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Autoimmune Pancreatitis Type 1: A Rare Cause of Epigastric Pain, About a Case

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Abstract **Case Report**

Type 1 autoimmune pancreatitis is a rare autoimmune disorder, part of a systemic disease known as IgG4 related disease. Its diagnosis is based on a group of criteria defined according to an international consensus on the disease (ICDC criteria). This diagnosis is challenging, as the clinical, biological and radiological signs of the disease can be similar to those of pancreatic cancer. We report a case of type 1 AIP diagnosed after a suspicion of pancreatic cancer.

Keywords: Auto-Immune Pancreatitis, IgG4 Related-Disease, Endoscopic Ultrasound, Imaging, Steroids.

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INTRODUCTION

Autoimmune pancreatitis (AIP) is a rare disease with two subtypes (type 1 and type 2). Type 1 AIP represents the pancreatic localisation of a systemic disease, IgG4 disease, which is characterised by multi-organ involvement associated with elevated serum IgG4 levels. The diagnosis of AIP type 1 is based on a combination of clinical, biological, radiological, histological and therapeutic criteria. The main difficulty is distinguishing autoimmune pancreatitis from pancreatic cancer, since the symptoms, biology and imaging may be similar. The differential diagnosis must be made with care in order not to misdiagnose pancreatic cancer on the one hand, and to avoid unnecessary major surgery on the other. We report here a case of a patient with clinical presentation suggestive of malignancy, whose final diagnosis was type 1 AIP.

CASE REPORT

The patient was a 40-year-old man with a history of chronic smoking, who came to our department with transfixing epigastric pain associated with vomiting dating back one month, with the appearance 15 days prior to the admission, of jaundice associated with dark urine and discolored stools, and pruritus. The patient reported a weight loss of 20 kg. Clinical examination revealed no abnormalities other than jaundice. The initial laboratory tests showed cholestasis and hepatic cytolysis (GGT = 1403 IU/L (25N), AST = 162 IU/L (4N) / ALT = 396 IU/L (9N), total bilirubin = 107 mg/L / direct bilirubin = 101mg/L), with serum lipase at 211 U/L (3N) and fasting blood glucose at 1.5 g/dL. Abdominal ultrasound revealed a hypoechogenic pancreas with a borderline commun bile duct. A CT scan showed diffuse hypertrophy of the pancreas with delayed contrast (see Figure 1).

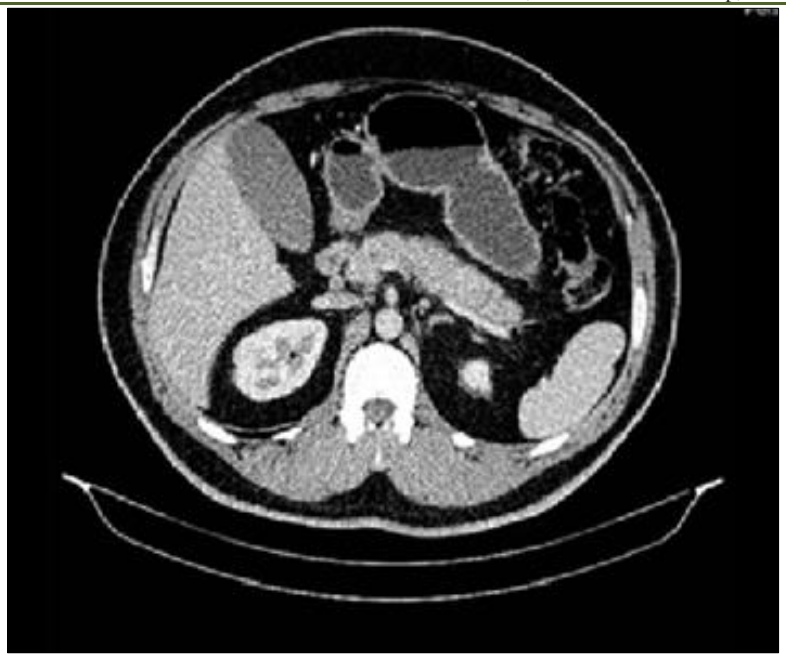

Figure 1: transversal section of an injected abdominal CT scan showing global hypertrophy of the pancreas

We completed the investigation with a Cholangiopancreatography (MRCP), which revealed the presence of a sausage-like pancreas, amputation of the initial part of the Wirsung and dilatation of the intrahepatic bile ducts, with stenosis of the lower third of the main bile duct with no individualisable obstruction (Figure 2).

