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► **To cite this version:**

Vinciane Rebours, Philippe Lévy. Pancreatic and biliary tract involvement in IgG4-related disease. La Presse Médicale, 2020, 49, pp.104015 -. 10.1016/j.lpm.2020.104015 . hal-03490380

HAL Id: hal-03490380

<https://hal.science/hal-03490380v1>

Submitted on 22 Aug 2022

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LPM

QMR Igg4-related Disease

Pancreatic and biliary tract involvement in IgG4-related disease

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Conflit d'intérêt: aucun

Abstract

The diagnosis and treatment of pancreatic and biliary tract involvement in IgG4 disease can be challenging for physicians. A French series shows that the pancreas is the most frequently involved organ in systemic IgG4 disease. Pancreatitis may be found in more than 50% of patients with IgG4 disease and the biliary tract is involved in one third. Pancreatic or biliary involvement may be isolated, metachronous or synchronous of other IgG4-related organ injuries.

Pancreatitis related to IgG4 disease is called autoimmune pancreatitis (AIP) type 1. The diagnosis is mainly suspected in the presence of symptoms and morphological features. Changes observed on conventional imaging are not typical and are usually similar to lesions observed in autoimmune pancreatitis type 2. AIP type 1 can also sometimes have a clinical or morphological presentation that mimics pancreatic cancer, especially pseudo-tumoral forms, associated with obstructive jaundice, weight loss and fatigue. Thus, the first challenge is to confirm the diagnosis of autoimmune pancreatitis and to exclude cancer. The AIP type must then be determined to decide on the most appropriate treatment.

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Autoimmune type 1 or type 2

The first published cases of autoimmune pancreatitis reported abundant infiltrate of inflammatory cells including significant inflammation, lack of acinar dilatation or thin-walled ducts, destruction of the pancreatic parenchyma, and epithelial damage. In 1995, a case report from Japan suggested calling this specific form of pancreatitis: lymphoplasmacytic sclerosing pancreatitis (LPSP) and introduced the concept of “autoimmune pancreatitis”. During the next decade, multiple reports were published and some specific pathological features of AIP have been described such as diffuse lymphoplasmacytic infiltration, marked interstitial fibrosis and obliterative phlebitis. Results in the literature suggested that there were 2 different types of AIP associated with different clinical profiles and outcomes (2).

In 2011, an expert consortium proposed a classification of 2 types (types 1 and 2) based on pathological features (2). Although the scientific mechanisms are still unknown, these two types have probably different physiopathological origins. Despite certain overlaps, 2 types of AIP have been recognized. Lymphoplasmacytic sclerosing pancreatitis (LPSP) (AIP type 1) or

IgG4 disease-related autoimmune pancreatitis is characterized by dense periductal lymphoplasmacytic infiltrate, inflamed cellular stroma with storiform fibrosis and obliterative phlebitis, while AIP type 2 is distinguished from type 1 by the presence of granulocytic epithelial lesions (GEL): neutrophils in the epithelium duct and lumen and damage to epithelial cells. The presence of positive immuno-taining for IgG4 in plasma cell (plasmocytes) infiltrates (>10 cells per high power field for pancreatic biopsy) supports the presence of LPSP. Pancreatic necrosis, pseudocysts and calcifications are usually not observed.

AIP type 1 and 2 can not be differentiated on imaging, and the clinical presentation may be similar with possible overlap. But it is clinically important to obtain the correct diagnosis because AIP type 1 is usually more aggressive with a high rate of relapse and synchronous or metachronous involvement of extra-pancreatic organs.(3)

Clinical presentation

Patients with AIP type 1 are usually males (75% of cases). The median age at diagnosis is normally 60-70 years or older. Two main clinical presentations suggest the diagnosis of AIP type 1: obstructive jaundice (usually painless) associated with weight loss and fatigue (mimicking pancreatic adenocarcinoma) or acute pancreatitis (usually benign with no necrosis).(3-4)

The morphological presentation includes a pancreatic mass on imaging, focal or diffuse pancreatic enlargement, pancreatic ductal strictures and rarely, benign acute pancreatitis with no necrosis.(5)

Involvement of other organs is highly frequent >50% and strongly suggest AIP related to IgG4 disease. This association can be metachronous or synchronous. Table 1. All organs may be involved and thorough clinical and morphological examinations should be performed: lacrimal and salivary glands, pulmonary nodules and interstitial fibrosis, mediastinal lymph nodes, retroperitoneal fibrosis, nephritis, aortitis.... (1,3-7)

Biliary involvement

Jaundice may be due to diffuse cholangitis of the entire biliary tract or focal cholangitis of the retropancreatic portion of the main biliary duct. In the IgG4 disease, the biliary tract is involved in one third of the patients but in case of pancreatic involvement, cholangitis (with or without jaundice) is associated (with AIP) in 80% of the cases. Compression may be present because of a focal pancreatic mass of the head or to diffuse pancreatic enlargement.

