CASE REPORT

Case Report: Painless obstructive jaundice caused by IgG4 autoimmune pancreatitis; the role of endoscopic ultrasound in diagnosis [version 1; peer review: 2 not approved]

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Abstract

We report the case of a 60-year-old woman, presenting with painless obstructive jaundice of unknown etiology, who was finally found to suffer from type I autoimmune pancreatitis (AIP). This case emphasizes AIP as a rare cause in the differential diagnosis of obstructive jaundice and the role of endoscopic ultrasound (EUS) in final diagnosis, which is difficult to establish. According to diagnostic criteria, we combined the results from serologic, imaging and histological features (specifically IgG4 levels, computed tomography, magnetic resonance imaging/magnetic resonance cholangiopancreatography and EUS) with cytological results, leading to a final diagnosis. Our patient's response to corticosteroids was impressive, confirming the diagnosis, leading to complete remission of the disease. Whilst diagnosis of AIP is challenging, the application of diagnostic criteria can lead to correct diagnosis. Therapy is corticosteroid based, with very satisfying outcomes.

Keywords

autoimmune pancreatitis, obstructive jaundice, IgG4-related disease, endoscopic ultrasound, corticosteroids.

Open Peer Review

Approval Status **XX**

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Any reports and responses or comments on the article can be found at the end of the article.

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Introduction

Autoimmune pancreatitis (AIP) is a rare disease, meaning that clinicians have little experience in diagnosis¹. Clinical suspicion is the first step for correct diagnosis, arising from the patient's demographics and clinical presentation. This case presented here emphasizes the major role of endoscopic ultrasound (EUS) and biopsy in the final diagnosis of AIP, when other diagnostic procedures fail to offer an accurate answer.

Case description

A female patient, 60-years-old, was admitted to the emergency department with painless jaundice. The patient did not have any history of alcohol consumption, drug abuse, or previous liver and biliary or hematologic diseases.

Clinical findings

On clinical examination, the patient's eyes and skin were yellow. Murphy and Giordano signs were negative. Blood tests showed serum lipase and amylase within normal limits, total bilirubin at 11.2mg/dl [normal range: 0.3–1.5mg/dL] (direct fraction 5.9 mg/dL, indirect fraction 5.3 mg/dL), hematocrit within normal limits, white blood cell count of 5.5 K/ μ L [normal range: 4.5–11 K/ μ L], and a normal fasting blood glucose level. Patient's liver enzymes were elevated (aspartate aminotransferase 109 U/L [normal range 7–40U/L]; alkaline aminotransferase 230U/L [normal range: 5–45U/L]; alkaline phosphatase 238U/L [normal range: 40–150U/L]). Initial ultrasound examination revealed enlargement of the pancreas, with low echogenicity and dilatation of the biliary tree. The diameter of the pancreatic duct was normal (Figure 1).

Diagnostic assessment

Dynamic computed tomography revealed free peripancreatic fat with no other signs, indicating acute pancreatitis and mild enlargement of the pancreas with homogeneous density and enhancement. There were no signs indicating neoplasm.

For better evaluation of the pancreaticobiliary tree, an magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MPCP) was performed, showing mild pancreatic enlargement. There was no obvious dilatation of pancreatic duct, with stenosis of the final part of common bile duct (Figure 2).

Since MRCP has inferior resolution in the imaging of pancreatic duct, an endoscopic retrograde cholangiopancreatography (ERCP) was performed, which confirmed the MRCP findings, showing no significant prestenotic dilatation of the common bile duct. During the procedure, a dilatation of common bile duct with a balloon-catheter and a plastic stent placement was performed to alleviate the patient from jaundice. Furthermore, tissue-sampling was conducted from the stenosis, with results indicating inflammatory process of the duct wall. The patient was transferred to a tertiary centre, where, in order to obtain a more precise and direct imaging of the pancreas, EUS and EUS elastography was performed, showing a diffusely enlarged gland with hypoechoic, patchy, heterogeneous appearing parenchyma, with regions of stiffness, suggesting AIP. In addition, the presence of a hypoechoic mass in the final part of the

intrapaneatic portion of common bile duct was found, which increased the suspicion of cholangiocarcinoma, deteriorating the diagnostic procedure (Figure 3). EUS with fine needle aspiration of the mass, using a 25-gauge needle, was performed. Several inflammatory cells, fibroblasts and traces of fibrous tissue were found in the samples. IgG4 levels were elevated, measuring 250mg/dl [normal range: <140mg/dL]. The combination of clinical, imaging and cytological findings pointed to the diagnosis of AIP.

