

Autoimmune Pancreatitis: Instrumental Diagnosis

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Autoimmune pancreatitis (AIP) is an unusual type of chronic pancreatitis having an underlying autoimmunity mechanism. Lymphoplasmacytic infiltration and fibrosis on histology, and elevated IgG levels or detected autoantibodies on laboratory data support the concept of AIP. Periductal lymphoplasmacytic infiltration and fibrosis, its preferential occurrence in the pancreatic head, and venulitis characterize autoimmune pancreatitis [1]. AIP should be distinguished from alcoholic chronic pancreatitis because steroid therapy for the former type is effective, morphologic changes are reversible, and pancreatic function can return to normal levels [2]. Difficulties can also arise in differentiating AIP from pancreatic carcinoma, as AIP predominantly affects elderly men, who frequently present with jaundice but without the features of acute pancreatitis, while there can be elevation of serum tumor markers. Other than clinical findings, there are also imaging findings which can be confusing: stenosis of the bile duct, segmental pancreatic enlargement or narrowing of the main pancreatic duct, and angiographic abnormalities which can cause confusion in the differential diagnosis between AIP and pancreatic carcinoma [3]. In fact, in many cases, patients with the focal form of AIP undergo surgery with a clinical and radiological diagnosis of pancreatic carcinoma [4, 5].

In order to obtain a correct diagnosis it is necessary to investigate all available information.

1. Clinical information: clinical features are non-specific and include upper abdominal pain, easy fatigability, and jaundice, which can simulate a neoplastic process. A high titer of serum gamma-globulin and IgG, the presence of autoantibodies and other autoimmune disorders in about 50% of the patients, are characteristically found in AIP [6, 7]. In particular, there is an association between AIP and other autoimmune disorders such as Sjögren syndrome, primary sclerosing cholangitis, primary biliary cirrhosis, ulcerative colitis, and systemic lupus erythematosus [7, 8, 9, 10].

2. Morphological information: with all the currently available imaging techniques (US, CT, MR), we can explore the morphology of the pancreatic gland with high sensitivity. AIP can be expressed by a focal or diffuse enlargement of the pancreatic gland. Whether the distribution is diffuse or focal seems to be related to the stage or the extent of the disease [11]; some cases of AIP starting as localized "mass-forming" pancreatitis and evolving to a diffuse form have been reported [12]. Ultrasound (US) is often the first imaging technique to be utilized in a patient with obstructive jaundice or with upper abdominal pain. At US, a hypoechoic diffuse swelling in

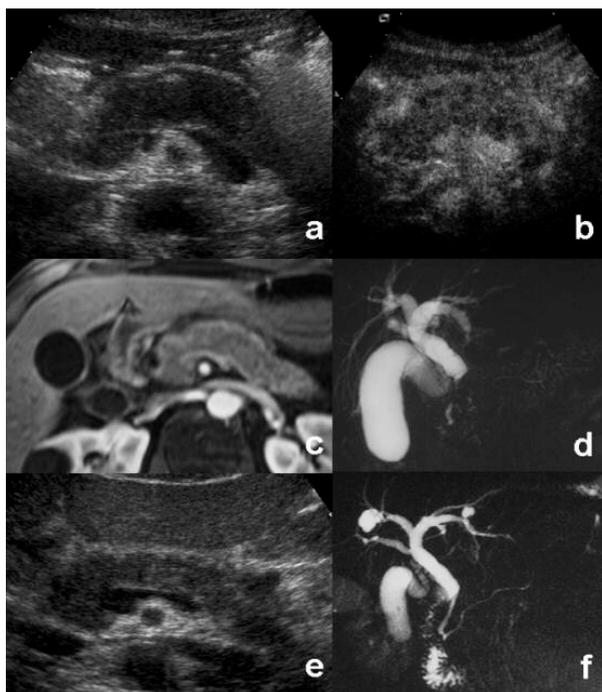


Figure 1. A 45-year-old male with diffuse autoimmune pancreatitis (a. b. c. d.). US shows a diffuse enlargement of the pancreas with sharp margins (a.). CEUS with 2.4 mL of Sonovue (Bracco, Milano, Italy): a diffuse enhancement of the pancreatic gland can be appreciated (b.). Contrast enhanced MR, arterial phase: the affected gland shows delayed enhancement, with sparing of the peripheral portion of the gland (c.). MRCP: a clearly visible stenosis of the main pancreatic duct as well as of the intrapancreatic portion of the biliary duct, which is distended in its extrapancreatic tract (d.). Fifteen days after steroid therapy (e. f.). The volume and the echogenicity of the gland is normal (e.). At MRCP, the Wirsung duct and the biliary duct are better visualized (f.).