(6)

Table 1: Characteristics of AIP types 1 and 2

<i>AIP type 1 – IgG4-related pancreatitis</i>	<i>AIP type 2 – GEL pancreatitis</i>
<p>Clinical Median age at diagnosis: 50 years Sex: Male, 80%</p> <p>Symptoms:</p> <ul style="list-style-type: none"> - Jaundice - Pseudo tumoral presentation - Pancreatic exocrine insufficiency - Diabetes - Acute pancreatitis - Other organ involvement > 50% <ul style="list-style-type: none"> - Cholangitis - Tubulo-interstitial nephritis - Lymph nodes - Lung 	<p>Clinical Median age at diagnosis: 40 years Sex ratio ~ 1</p> <p>Symptoms</p> <ul style="list-style-type: none"> - Acute pancreatitis - Associated with inflammatory bowel diseases in 20 -30%

GEL: granulocytic epithelial lesions

Biochemical biomarkers

In patients with cholangitis, cholestasis is usually observed with elevated liver enzymes: transaminases, alkaline phosphatases, and bilirubin. No specific threshold was published and every serum level can be observed, sometimes very high. The particularity of liver enzymes abnormalities is the very rapid relief from corticosteroids. In every studies, a partial resolution of biliary strictures was observed in less than 15 days and a complete relief in quite 100% of the cases within 4 weeks.

Biochemical biomarkers are poorly helpful to confirm related IgG4- AIP or cholangitis. Some antibodies have been reported to be associated with autoimmune pancreatitis including antibodies to carbonic anhydrase, Lactoferrin, plasminogen binding peptide, anti-

mitochondrial antibodies, anti-smooth muscle antibodies, rheumatoid factor and antithyroglobulin. However, these antibodies are not specific and are positive in less than 20% of the cases. Experts did not recommend performing these biochemical tests. Besides this, only IgG4 serum level is relevant. Generally IgG4 serum levels are elevated, and twice the upper normal limit in around 80% of patients. This biochemical biomarker is one of the diagnostic criteria published by experts. (7) The IgG4 level is not a relevant marker to exclude cancer in pseudotumoral forms of the disease that mimic cancer (see specific paragraph below). Ten percent of patients with pancreatic cancer can have elevated IgG4 serum levels.(8)

Morphological characteristics

The morphological features of AIP take two different anatomical forms. Parenchymal and ductal changes may be diffuse (70% of cases) or present as a pseudotumour (30%), usually mimicking pancreatic cancer. Figures 1 and 2.

Abdominal CT scan and magnetic resonance imaging (MRI) with pancreatic sequences (MRCP) are needed to diagnose AIP. Morphological features on CT include:

- Diffuse enlargement of the entire gland (sausage pancreas) with delayed enhancement and loss of lobulations,
- Hypodense pseudo tumoral form with delayed enhancement,
- Peripheral hypodense pseudo rim (capsule),
- Cut-tailed form,
- Rare calcifications
- Involvement of other organs

On MRI and MRCP, abnormalities include hypointense diffuse pancreatic enlargement with loss of lobulations on T1 weighted sequences and a hypointense pseudo rim on T2 weighted sequences. Involvement of other organs and associated biliary tract abnormalities should be searched for on biliary sequences.(9-10) MRCP is the gold standard exam to assess pancreatic duct abnormalities. The main pancreatic duct (MPD) is thin and irregular, with

diffuse narrowing, long (>one third of the MPD) or multifocal stenoses, and no upstream dilatation or side branches originating from a strictured segment(10). This specific criteria was confirmed in one series, in which patients with AIP n= 38, cancer n = 40 and controls= 40 were included. No MPD dilatation (or less than 5 mm) was observed on MRCP in the AIP group (11). In AIP, The main duct never disappears completely in AIP even into pseudo-tumoral forms, corresponding to the “duct penetrating sign”.

MRI and biliary sequences, especially, have to be performed to search for cholangitis criteria (9-10).