Therapeutic intervention

Prednisolone 40mg daily for a month was given as therapy, leading to clinical and radiological disease remission. MRI one month following treatment revealed almost a normal pancreas (Figure 4), with subsequent normalization of IgG4 levels in serum. Nine months later, during dosage reduction with a taper of 5mg/week, the patient attended the emergency room once again, presenting with painless jaundice. Ultrasound indicated pancreas enlargement, with elevation of IgG4 in serum and

Figure 1. Initial ultrasound showing diffuse pancreatic enlargement and common bile duct dilatation. Anteroposterior diameter of pancreatic head was 48.9mm and body up to 23.6mm. Diameter of bile duct was 12.9mm.

Figure 2. MRI/MRCP showing mild pancreatic enlargement with normal pancreatic duct and narrowing of the final part of common bile duct.

[200mg/dL] the relapse of the disease. “Rebound phenomenon” was the most possible scenario. Re-induction/increased dose of steroid therapy to 40mg/daily for a two month period caused the remission of the disease. A dose reduction rate of 5mg every 1–2 weeks followed, until prednisolone dose reached 15 mg/day. Then the reduction rate was decreased to 2.5mg every 2 weeks, until a dose of 3.0mg/day was reached.

Follow-up and outcomes

Maintenance therapy for three years was decided to prevent disease relapse, since most relapses occur in the first three years after diagnosis². At the moment, three years later, the patient stays in remission, receiving 3.0mg/day of prednisolone.

Discussion

Autoimmune pancreatitis (AIP) consists of an uncommon type of chronic pancreatitis, accounting for 2–11% of all cases of

chronic pancreatitis³. Two subtypes of the disease, defined by their histopathology, are clearly recognized since 2010⁴: lymphoplasmacytic sclerosing pancreatitis, known as Type 1; and idiopathic duct-centric pancreatitis (ICDC), Type 2. Both types are steroid responsive. Type 1 is the pancreatic manifestation of IgG4-related disease. There are many extrapancreatic organs that may be involved, such as the biliary tree and gallbladder, kidneys, retro-peritoneum, prostate, the mesentery, blood vessels, gastrointestinal tract, thyroid, lacrimal glands and orbits, salivary glands, lymph nodes, and lungs⁵. The biliary tract is the most commonly involved extrapancreatic site, hence the painless jaundice in AIP patients, as in the present case⁵. The clinical features of AIP depend on the phase, acute or subacute. In the acute phase, the most common clinical presentation for both subtypes of AIP is obstructive jaundice, usually painless. In the subacute phase, AIP imitates chronic pancreatitis due to pancreatic atrophy, leading to steatorrhea. The incidence of diabetes mellitus

Figure 3. Endoscopic ultrasound/elasticity. Hypoechoic mass in the distal part of intrapancreatic portion of common bile duct can be seen and diffusely enlarged gland with hypoechoic, patchy, heterogenous appearing parenchyma, with regions of stiffness.

in patients with AIP is up to 50%⁶. There are three established patterns of autoimmune pancreatitis depending on pancreatic appearance macroscopically: diffuse, as described in the current case, focal, and multifocal.

Diagnosis of AIP is challenging, and many clinical, imaging and biochemical features overlap with other conditions, such as idiopathic pancreatitis, primary sclerosing cholangitis and

malignancies, mainly pancreatic cancer and cholangiocarcinoma. A plethora of diagnostic criteria have been proposed by different groups around the world. The first was proposed by the Japan Pancreas Society in 2002⁷, combining cardinal features, concerning histology, imaging, serology, other organ involvement, and steroid effect³ (Table 1). ICDC is the first universally accepted criterion of AIP because it considers national differences and establishes two types⁸.

Figure 4. Magnetic resonance imaging one month after treatment reveals almost normal pancreas.

Table 1. Diagnostic criteria in different countries.