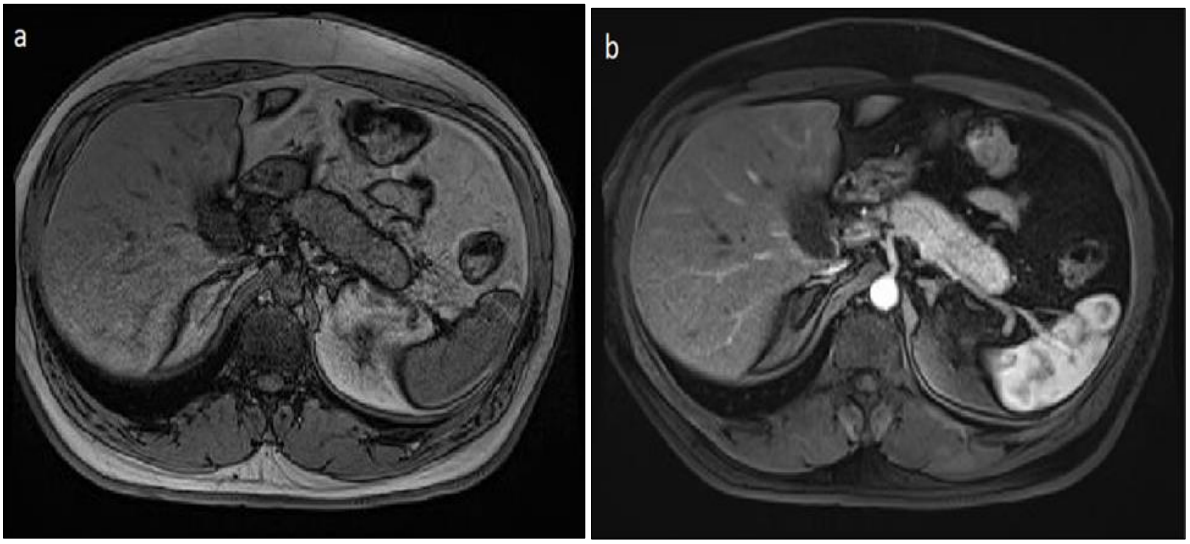

Figure 2 (a et b): T1-weighted MRCP without injection (a) and after injection (b) showing a sausage-like pancreas with irregularity of the duct of the Wirsung

In light of these findings, an IgG4 serum level was requested, which came back slightly elevated at 0.895 g/l (N = 0.040 to 0.870 g/l). The diagnosis of type 1 autoimmune pancreatitis was made and the patient received prednisolone-based corticosteroid therapy at a dose of 0.6mg/Kg/d, with marked improvement within 5 days.

DISCUSSION

Autoimmune pancreatitis is a rare form of chronic pancreatitis (5-6% of all chronic pancreatitis [1]). In Japan, where AIP is much more common, the incidence is arround 1.4 per 100,000 people [2]. There are two types of AIP: type 1, which represents the pancreatic site of a systemic autoimmune disease known as IgG4-related disease, and type 2, which is less common, is an autoimmune disease that specifically affects the pancreas and is associated in 20-30% of cases with inflammatory bowel disease (most often ulcerative colitis). AIP type 1 was first described by Yoshida *et al*.,

[3], in 1995, who identified a form of chronic pancreatitis linked to an autoimmune mechanism. In 2001, Hamano *et al*., [4], described elevated serum IgG4 levels in this form of pancreatitis and in 2003 Kamisawa *et al*., [5], identified a new systemic autoimmune disease and proposed the concept of IgG4-related sclerosing disease. Finally, it was in 2011 that the name IgG4-related disease was adopted by the 1st international consensus on this disease [6]. The pathophysiological mechanisms involved in the disease are clearly autoimmune. This has been argued by the involvement of several organs, the elevation of serum IgG4 present in more than 80% of cases, the association with a particular predisposing HLA genotype: HLA DRB1*0405 - DQB1*0401 [7], the presence of immune complex deposits on the affected tissues and, finally, the good response to corticosteroid therapy.

The initiation phases of the disease are probably due to molecular mimicry. The role of Helicobacter pylori has been suggested but not confirmed to date [8-10].

Type 1 AIP is more common in men, with an average age of between 60 and 70 years [11]. Clinical presentation includes abdominal pain, often associated with jaundice. Asthenia and weight loss are common, so the diagnosis is often oriented towards a malignant cause. Extra-pancreatic involvement of other organs is possible, including the liver, biliary tree, kidneys, retroperitoneum, salivary and lacrimal glands, orbital tissues, pituitary gland, thyroid, lungs, lymph nodes, breasts, prostate, testicles and vascular structures [12].