Endoscopic ultrasound (EUS) can be performed and the following abnormalities are usually observed: diffuse hypoechoic enlargement into the pancreatic parenchyma, hypoechoic rim, heterogeneous parenchymal hypertrophy corresponding to a « salt and pepper » appearance, segmental hypertrophy or nodules with no upstream dilatation of the main pancreatic duct. Duct changes include ductitis, defined by a thin and irregular MPD, with « vanishing duct » zones, abnormal MPD wall and biliary tract involvement. The sensitivity, specificity, positive predictive value and negative predictive value of ductitis compared to a control group of patients with alcoholic chronic pancreatitis, pancreatic cancer, neuroendocrine tumours or biliary lithiasis were 99%, 90%, 98% and 97%, respectively (12).

Positron emission tomography (PET) can show intense, diffuse or focal FDG uptake in the pancreas and other involved organs (13).

Pancreatitis or cancer: Distinguishing between AIP and pancreatic tumors

Pseudo tumors (30%), that usually mimic pancreatic cancer, can be difficult to distinguish from adenocarcinoma.

Biochemical markers, like IgG4 levels, are not helpful in distinguishing AIP from cancer. IgG4 serum levels are normal in 20% of AIP type 1 patients and elevated (>2N) in 10% of pancreatic cancers.(8) With a cut-off of 1.09 g/L, the sensitivity and specificity for differentiating AIP type 1 from cancer is 68% and 88%, respectively. In a series of patients with pancreatic cancer (n = 548) and with AIP type 1 (n = 99), patients with AIP were more likely to have elevated IgG4 serum levels (65% vs 10.4%, p< 0.001) and more than 2 times upper limit of normal (40% vs 2.4%, p< 0.001) (14).

The serum levels of anti-plasminogen binding peptide, anti-carbonic anhydrase-II, anti-nuclear antibodies, anti-lactoferrin, a-CA-II, and rheumatoid factor were also evaluated. No statistically significant difference was observed to distinguish AIP and cancer (15).

In a Dutch series published in 2012, 274 Whipple procedures were performed between 2000 and 2009 for suspected cancer. Twenty-three patients (8.4%) had benign lesions (versus 5-11% in the literature) including 7 patients (2.6%) with AIP. Some unnecessary Whipple procedures are still performed. A thorough morphological work-up (including CT scan, MRI, Endoscopic Ultrasound and PET scan) is the key to distinguishing between AIP and pancreatic tumor (16-17).

Morphological criteria to distinguish AIP from cancer are summarized in the table 2.

Table 2: Clinical, biochemical and morphological criteria for pancreatic cancer or AIP.

<i>Autoimmune pancreatitis Criteria</i>	<i>Cancer Criteria</i>
<p>Clinical</p> <ul style="list-style-type: none"> - Age <50 years old - Involvement of other organs - No weight loss <p>Biology</p> <ul style="list-style-type: none"> - IgG4 blood level > 2N <p>Morphology</p> <ul style="list-style-type: none"> - Diffuse pancreatic enlargement - Multiple masses - Late IV enhancement - Diffuse positive diffusion - Hypodense pancreatic rim - Lack of upstream dilatation (<5mm) - Duct irregularities - Duct penetrating sign - Diffuse cholangitis - No metastases 	<p>Clinical</p> <ul style="list-style-type: none"> - Age >50 years old - No other organ involvement - Weight loss, pain <p>Biology</p> <ul style="list-style-type: none"> - Normal IgG4 blood level <p>Morphology</p> <ul style="list-style-type: none"> - Main pancreatic duct dilatation >6mm - Pancreatic atrophy upstream of the mass - Localised mass (Ctscan, MRI diffusion) - No peripheral inflammation (no rim) - Homogenous dilatation of the biliary tree - Metastases

MRI: magnetic resonance imaging

EUS +/- fine needle aspiration (FNA) or biopsy (FNB) must be performed to exclude cancer in pseudo-tumoral forms.

In case of pseudo tumoral forms of the disease, contrast harmonic EUS can help confirm the diagnosis of AIP or cancer. In all cases, EUS FNA or FNB should be performed to exclude cancer and obtain pathological criteria for AIP (plasmocyte and lymphocyte infiltrates, IgG4 positive immunochemistry) (17). Large tissue samples may be needed to confirm the diagnosis of AIP and the use of large needles (22G and 19G) can be proposed. Cytology is insufficient and leads to numerous false positive samples (18). In a surgical series of 20 patients with AIP, preoperative cytological analyses showed atypical cells in 50% of patients, mucinous neoplasms in 5% and adenocarcinoma in 5%. In a comparison of FNA and FNB, biopsies more found to more accurately confirm the diagnosis of AIP (19).