	Japanese criteria (2006)	HISORTs (2006)	Korean criteria (2007)	Asian criteria (2008)
A: Imaging	Diffuse or segmental narrowing of the MPD; diffuse or localized enlargement of the pancreas	Typical imaging features: diffusely enlarged gland with delayed rim enhancement; diffusely irregular and attenuated MPD Atypical imaging features: focal pancreatic mass, focal pancreatic duct stricture	Diffuse enlargement of pancreas and diffuse or segmental irregular narrowing of MPD	Typical imaging features: diffusely enlarged gland with delayed rim enhancement, diffusely irregular and attenuated MPD Atypical imaging features: focal pancreatic mass, focal pancreatic duct stricture
B: Serology	High serum γ globulin, IgG, IgG4, or the presence of antibodies	Elevated serum IgG4 level	Elevated levels of IgG and/or IgG4 or detected autoantibodies	High level of IgG or IgG4 or detected autoantibodies
C: Histology	Infiltration of lymphocytes and plasma cells	Lymphoplasmatic infiltrate with storiform fibrosis showing abundant (>10 cells/HPF) IgG4-positive cells	Fibrosis and lymphoplasmatic infiltration	Lymphoplasmatic infiltration with fibrosis, with abundant IgG4-positive cell infiltration
D: Other organ involvement	Not included	Biliary stricture, parotid/lacrimal gland involvement, mediastinal lymphadenopathy, retroperitoneal fibrosis	Included	Not included
E: Steroid effect	Not included	Included	Included	Included
Definitive diagnosis	Criterion A + B Criterion A + C	Criterion A + B Criterion A + C Criterion A + B Criterion A + E	Criterion A + B Criterion A + C Criterion A + D Criterion A + E	Criterion A + B Criterion A + C Histology shows the presence of lymphoplasmatic sclerosing pancreatitis

MPD, main duct dilation; This table was adapted from Cai and Tan⁹ under a [Creative Commons Attribution License \(CC-BY 4.0\)](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Exclusion of malignancy is crucial for the clinician to choose either conservative or surgical treatment. Focal pattern is most difficult to distinguish from cancer, especially ductal adenocarcinoma (PDAC)¹⁰, for which there is no pathognomonic biomarker, including IgG4 levels and CA 19-9^{2,11}. The mistaken diagnosis of AIP as PDAC, or vice versa, can result in unnecessary or life-threatening surgery or delayed treatment. Among diagnostic procedures (Table 2), EUS-FNA consists of a sensitive method for detecting/excluding pancreatic cancer, as in our case¹².

The prognosis of AIP is generally good and complications rare. Our patient remains free from symptoms three years after diagnosis with a successful treatment of relapse. However, the role of AIP as a predisposing factor for pancreatic cancer needs to be investigated. Internists should keep in mind AIP as a rare entity in the diagnostic spectrum of pancreatic diseases and when high clinical suspicion exists, based on clinical presentation,

demographics and patient's history, should consider this diagnosis. Diagnosis can be made according to ICDC 2011⁸. Clinicians, pathologists and radiologists have to be aware of this recently recognized entity¹³, to suspect and timely diagnose it, to give patient the appropriate steroid therapy, avoiding inappropriate pancreatic resections, which lead to increased morbidity and mortality.

Although diagnosis of AIP is challenging, respect to the established diagnostic criteria helps to have a definite and patient-safe result. When a clinical/radiological or other suspicion exists, clinicians should follow diagnostic algorithms to rule out other pathologies, especially pancreatic and biliary cancer. In our case, based on clinical presentation, the preferable diagnosis was malignancy, but imaging features of CT, ERCP and MRI/MRCP were not indicating this. EUS imaging deteriorated the diagnostic procedure, as it showed a hypoechoic mass, which is highly suspicious for malignancy, specifically cholangiocarcinoma.

Table 2. Advantages and disadvantages of imaging modalities.

Imaging	Imaging findings	Advantage	Disadvantage	When to select
Ultrasound	Diffuse enlargement, hypoechoic pancreas	Low price, noninvasive, easy to operate.	Low specificity.	Initial imaging.
Computed tomography (CT)	Diffuse/focal pancreatic enlargement, late enhancement, hypoattenuating halo	Non-invasive, easy to operate, differentiate AIP from pancreatic cancer and other pancreatitides.	Low sensitivity in evaluation of pancreatic and bile duct.	Evaluate pancreatic parenchyma, exclude other pancreatitides/cancer.
Magnetic resonance imaging	Hypointense signal on T1 weighted images and relatively T2 hyperintense signal	Noninvasive showing pancreatic fibrosis.	Less sensitivity in pancreatic parenchyma evaluation than CT.	Evaluate pancreatic parenchyma.
Magnetic resonance cholangiopancreatography	Diffused narrow or segmental stenosis of main pancreatic duct, the pancreatic segment of common bile duct stricture, proximal bile duct dilatation, gallbladder enlargement	Noninvasive, obtaining high quality images of the pancreatobiliary tree.	Less sensitivity in pancreatic/biliary duct evaluation, no treatment in case of jaundice.	Evaluate the bile duct, pancreatic duct and bile duct stricture.
Endoscopic retrograde cholangiopancreatography	Diffuse, irregular narrowing of the main pancreatic duct	Better evaluate pancreatic and biliary duct, treatment simultaneously, especially in case of jaundice.	Invasive.	Evaluating bile and pancreatic duct and bile duct stricture, treatment for jaundice.
Endoscopic ultrasound-fine needle aspirate	Diffusely enlarged gland ("sausage-shaped") with hypoechoic, patchy, heterogenous appearing parenchyma.	Less invasive than surgery in tissue-sampling.	Invasive. May not get adequate tissue.	Get the pancreatic tissue sample.
Positron emission tomography	Uptake of fluorodeoxyglucose in organs other than the pancreas.	Other organ involvement is easily detected.	Expensive	Evaluate other organ involvement, exclude malignant tumor

