Autoimmune pancreatitis and extrapancreatic manifestations of IgG4-related sclerosing disease

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Abstract

In a review of the literature concerning autoimmune pancreatitis we had special interest for the concept of IgG4-related pathology as a systemic disease with several clinical manifestations. In general, IgG4-positivity can not only be found in the pancreas, but also at the level of the kidneys, extrahepatic biliary ducts, gallbladder, lungs, salivary glands, lacrimal glands, retroperitoneal tissue, ureters, prostate, meninges and lymph nodes. IgG4 seems to be a central key player in the pathophysiology of this disease. (Acta gastroenterol. belg., **2010**, 73, **239-246**).

Key words : autoimmune pancreatitis, extrapancreatic manifestations, retroperitoneal fibrosis, IgG4, IgG4-related sclerosing disease.

Abbreviations

AIP	autoimmune pancreatitis
ANA	antinuclear antibody
CA-II	carbonic anhydrase II
CT	computed tomography
ERCP	endoscopic retrograde cholangiopancreaticography
HISORt	Histology Imaging Serology Other organ involvement Response to steroid therapy
IgG4	immunoglobulin G (fourth subtype)
IgG4-SD	IgG4-related sclerosing disease
IBD	inflammatory bowel disease
JPS	Japan Pancreas Society
MFS	multifocal fibrosclerosis
PET	positron emission tomography
Ref.	reference value
RF	retroperitoneal fibrosis
SD :	sclerosing disease

Introduction

We discuss IgG4-related sclerosing disease, with special interest for the various localisations – suggesting a possible 'overlap syndrome', where not only autoimmune pancreatitis (AIP) but also retroperitoneal fibrosis (RF) and many other entities could be part of. The paucity in information persisting for several decades concerning AIP and RF, is already reflected in the different names used for this diseases in the past.

This systemic disease received more attention in the literature recently and has increasingly been recognized worldwide without knowing much about the underlying pathogenetic mechanisms. IgG4 is probably a clue in revealing underlying pathophysiological processes, but at this moment, the exact mechanism remains unclear.

Discussion

A. *Autoimmune pancreatitis*

History

In 1961, Sarles *et al.* described a 'chronic inflammatory sclerosis of the pancreas' and suspected an autoimmune etiology for this pancreatic disease. It was already known that an elevation of gamma globulins was associated with this pancreatic pathology (1). In 1978, Nakano *et al.* showed that corticosteroid therapy could be beneficial for the course of this disease entity that did not receive much attention uptill the 1990's. In 1992, Toki *et al.* made a report of four cases of pancreatic disease with diffuse enlargement of the pancreas with the presence of a lymphocytic infiltration (2,3). Since then, there was a growing interest for this pathology. Three years later, 'autoimmune pancreatitis' (AIP) was suggested by Yoshida *et al.* to describe this pathology. The use of a variable terminology made it difficult for clinicians who were not familiar with this disease (4,5). Primary chronic pancreatitis, non-alcoholic duct-destructive chronic pancreatitis, duct-narrowing chronic pancreatitis (DNCP), lymfoplasmocytic sclerosing pancreatitis (LPSP), (idiopathic) tumefactive chronic pancreatitis, … are part of the 'tower of Babel' of names commonly used for the same disease (4,6-8). Although still being rare, AIP is more frequently recognized and has generated significant interest (9).

