of the International Association of Pancreatology. Pancreas. 2011;40(3):352-58
4. Masood M. Autoimmune pancreatitis: What we know so far. JGH Open. 2022;6(1):3-10
5. Sayed Ahmed A, Abreo M, Thomas A, Chari ST. Type 3 autoimmune pancreatitis (immune checkpoint inhibitor-induced pancreatitis). Curr Opin Gastroenterol. 2022;38(5):516-20
6. Abu-Sbeih H, Ali FS, Naqash AR, et al. Clinical characteristics and outcomes of immune checkpoint inhibitor-induced pancreatic injury. J Immunother Cancer. 2019;7(1):31
7. Shirwaikar Thomas A, Chari ST. Immune checkpoint inhibitor-induced (Type 3) autoimmune pancreatitis. Curr Gastroenterol Rep. 2023;25(10):255-59
8. Kamisawa T, Chari ST, Lerch MM, et al. Republished: Recent advances in autoimmune pancreatitis: Type 1 and type 2. Postgrad Med J. 2014;90(1059):18-25
9. Psarras K, Baltatzis ME, Pavlidis ET, et al. Autoimmune pancreatitis versus pancreatic cancer: A comprehensive review with emphasis on differential diagnosis. Hepatobiliary Pancreat Dis Int. 2011;10(5):465-73
10. Martins C, da Silva MF, Lopes J, et al. Type 2 autoimmune pancreatitis: A challenge in the differential diagnosis of a pancreatic mass. GE Port J Gastroenterol. 2017;24(6):296-300
11. Hart PA, Zen Y, Chari ST. Recent advances in autoimmune pancreatitis. Gastroenterology. 2015;149(1):39-51
12. Lo RSC, Singh RK, Austin AS, Freeman JG. Autoimmune pancreatitis presenting as a pancreatic mass mimicking malignancy. Singapore Med J. 2011;52(4):e79-81
13. Shimosegawa T, Chari ST, Frulloni L, et al. International consensus diagnostic criteria for autoimmune pancreatitis. Pancreas. 2011;40(3):352-58
14. Miura F, Sano T, Amano H, et al. Long-term surgical outcomes of patients with type 1 autoimmune pancreatitis. World J Surg. 2013;37(1):162-68
15. van Heerde MJ, Biermann K, Zondervan PE, et al. Prevalence of autoimmune pancreatitis and other benign disorders in pancreatoduodenectomy for presumed malignancy of the pancreatic head. Dig Dis Sci. 2012;57(9):2458-65
16. Yurci A, Turhan N, Şentürk H, et al. Evolution in the diagnosis and treatment of autoimmune pancreatitis: Experience from a single tertiary care center. Int J Clin Exp Pathol. 2013;6(7):1317-26
17. Vitali F, van Heerde MJ, Zondervan PE, et al. Frequency and characterization of benign lesions in patients undergoing surgery for the suspicion of solid pancreatic neoplasm. Pancreas. 2014;43(8):1329-33
18. Macinga P, Sákantamis A, Tzovaras G, et al. Simultaneous occurrence of autoimmune pancreatitis and pancreatic cancer in patients resected for focal pancreatic mass. World J Gastroenterol. 2017;23(12):2185-93
19. Seki M, Yoshida H, Uchida E, et al. Clinicopathological study of surgically treated non-neoplastic diseases of the pancreas with special reference to autoimmune pancreatitis. Langenbecks Arch Surg. 2023;408(1):223
20. Detlefsen S, Drewes AM, Petersen JM, et al. Clinical features and relapse rates after surgery in type 1 autoimmune pancreatitis differ from type 2: A study of 114 surgically treated European patients. Pancreatology. 2012;12(3):276-83