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Finally, the combination of histological results, obtained after EUS biopsy, and elevated IgG4 levels established AIP diagnosis. In the current literature, the important role of EUS in the diagnosis of AIP has been highlighted. Our case emphasizes the role of EUS/elastography and EUS biopsy in diagnosis of the disease.

Exclusion of malignancy is crucial for the clinician to choose either conservative or surgical treatment. The misdiagnosis of AIP, especially focal pattern, as pancreatic duct adenocarcinoma, or the reverse, can result in medical malpractice. Sometimes biopsy is necessary, as in the present case and EUS is an ideal method for tissue sampling.

Glucocorticoids are the cornerstone in the therapeutic approach of AIP and effectiveness of steroid treatment consists of a major diagnostic criterion. Therapeutic goal of AIP is to achieve clinical, serologic and radiological remission of the disease.

Consent

Written informed consent for publication of clinical details and clinical images was obtained from the patient.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

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Zaheer Nabi

Asian Institute of Gastroenterology, Hyderabad, Telangana, India

This is a case report entitled "Painless obstructive jaundice caused by IgG4 autoimmune pancreatitis; the role of endoscopic ultrasound in diagnosis". The authors reported a classic case of autoimmune pancreatitis (AIP) presenting as obstructive jaundice. I have the following comments to make:

1. The report presents a typical case of AIP with no new information. Why do the authors feel it is important to highlight this case? Since, multiple studies have reported the clinical and histopathological features as well as the role of steroids in cases with AIP an atypical presentation or use of a new treatment approach would have been a welcome addition.
2. The quality of images need a great deal of improvement. Imaging forms the core of diagnosis in AIP and compromise in their quality may not be acceptable. The MRI image (Figure 4) shows several dates which should be otherwise masked.
3. What was the follow-up duration in this case? The date on MRI (Fig 4) suggests it to be around six years in contrast to 3-years as mentioned in the manuscript.
4. I would suggest the authors to include histology images. In case the number of figures exceeds the requirements of the journal, ultrasound images may be omitted.

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Partly

Is the case presented with sufficient detail to be useful for other practitioners?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pancreatitis (acute and chronic), EUS, drainage of pancreatic collections, Third space endoscopy

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 08 March 2021

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Shin Miura

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This paper is a case report of autoimmune pancreatitis (AIP). AIP is a disease for which diagnostic criteria have been established and is a common disease for specialists in our area. Many papers on autoimmune pancreatitis have already been reported. This case is a typical case as AIP and is not novel. In addition, you do not provide proper images or patient information. You should submit a clear image of abdominal echo, endoscopic ultrasonography. The position of the body mark on the echo is also incorrect. Is the image you diagnosed with a bile duct tumor in Figure 3 appropriate? The tumor cannot be pointed out on MRI images. Did you misidentify the intestinal tract? If you insist on the importance of EUS, please provide the appropriate image that the reader will be satisfied with. The contents of Table 1 are not accurate. The latest guidelines for Japan were published in 2013. You state that the Japanese guidelines for other organ involvements and steroid effect for diagnostic items are not included. This is a mistake. You are providing incorrect information. There is no novel or useful information about Table 2. This paper does not contain any useful information for the reader and I disagree.

Is the background of the case's history and progression described in sufficient detail?

Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

No

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

No

Is the case presented with sufficient detail to be useful for other practitioners?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: My specialty is biliary pancreatic disease. I also have a lot of clinical experience with autoimmune pancreatitis

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

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