Diagnostic criteria

The 'Diagnostic criteria 2002 of autoimmune pancreatitis' (see Table 1) – as introduced in 2002 by the Japan Pancreas Society (JPS) – were revised in 2006 by Okazaki. IgG4 was added into this list of criteria. The extent of affected pancreas tissue was not mentioned

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Table 1. — **Different diagnostic criteria for AIP (10-19)**

criteria	JPS	revised JPS	Kim	HISORt	Italian
I. imaging	diffuse narrowing of the main pancreatic duct with an irregular wall (more than 1/3 the length of the entire pancreas) and enlargement of the pancreas	pancreatic imaging studies show narrowing of the main pancreatic duct and enlargement of the pancreas	**I. CT** : diffuse enlargement (swelling) of pancreas or **II. ERCP** : diffuse or segmental irregular narrowing of main pancreatic duct	**I. TYPICAL** : CT/MRI : diffusely enlarged gland with delayed (rim) enhancement or ERCP : diffusely irregular, attenuated main pancreatic duct ; **II. ATYPICAL** : pancreatitis, focal pancreatic mass, focal pancreatic duct stricture, pancreatic atrophy or calcification	
II. laboratory	abnormally elevated levels of serum gammaglobulin or the presence of auto-antibodies	elevated levels of serum gammaglobulin or IgG4 OR presence of auto-antibodies	**I.** elevated levels of IgG or IgG4 or **II.** auto-antibodies detected	elevated serum IgG4	
III. histopathology	marked lymphoplasmacytic infiltration and dense fibrosis	fibrosis and pronounced infiltration of cells, mainly lymphocytes and plasmacytes	fibrosis and lymphoplasmacytic infiltration	**I. DIAGNOSTIC** : lymphoplasmacytic sclerosing pancreatitis or abundant IgG4-positive cells in the pancreas ; **II. SUPPORTIVE** : abundant IgG4-positive cells in the extrapancreatic organ involved or lymphoplasmacytic infiltrate with fibrosis in the pancreas	dense lymphocyte infiltration and destruction of the exocrine glands, "destructive pancreatitis" on histology, or rich inflammatory cells on cytology
IV. response to steroid therapy			YES	resolution/marked improvement of pancreatic/extrapancreatic manifestation with steroid therapy	YES
V. association with …		malignant diseases have to be *excluded*		other organ involvement : hilar/intrahepatic biliary strictures, persistent distal biliary strictures, parotid/lacrimal gland involvement, mediastinal lymphadenopathy, retroperitoneal fibrosis	other postulated autoimmune diseases (such as ulcerative colitis, Crohn's disease, sclerosing cholangitis, primary biliary cirrhosis, Sjögren's syndrome)
DIAGNOSIS	criterion I together with II and/or III	criterion I together with II and/or III	criterion I together with any of II - IV	Three diagnostic groups : **A.** suggestive histology or positive IgG4-immunostaining ; **B.** typical imaging features and elevated serum IgG4 ; **C.** pancreatic disease with serology or other organ involvement and response to a steroid	histology as gold standard

anymore. Worldwide different diagnostic criteria are used and this generates confusion amongst most clinicians. In Table 1, a summary of the JPS criteria as mentioned above, the Kim criteria of the Asan Medical Center of Korea, the HISORt criteria from the Mayo Clinic and finally the Italian criteria shows the main differences. Several groups all over the world made different classification criteria which emphasized the role of CT, ERCP and IgG4 and contained a specification of some elements of the Diagnostic JPS criteria (10-19). In the further refinement of these criteria, there were suggestions about the addition of the criteria 'response to steroid therapy', 'IgG4 immunostaining of biopsied extrapancreatic lesions', 'focal pancreatic lesions' and 'association with other autoimmune diseases'. The incorporation of additional features into the current diagnostic criteria can offer an integrated approach to this disease. It creates the possibility to identify the full spectrum of clinical presentations of AIP and the extrapancreatic manifestations of IgG4-related sclerosing disease. Nevertheless, avoiding unnecessary surgery and misdiagnosis (when a pancreatic carcinoma could be present) and early starting of adequate corticosteroid therapy is only possible when an accurate diagnosis of AIP had been made. The combination of the Japanese and Korean criteria led to the recent consensus about the Asian diagnostic criteria (14,17,20).