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

21. Dickerson LD, Oh DS, Panossian H, et al. Differentiation of autoimmune pancreatitis from pancreatic cancer remains challenging. World J Surg. 2019;43(6):1604-11
22. Nikolic S, Abu-Sbeih H, Fares AF, et al. Surgery in autoimmune pancreatitis. Dig Surg. 2022;39(1):32-41
23. Zhang R, Shen S, Shen Y, et al. Clinicopathological analysis of 12 patients with autoimmune pancreatitis. Exp Ther Med. 2015;10(1):121-26
24. Zhang X, Liu X, Joseph L, et al. Pancreatic ductal adenocarcinoma with autoimmune pancreatitis-like histologic and immunohistochemical features. Hum Pathol. 2014;45(3):621-27
25. Kimura A, Yamada S, Nakao K, et al. Multifocal lesions with pancreatic atrophy in IgG4-related autoimmune pancreatitis: Report of a case. Surg Today. 2014;44(6):1171-76
26. Ikeura T, Yoshida N, Mimura J, et al. Retrospective comparison between preoperative diagnosis by International Consensus Diagnostic Criteria and histological diagnosis in patients with focal autoimmune pancreatitis who underwent surgery with suspicion of cancer. Pancreas. 2014;43(5):698-703
27. Wojcicki J, Rogowski W, Kruszewski WJ, et al. Benign histology after pancreaticoduodenectomy for suspected malignancy. Lessons to be learned – a single centre experience. Pol Przegl Chir. 2015;87(1):6-15
28. Unalp O, Erol V, Yeniay L, et al. Autoimmune pancreatitis and treatment approaches with case reports. Balkan Med J. 2012;29(4):431-33
29. Vujasinovic M, Valente R, Capurso G, et al. Diagnosis, treatment and long-term outcome of autoimmune pancreatitis in Sweden. Pancreatology. 2018;18(8):900-4
30. Tran CT, Chan OTM, Wong LMF, Wong LL. Autoimmune pancreatitis in an Asian-dominant American population. Hawaii J Med Public Health. 2012;71(1):13-18
31. Clark CJ, Dodson R, Dornelas C, et al. Short-term and long-term outcomes for patients with autoimmune pancreatitis after pancreatectomy: A multi-institutional study. J Gastrointest Surg. 2013;17(5):899-906
32. Ghazale A, Chari ST, Zhang L, et al. Value of serum IgG4 in the diagnosis of autoimmune pancreatitis and in distinguishing it from pancreatic cancer. Am J Gastroenterol. 2007;102(8):1646-53
33. Hamano H, Kawa S, Horiuchi A, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med. 2001;344(10):732-38
34. Gong PL, Liu TT, Shen XZ. Differentiation of autoimmune pancreatitis with pancreatic carcinoma remains a challenge to physicians. J Dig Dis. 2012;13(5):267-73
35. van Heerde MJ, Buijs J, Ten Kate FJ, et al. Serum level of Ca 19-9 increases ability of IgG4 test to distinguish patients with autoimmune pancreatitis from those with pancreatic carcinoma. Dig Dis Sci. 2014;59(6):1322-29
36. Chang MC, Liang PC, Jan S, et al. Increase diagnostic accuracy in differentiating focal type autoimmune pancreatitis from pancreatic cancer with combined serum IgG4 and CA19-9 levels. Pancreatology. 2014;14(5):366-72
37. O'Reilly DA, Malde DJ, Duncan T, et al. Review of the diagnosis, classification and management of autoimmune pancreatitis. World J Gastrointest Pathophysiol. 2014;5(2):71-81
38. Dong Y, Zhang Y, Wang X, et al. Autoimmune pancreatitis: Imaging features. Endosc Ultrasound. 2018;7(3):196-203
39. Ogawa H, Takehara Y, Naganawa S. Imaging diagnosis of autoimmune pancreatitis: Computed tomography and magnetic resonance imaging. J Med Ultrason (2001). 2021;48(4):565-71
40. Khandelwal A, Inoue D, Takahashi N. Autoimmune pancreatitis: An update. Abdom Radiol (NY). 2020;45(5):1359-70
41. Blaho M, Dítě P, Kunovský L, Kianička B. Autoimmune pancreatitis – an ongoing challenge. Adv Med Sci. 2020;65(2):403-8
42. Takuma K, Kamisawa T, Tabata T, et al. Strategy to differentiate autoimmune pancreatitis from pancreas cancer. World J Gastroenterol. 2012;18(10):1015-20
43. Matsubayashi H, Furukawa H, Sasaki K, et al. Steroid therapy and steroid response in autoimmune pancreatitis. Int J Mol Sci. 2019;21(1):257
44. Luo Y, Pan Q, Zhang W, Li F. Intense FAPI uptake in inflammation may mask the tumor activity of pancreatic cancer in 68Ga-FAPI PET/CT. Clin Nucl Med. 2020;45(4):310-11
45. Ozaki Y, Oguchi K, Hamano H, et al. Differentiation of autoimmune pancreatitis from suspected pancreatic cancer by fluorine-18 fluorodeoxyglucose positron emission tomography. J Gastroenterol. 2008;43(2):144-51
46. Lee TY, Lee CM, Lee WJ, et al. Utility of 18 F-FDG PET/CT for differentiation of autoimmune pancreatitis with atypical pancreatic imaging findings from pancreatic cancer. Am J Roentgenol. 2009;193(2):343-48
47. Hegade VS, Sheridan MB, Huggett MT. Diagnosis and management of IgG4-related disease. Frontline Gastroenterol. 2019;10(3):275-83
48. Detlefsen S, Klöppel G. IgG4-related disease: with emphasis on the biopsy diagnosis of autoimmune pancreatitis and sclerosing cholangitis. Virchows Arch. 2018;472(4):545-56
49. Okazaki K, Kawa S, Kamisawa T, et al. International consensus for the treatment of autoimmune pancreatitis. Pancreatology. 2017;17(1):1-6
50. Buscarini E, Frulloni L, De Lisi S, et al. Autoimmune pancreatitis: A challenging diagnostic puzzle for clinicians. Dig Liver Dis. 2010;42(2):92-98
51. Brito-Zerón P, Bosch X, Ramos-Casals M, Stone JH. IgG4-related disease: Advances in the diagnosis and treatment. Best Pract Res Clin Rheumatol. 2016;30(2):261-78
52. Chen LYC, Mattman A, Seidman MA, Carruthers MN. IgG4-related disease: What a hematologist needs to know. Haematologica. 2019;104(3):444-55

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]