An elevated IgG4 level is specific for PAI type 1 [13]. Serum IgG4 levels above 140 mg/dl are considered 86% sensitive and 90-96% specific for the diagnosis of the disease [14, 15]. Other serological markers have been reported to be elevated, such as γ-globulin (>2.0 g/dL), rheumatoid factor (20-30%) and antinuclear antibodies (60%), but these are not specific [16]. It is important to note that 5-10% of patients with pancreatic cancer, acute or chronic pancreatitis may have elevated serum IgG4 [17].

Imaging has an important role in the diagnosis of the disease. Abdominal ultrasound is a non-invasive method used to examine the pancreas. It is particularly useful in the differential diagnosis of abdominal pain or jaundice. Abdominal ultrasound with contrast may be useful in differentiating focal AIP from pancreatic cancer [18]. Abdominal CT scan may show a diffusely or focally enlarged pancreas, with delayed enhancement depending on disease activity or stage [19]. Peri-pancreatic hypodensity, or "ring sign", may be seen. It reflects fibro-inflammatory changes involving peri-pancreatic adipose tissue. The same signs can be seen on MRI with low signal on T1-weighted images and delayed enhancement on dynamic sequences. The ring sign is seen on MRI in approximately 36% of cases [20]. In focal forms, diagnosis is even more difficult and a biopsy is required to exclude pancreatic cancer [21]. In this case, the presence of involvement of other organs is suggestive of autoimmune pancreatitis. MRCP may show narrowing of the Wirsung duct, or multifocal strictures, without upstream dilatation, and in around 80% of patients an associated stenosis of the biliary tree. In the typical case, the narrowing is more than 1/3 of the pancreatic duct. If the narrowing is les than 1/3 of the pancreatic duct, it is necessary to exclude pancreatic ductal carcinoma [22-24].

Endoscopy is an important tool for differential diagnosis. it allows the performance of a targeted biopsy. However, some studies have shown lower sensitivity and specificity of EUS-guided biopsy in the diagnosis of AIP [25]. The histological signs of AIP type 1 are characterized by fibrosis with strong lymphoplasmacytic infiltration, abundant infiltration of IgG4-positive plasma cells, storiform fibrosis, obliterative phlebitis and periductal inflammation [19]. When histological findings are typical, the diagnosis of AIP is certain. However, it is not always easy to obtain pancreatic biopsies. Furthermore, the cost-effectiveness of these biopsies remains debated due to the low diagnostic yield. This has led experts to establish decision-making algorithms combining histological, clinical and morphological criteria. The International Consensus Criteria for Autoimmune Pancreatitis (ICDC) published by the expert conference in 2011 [6], is the current reference. According to these criteria, type 1 PAI can be confirmed in the event of typical histological findings or the presence of 2 of the following 4 criteria:

- High level of IgG4 in serum
- Characteristic imaging findings, such as an increase in overall pancreatic size ± associated with a ring sign.
- Response to corticosteroid therapy
- Extra-pancreatic involvement, confirmed by histology or imaging.

Corticosteroid therapy is the treatment of choice and is almost always effective [26, 27, 28]. Recurrences or relapses are more common in type 1 AIP than in type 2 [28]. The dose of corticosteroids is 0.6 mg/kg/day for 4 weeks, with a classic decrease (10 mg every 10 days up to 20 mg/day, then 5 mg every 10 days until stopping). The total duration of treatment is 3 months. In Japan, most teams maintain a low dose of corticosteroids (5 to 7.5 mg/day) for 3 years to reduce the risk of disease relapse. This continuation of corticosteroid therapy reduces the relapse rate by 2 (23%/58%) at 3 years [29]. However, long-term corticosteroid therapy can cause significant side effects. In low-incidence countries, maintenance therapy is generally used only in relapsed patients. Progression to chronic pancreatitis with a high risk of diabetes is possible. Monitoring is clinical (jaundice and pain), biological (liver and blood sugar tests) and radiological (MRCP). Several risk factors for

relapse have been described: diffuse hypertrophy of the pancreas at the time of diagnosis, slow response to corticosteroid therapy, slow or absence of decrease in serum IgG4 level after induction treatment, and more than one involvement of the extra-pancreatic organs [30, 31].

In case of non-response to steroids, rituximab is a good therapeutic alternative, with a significantly higher efficacy rate than immunomodulators (azathioprine, cyclosporine A and rapamycin) (94% Vs 67%) [32]. However, immunomodulators are relatively cheaper and can be used to reduce the lifetime cumulative steroid dose [33]. Methotrexate [34], and tacrolimus [35], are also a treatment choice for steroid-refractory cases.

CONCLUSION

In conclusion, type 1 AIP is a rare condition, but one that needs to be well understood, because of the similarities it may have with other diseases, especially pancreatic cancer. Diagnosis must be based on a set of well-defined criteria. Response to corticosteroid therapy is the rule, but relaps are frequent, so patients need to be carefully monitored.

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