the pancreas (sausage-like appearance: Figure 1a) [13] or a focal swelling of the pancreas (Figure 2a) simulating a neoplastic lesion can be observed at AIP, as well as a dilation of the extrapancreatic bile duct, secondary to an involvement of its intrapancreatic portion. On color-Doppler, the enlarged pancreas can show hypervascularity [14]. Conventional US is not able to show the irregular focal or diffuse narrowing of the main pancreatic duct or of the intrapancreatic bile duct, which represents one of the main diagnostic criteria for AIP at ERCP [6]. Moreover, extrapancreatic bile duct changes such as the stricture of the bile duct at the hilus or intrahepatic area can be observed in patients with AIP [15], with a similar pathogenic mechanism of pancreatic abnormalities and

response to steroid therapy [10, 16], not demonstrated with conventional US. Furthermore, US is very operator-dependent and is limited when studying obese patients or patients with excessive meteorism. The recent development of contrast agents for ultrasound has significantly extended its clinical applications, not only in the detection and characterization of focal liver lesions, but in permitting a real-time evaluation of the different vascular phases. Contrast-enhanced ultrasonography (CEUS) can successfully visualize fine vessels in pancreatic lesions and may play a pivotal role in the depiction and differential diagnosis of pancreatic tumors [17, 18].

In particular, some Authors have analyzed the enhancement of focal pancreatic lesions and it has been shown that, while most of the inflammatory pancreatic masses, show a pattern of enhancement similar to the normal pancreatic gland (“isovascular”: Figure 1b), a focal pancreatic tumor is hypovascular to the surrounding normal parenchyma (Figure 3), with a sensitivity and accuracy rate of differentiating both diseases on CEUS of 98% and 95%, respectively, while on CT they were both 73% [18]. Similar results were found by Ozawa *et al.* [19]. Numata *et al.* [20] compared the vascularity of pancreatic lesions on CEUS with the pathologic findings (fibrosis and inflammation) in 6 patients with AIP. The AIP lesions exhibited mild (n=1),

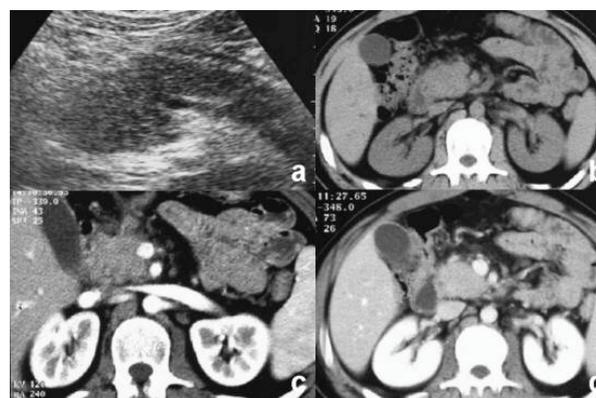


Figure 2. A 27-year-old male with focal autoimmune pancreatitis (a. b. c. d.). US shows a focal enlargement of the head of the pancreas (a.). At CT (b. c. d.) the lesion shows homogeneous delayed enhancement, better visualized in the venous phase (d.). The peripancreatic vessels are not involved by the lesion.

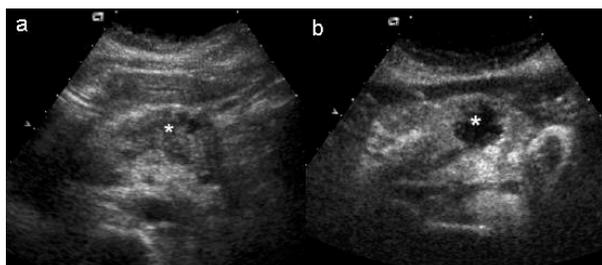


Figure 3. A 65-year-old male with adenocarcinoma of the head of the pancreas (a. b.). Conventional US (a.): a focal enlargement of the body of the pancreas can be observed (*). CEUS with 2.4 mL of Sonovue (Bracco, Milano, Italy) (b.): normal enhancement of the pancreas with exception of a mass (*) which results constantly hypoechoic.

moderate (n=3), or marked (n=2) enhancement in almost all the lesions in both the early and the delayed phases, having a direct correlation with the pathologic degree of inflammation and an inverse correlation with the degree of fibrosis associated with AIP. The vascularity of all 3 lesions which were followed-up had decreased on the CEUS images after steroid therapy [20]. In another observation, CEUS showed diffuse strong enhancement of the thickened bile duct wall, possibly due to inflammation [21].

At both CT and MR a focal or diffuse swelling of the pancreatic gland can be observed, similarly way to US [22]. Dynamic imaging at CT or MR shows a delayed enhancement of the involved segments of the gland (Figures 1c, 2c, 2d, 4b, 4c) [11, 23]. In some cases, minimal peripancreatic stranding suggesting inflammation can be seen [4]. Moreover a capsule-like smooth rim can be observed, which is hypodense on CT and hypointense on T2 weighted images, showing delayed enhancement on dynamic imaging (Figure 4d) [12, 22], which is thought to correspond to an inflammatory process involving peripancreatic tissues (fluid collection, phlegmon, or fibrosis), and this appears to be a characteristic finding of AIP [22]. However, such a finding is not always reported by other authors, especially at CT [4]. Pancreatic calcifications are absent in AIP [24], although pancreatic stone formation in some patients with AIP has been seen, suggesting that autoimmune pancreatitis has

the potential of being a progressive disease with pancreatic stones [25].