Pancreatitis and the risk of cancer

Several small series have been published in the past decade on pancreatic cancer and AIP. Although the relationship between autoimmune pancreatitis and pancreatic cancer has now been clearly established, the risk has not been determined. There are no prospective cohorts of AIP patients to assess the actuarial and crude risks of cancer in AIP.

In a series of 63 patients with AIP, cancer developed in 3 patients (4.8% - 3/63) after a median follow-up of 94.7 months (31-186). In these 3 AIP patients, clinical remission of AIP was obtained in all with maintenance steroid therapy when the tumors were discovered. Pathological examination of the surgical specimen showed lympho-plasmacytic infiltration in storiform fibrosis with abundant IgG4-positive cell infiltration around cancerous cells (20).

Chronic inflammatory process has been clearly defined as a risk factor of pancreatic cancer and play a key role in carcinogenesis. Moreover, the immunosuppressed state of AIP patients due to immuno-modulators (such as steroid therapy, rituximab, aziathropine...) may also be associated with the development of pancreatic cancer in this group. This paradox needs to be evaluated (21).

Natural history of IgG4 related AIP type 1 and cholangitis

Data on the long term functional outcome of AIP patients are limited in the literature. Diabetes mellitus has been reported in 19%-67% of these patients and exocrine insufficiency in 36-85%. The wide range of results might be due to small populations, short follow-up and different criteria for endocrine and exocrine insufficiency (3-4). One survival analysis did not

identify any significant difference between AIP type 1 and 2 and between AIP and the general population. Specific survival rates were 91% and 72% at 5 and 10 years, respectively (22).

Natural history of IgG4-associated cholangitis is poorly known probably because of the rarity of the disease and lack of globally accepted diagnostic criteria in first series. In a retrospective cohort study of 527 patients with IgG4-cholangitis (436 females; median age, 66.2 years) in Japan, authors described rare presentations of decompensated cirrhosis. Response to prednisolone was excellent in 90% of patients. No patients received liver transplants, and cholangiocarcinoma was found in only 4 patients (0.7%). Restenosis of bile ducts was observed in 19% of patients but did not affect overall survival. Only 4 patients died because of liver-related or bile duct-related diseases. Cirrhosis progression accounted for 2 deaths. Overall 5- and 10-year survival rates were 94.5% and 81.0%, respectively and the 5- and 10-year survivals free from death caused by liver-related or bile duct-related diseases were 98.9% and 97.7%, respectively. (23)

Treatment

Steroids are considered to be the gold standard for initial treatment. The response rate to steroids is excellent (98%) (24-25). This suggests that biliary stenting is not mandatory in combination with steroids in case of obstructive jaundice because of the risk of cholangitis (25). Jaundice is totally resolved in less than 15 days with steroids without stenting with a rapid decrease and normalization in liver enzymes. As suggested by Yukutake et al. liver enzymes are normal in 80% and 100% at 15 and 21 days, respectively (26).

Biliary drainage can be indicated in case of doubt of cholangiocarcinoma only in order to use brushing and cytology to rule out malignancy.

International expert recommendations were recently published (25). These guidelines recommended using high dose prednisone at 40mg/day for 4 weeks, then tapered by 5mg/week. The response can be assessed at 4 weeks based on clinical and morphological progression and IgG4 levels. Indications for treatment were symptomatic AIP patients with obstructive jaundice (due to main pancreatic duct obstruction or diffuse cholangitis) as well

as abdominal and back pain. Treatment was recommended in asymptomatic patients in case of a persistent pancreatic mass on imaging (to rule out cancer) or persistent liver test abnormalities (25).

The relapse rate is high and range from 26% to more than 70% in the literature. The risk factors for relapse are now well understood. However, some predictors of relapse may be high serum IgG4 levels, persistently high serum IgG4 levels after steroid treatment and multiple organ involvement.

Experts did not recommend maintaining low dose steroids to prevent relapse.(27) However, there is evidence on the use of other immunomodulators and rituximab especially in case of relapsing forms. Therefore they proposed a therapeutic algorithm (28); Figure 3.

The diagnosis and treatment of pancreatic and biliary tract involvement in IgG4 disease can be challenging for physicians. Pancreatitis may be found in more than 50% of patients with IgG4 disease and the biliary tract is involved in one third. Morphological features observed on conventional imaging are not often typical and can mimic cholangiocarcinoma or pancreatic cancer. Corticotherapy is the gold standard treatment for inducing remission. The reference treatment for maintenance or recurrence is rituximab (CD20 anti-body). The risk of recurrence is high and was estimated at more than 30% for AIP type 1 in case of initial treatment. More than 50% of recurrences appear in the first year after initial corticosteroid treatment, 3/4 in two years and > 90% within three years.

