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Review article

Autoimmune Pancreatitis: A Surgical Dilemma☆,☆☆

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ABSTRACT

Autoimmune pancreatitis (AIP) is defined as a particular form of pancreatitis that often manifests as obstructive jaundice associated with a pancreatic mass or an obstructive bile duct lesion, and that has an excellent response to corticosteroid treatment. The prevalence of AIP worldwide is unknown, and it is considered as a rare entity. The clinical and radiological presentation of AIP can mimic bilio-pancreatic cancer, presenting difficulties for diagnosis and obliging the surgeon to balance decision-making between the potential risk presented by the misdiagnosis of a deadly disease against the desire to avoid unnecessary major surgery for a disease that responds effectively to corticosteroid treatment. In this review we detail the current and critical points for the diagnosis, classification and treatment for AIP, with a special emphasis on surgical series and the methods to differentiate between this pathology and bilio-pancreatic cancer.

Pancreatitis autoinmune: un dilema quirúrgico

RESUMEN

La pancreatitis autoinmune (PAI) es una enfermedad fibroinflamatoria benigna del páncreas, se manifiesta frecuentemente como ictericia obstructiva asociada a masa pancreática o lesión obstructiva de la vía biliar y presenta una respuesta excelente a corticoides. Aunque no existen estudios a nivel mundial que definan su epidemiología, la PAI se considera una entidad poco frecuente, con una prevalencia estimada del 2% de los pacientes con pancreatitis crónica. Su frecuente presentación clínica y radiológica en forma de masa pancreática e ictericia similar al cáncer de páncreas y la falta de elementos diagnósticos específicos son causa de un elevado porcentaje de resecciones quirúrgicas pancreáticas por una enfermedad benigna que responde a tratamiento médico. En esta revisión detallamos los acuerdos actuales para el diagnóstico, clasificación y tratamiento de la PAI, enfatizando en las series quirúrgicas y en estrategias para mejorar el diagnóstico diferencial con el cáncer de páncreas y evitar así resecciones pancreáticas innecesarias.

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Definition

Autoimmune pancreatitis (AIP) is a benign fibro-inflammatory illness of the pancreas, reported for the first time in 1961 as a pancreatitis case related to hypergammaglobulinemia.[1] In 1995, Yoshida et al. proposed the concept of AIP.[2] Recently, the International Association of Pancreatology defined AIP as a specific form of pancreatitis that often manifests as obstructive jaundice, sometimes related to a pancreatic mass with characteristic histological changes that include lymphoplasmacytic infiltrate and fibrosis, and shows an excellent response to cortico-steroid treatment.[3]

Types of Autoimmune Pancreatitis

Histopathological analysis of the pancreas defines 2 patterns with differential characteristics: (1) lymphoplasmacytic sclerosing pancreatitis (LPSP) or AIP without granulocyte epithelial lesions and (2) idiopathic duct centric pancreatitis (IDCP) or AIP with granulocyte epithelial lesions. However, given that the histological description is not always available, the terms type 1 and type 2 AIP have been introduced aiming to describe LPSP or IDCP related clinical manifestations, respectively.[4]

Type 1 pancreatitis is the predominant form in Asian countries. It is most frequent in males (3–4:1), peaking in the sixth decade of life; it may include elevation of serum immunoglobulin G4 (IgG4), and it is often related to fibroinflammatory involvement of other organs. Resolution of pancreatic and extrapancreatic manifestations with steroids is characteristic in type 1 patients, although relapse is frequent after treatment is stopped, in particular for cases with extrapancreatic involvement.[5]

Type 2 pancreatitis is reported more often in Europe and the United States. It affects mostly younger patients (one decade before type 1 AIP), without gender differences; it does not include IgG4 serum elevation, is not related to other organ involvement, and related inflammatory bowel disease exists in a high percentage of patients (11%–30%) (more frequently ulcerative colitis than Crohn's disease). Response to treatment with steroids is good and relapses are rare. Given that type 2 AIP lacks serum markers (no IgG4 elevation) and other organ involvement, its definitive diagnosis requires a histological analysis of the pancreas. This explains in part why type 2 AIP is diagnosed less frequently than type 1.[5]

Clinical Manifestations

The most frequent manifestation is obstructive jaundice caused by a pancreatic mass (up to 59% of cases) or by enlargement of the common bile duct wall.[6] It may also appear as single or recurrent acute pancreatitis or progress into chronic pancreatitis with exocrine and endocrine pancreatic calcification and failure.[7] Another form of presentation includes symptoms related to extrapancreatic involvement, for example: lacrimal or salivary tumour, cough, dyspnoea from pulmonary lesions or lumbago caused by retroperitoneal fibrosis or hydronephrosis.[6]

Histopathological Changes

AIP shows well-defined histopathological changes in the pancreas that are easily differentiated from changes occurring in other types of pancreatitis (alcoholic or chronic obstructive). Some of these types are common findings for type 1 and type 2 and others are used to differentiate both groups.[8,9]

Histopathological Findings Common to Type 1 and Type 2 Autoimmune Pancreatitis

Lymphoplasmacytic infiltration and *inflammatory cellular stroma* are highly characteristic findings of AIP.[8] Lymphoplasmacytic infiltrate is dense and becomes stronger around mid and large size ducts, compressing the ductal lumen (horseshoe or star shaped ductal image, highly characteristic of AIP) which differs from ductal dilation (characteristic of chronic pancreatitis from another origin). Lymphoplasmacytic infiltration extends diffusely through the pancreatic parenchyma, where it is accompanied by fibrosis and acinar atrophy and leads to inflammatory cellular stroma, with abundant lymphocytes, plasma cells, and eosinophil patched areas; the latter are specific to AIP, however, not to other types of chronic pancreatitis.

Characteristic Findings of Type 1 Autoimmune Pancreatitis

Storiform fibrosis, *obliterative phlebitis*, *prominent lymphoid follicles* and *IgG4+ plasma cells* are findings highly characteristic of type 1 AIP, although they are also found in lower proportions in type 2.[9] Storiform or whorled fibrosis is a peculiar type of fibrosis caused by a mesh of short collagen fibres intertwined in various directions and infiltrated by a dense lymphoplasmacytic component. This pattern is described in 90% of type 1 AIP and 29% of type 2 AIP. Obliterative phlebitis turns vein inflammation into lymphoplasmacytic infiltration, and then obstructs the vascular lumen. Although it is hard to recognise, its identification is of great interest because it is a pathognomonic sign of AIP. This change is described in 90% of type 1 AIP and 57% of type 2 AIP. The existence of prominent lymphoid aggregates and follicles in parenchyma and peripancreatic fat is another characteristic fact of AIP (100% for type 1 and 47% for type 2); however, it is also observed in approximately half of alcoholic chronic pancreatitis and obstructive chronic pancreatitis cases. Detecting abundant IgG4 plasma cells (>10 cells/high power field [HPF]) is the key detail in diagnosing type 1 AIP, provided that for type 2 AIP no IgG4 plasma cells exist or are few in number (<10 cells/HPF). It is important to consider that these cells can also be observed in other forms of chronic pancreatitis (11%–57%) and in pancreatic ductal adenocarcinoma (12%–47%).

Characteristic Findings of Type 2 Autoimmune Pancreatitis

Granulocytic epithelial lesions are pathognomonic of type 2 AIP.[9] These lesions are formed by neutrophil infiltrates affecting medium and small ducts, as well as acinar cells, causing cellular destruction and lumen obliteration.