Involvement of the main pancreatic duct and the biliary duct is well-described in the literature. Endoscopic retrograde cholangiopancreatographic criteria for the diagnosis of autoimmune pancreatitis include diffuse irregular narrowing of the main pancreatic duct [26, 27] and abnormalities which normalized after steroid therapy [6]. The same alterations can be observed at MR cholangiopancreatography (MRCP: Figures 1d, 1f) [4]. Biliary strictures resemble those observed in primary sclerosing cholangitis [28]. The invasion of vessels, vascular encasement, mass effect, and fluid collections are absent [4, 22].

In 1990 positron emission tomography (PET) was first applied in the diagnosis of pancreatic cancer. This modality is based on the functional changes in pancreatic cancer cells caused by an enhanced glucose metabolism. Increased glucose utilization is one of the characteristics of malignantly transformed cells, independent of their origin. Using

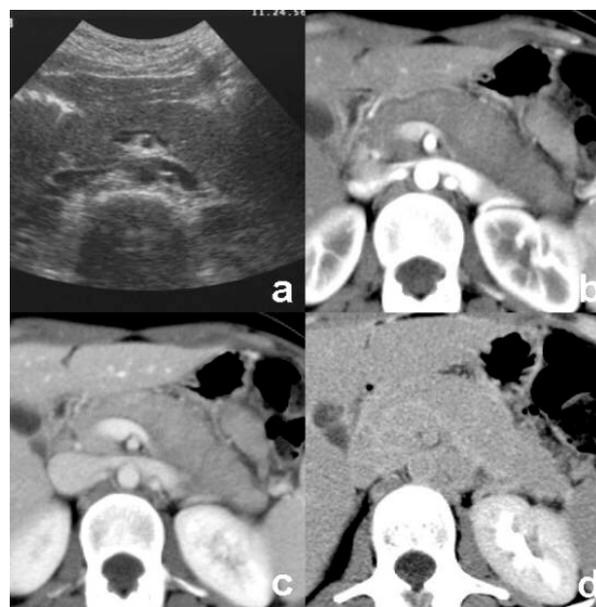


Figure 4. A 28-year-old female with UC and recurrent acute pancreatitis (a. b. c. d.). Conventional US (a.): diffuse enlargement of the body-tail of the pancreas can be observed. CT (b. c. d.): the pancreas shows diffuse delayed enhancement (b. c.) with a peripheral rim of enhancement during the distribution phase (d.), about 5 minutes after the contrast injection.

2-((18)F)-fluoro-2-deoxy-d-glucose (FDG), PET can effectively differentiate pancreatic cancer from benign lesions with high accuracy [29]. However, a relative overlap has been reported between uptake values obtained in cancer and those obtained in inflammatory lesions [30] as active chronic and autoimmune pancreatitis sometimes show high FDG accumulation and mimic pancreatic cancer having a focal form [31]. On the contrary, false negative cases in the detection of pancreatic cancer by FDG PET have been described, mainly because of the poor cellularity in cancer tissue. Accumulation of Ga-67 citrate has also been described in both autoimmune pancreatitis and in adenocarcinoma of the pancreas [32, 33], although a concomitant accumulation in the hilar region of the lung has been described only in autoimmune pancreatitis [34].

In conclusion, when dealing with a pancreatic lesion which does not present signs of malignancy, the radiologist should be aware of the diagnosis of AIP. Diagnosis by imaging methods (US, CT, MR) is more accurate in the diffuse form of AIP, especially in an appropriate clinical setting, such as a high titer of the IgG level and a history of autoimmune disease. Imaging features which can help in distinguishing AIP from pancreatic cancer include a mildly enlarged pancreas (sausage-shaped), with homogeneous delayed enhancement after contrast injection, sharp borders and rim-like hypoattenuation in the periphery of the pancreas which correspond to inflammation and fibrosis at pathologic analysis, as well as a diffuse pancreatic and common bile ductal narrowing. Moreover, the absence of the encasement of the mesenteric vessels and metastatic disease in the liver or the peritoneum constitute other findings which can suggest a diagnosis of AIP. However, in the absence of an appropriate clinical setting, a focal form of AIP can be extremely difficult to differentiate from pancreatic cancer on the basis of imaging features alone. In the case of a focal lesion of the pancreas without signs of local or distant diffusion, a cytological analysis of the lesion should be done in order

to try to exclude focal AIP, although this is not always possible.

Keywords Autoimmune Diseases /diagnosis /pathology /radiography /ultrasonography; Contrast Media; Cholangiopancreatography, Endoscopic Retrograde; Magnetic Resonance Imaging; Pancreas /immunology /pathology /radiography; Pancreatitis /diagnosis /immunology /pathology /radiography /ultrasonography; Tomography, X-Ray Computed

Abbreviations AIP Autoimmune pancreatitis; CEUS: contrast enhanced ultrasonography; FDG: 2-((18)F)-fluoro-2-deoxy-d-glucose; PET: positron emission tomography

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