Legends

Figure 1: A, CT scan: Sausage-form pancreas with peripheral pseudo-rim (white arrows). B, MRCP and C, MRI-T2 sequences: Main pancreatic duct irregularities with lack of upstream dilatation (white arrows)

Figure 2: MRI, Biliary sequences. Diffuse cholangitis with multiple dilatations and stenosis of the biliary tree.

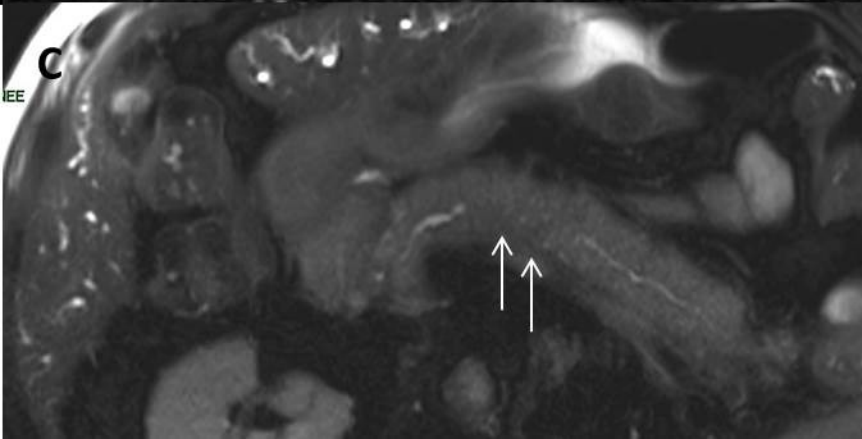
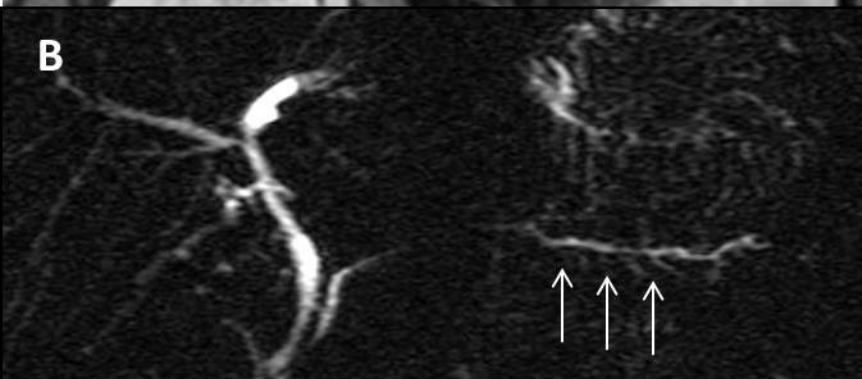
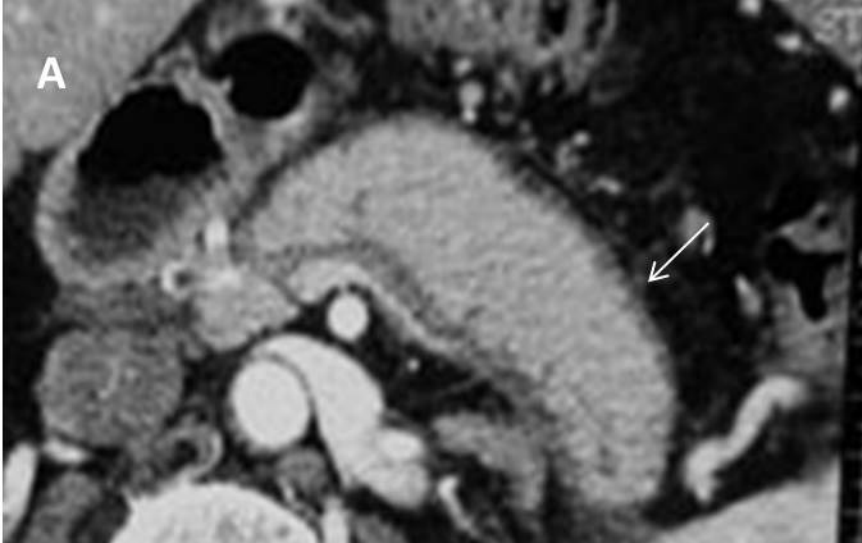
Figure 3: Therapeutic algorithm for pancreatic and biliary symptoms related to IgG4 disease.

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