Epidemiology

AIP is present in two to six percent of the group of chronic pancreatitis (5). Elderly (85% being older than 50 years) are more frequently affected, with a male/female-ratio of 4 to 1 (9). Some authors believe that the known cases nowadays are just 'the tip of the iceberg'. The use of different criteria makes it difficult to determine the exact incidence and prevalence of this disease (10,11). In this view, it is important to create unified criteria which will allow us to improve further understanding of this interesting disease and optimize diagnostic and therapeutic strategies. The main part of cases as described in the literature are of non-Western and more specifically Japanese and South Korean origin (2,3,10,21-23). Exact reasons why Asian people are more frequently affected are not known, most probably it will be a combination of genetic and environmental factors.

Pathophysiology

Not only a humoral immunity, but also a cellular immune response with CD4 and CD8-positive T-lymphocytes and IgG4-positive plasma cells seems to have a central function in the pathophysiology of AIP (15). After an initiation of the pathologic process, there is a phase of progression in which regulatory T cells have an important role (24). In 2001, Hamano stressed the importance of an elevated level of immunoglobulin IgG4 in patients with AIP (4,25). In 2005, it was obvious for Aoki *et al.* that IgG4 had a central role in the pathophysiology of AIP. Secondly, the presence of autoimmunity with antibodies to candidate target antigens such as lactoferrin (especially found in acinary pancreatic cells) and carbonic anhydrase II (CA-II, especially in ductal pancreatic cells) is contributive for the pathogenesis (4,21). Moreover, the similarity of the histopathological findings of AIP and the associated extrapancreatic lesions show that they are possibly related to an autoimmune phenomenon induced by an at this moment unknown autoantigen as a trigger in genetically predisposed patients and having the same (IgG4-related) fibroinflammatory process as a consequence (4,24,26,27). The presence of lactoferrin and CA II in several exocrine organs (such as the salivary glands, biliary tract and renal tubules) is concordant with the wide organ spreading of IgG4-SD (24).

Clinical presentation

A summary of several characteristics of AIP is made in Table 2 (21,28). The clinical presentation can be variable and depends on the stage. A mild, acute recurrent pancreatitis with abdominal pain, anorexia and weight loss is possible, also jaundice due to biliary stricture or even a pancreatic mass. Painless obstructive jaundice can mimick a pancreatic cancer and is the most frequent clinical presentation (9). Extrapancreatic manifestations such as sialadenitis, thyroiditis, sclerosing cholangitis, interstitial nephritis, RF and probably many others are also possible (see the theory of AIP as a pancreatic manifestation of an underlying autoimmune disease). Sclerosing fibrosis of the retroperitoneal and mediastinal space had been the subject of medical speculation for many decades (29). Bartholomew *et al.* and Comings *et al.* used 'multifocal fibrosclerosis' to describe the fibrosing processes that also could affect the retroperitoneal area (30). Table 3 shows the spectrum of the fibroproliferative disease with several manifestations : from the – for example – localised peri-aortitis to the systemic multifocal fibrosclerosis (31-33).

In one study, up to sixty percent of the patients with AIP had diabetes mellitus (DM) as being the most frequent complication of this disease, in which the clinical course improved in most cases when steroid therapy was started (20,34). In contrast to primary sclerosing cholangitis, the biliary strictures in AIP respond to steroid therapy (35).

Laboratory findings

Autoimmune factors such as ANA, anti-lactoferrin, anti-CA-II, rheumatoid factor and others can be present, also hypergammaglobulinemia and an elevated serum level of IgG4 are frequent. The exact role of an elevated IgG4 higher than a certain cut off level in differentiating AIP from pancreatic carcinoma has to be determined yet. Hamano *et al.* showed that a level of 135 mg/dL and higher for AIP could make the differentiation with pancreatic cancer with a sensitivity of 95 percent and a specificity of 97 percent (3,10,36). However, Ghazale *et al.* reported a sensitivity of 76% with a specificity of

Table 2. — **Characteristic findings of AIP : (21)**

- Increased levels of serum gammaglobulin or IgG
- Presence of auto-antibodies
- Diffuse enlargement of the pancreas
- Diffusely irregular narrowing of the main pancreatic duct on ERCP images
- Fibrotic changes with lymphocyte infiltration
- No symptoms or only mild symptoms, usually without acute attacks of pancreatitis
- Rare pancreatic calcification or pancreatic cysts
- Occasional association with other autoimmune diseases
- Effective steroid therapy
- Association with diabetes mellitus often improved by steroid therapy

Table 3. — **Former classification of inflammatory fibrotic disease (31,32)**

(a) localised
- ➢ peri-aortitis (including retroperitoneal fibrosis)
- ➢ orbital pseudotumor
- ➢ Riedel's thyroiditis
- ➢ sclerosing cholangitis
- ➢ pachymeningitis
- ➢ sclerosing sialadenitis

(b) systemic : multifocal fibrosclerosis (MFS)

93% for a IgG4 level of more than 140 mg/dL in making the diagnosis of AIP (37). According to a meta-analysis of Morselli-Labate *et al.*, the determination of IgG4 should be included in the diagnostic workup of AIP. The diagnostic value of IgG4 is high, despite the presence of heterogeneity of the studies in this meta-analysis (38). First, control persons had been selected heterogeneously. As mentioned earlier, also the different diagnostic criteria were used for the patient groups. Third, IgG4 was measured in different ways (nephelometric assay and radial immunoassay). Finally, only in 76% of the cases in which histology was available, it was compatible with the histopathologic criteria for AIP.

Medical imaging

Abdominal ultrasonography can show a diffusely hypoechogenic pancreas or sausage-like appearance. A capsule-like rim enveloping the pancreas can be observed with CT (3). Either a diffuse involvement of the pancreas or focal pancreatic lesions are possible, with the latter being indiscernible form a pancreatic carcinoma (5,39). On endoscopic retrograde cholangiopancreaticography (ERCP) narrowing of the pancreatic duct can be observed. Positron emission tomography visualizes the hot spots with avidity for fluoro-deoxyglucose and can be contributive not only to the diagnosis of AIP (determination of the extension of the disease with possible extrapancreatic lesions such as RF), but also to make an evaluation of the activity and show the response to therapy (likelihood of success from immunosuppression) with evaluation of the residual inflammation (40,41).

Histopathology

Biospy of the pancreas is preferably performed with echo-endoscopy and can confirm the diagnosis of AIP or exclude an underlying malignancy (42).

Histopathologically a lymphoplasmacytic infiltrate with a periductal collar and an obliterative lymphocytic phlebitis can be seen. The presence of a secondary fibrosis is possible. These microscopic characteristics are not specific, since they also can be present in chronic ethylic pancreatitis. At this point, immunohistochemical staining procedures for IgG4 are very valuable. Several subtypes are being recognized. Based on a model by Yadav *et al.* (2), a differentiation between ductocentric AIP and lobulocentric AIP is made for further classification. Nowadays, there is growing evidence about the existence of two distinct clinicopathologic patterns, in which type I is the classical AIP as described in Japanese literature as being the pancreatic manifestation of the IgG4-SD. Type II, a relatively new entity, has to be refined but the histology is characterized by dense neutrophilic infiltrates with microabscesses and very few infiltration with IgG4 positive plasma cells (24).

Therapy

In most cases, a spectacular clinicobiochemical response with a decrease and even a normalisation of IgG4 and auto-antibodies can be achieved with corticosteroids as the treatment of choice (a dose of 1 mg prednisolone/kg to start). In this view, the level of IgG4 could reflect the activity of the disease and be used as a parameter of relapse (3,24,43). In a recent prospective survey, the proposal for an initial dose of 0.6 mg prednisolone/kg/day was made (44). When effectiveness of this steroid therapy can be proven, a reduction scheme can be introduced (tapering the dose with 5 mg every 1-2 weeks up to 15 mg/day). After this, the dose can be tapered more gradually in the following 3 to 6 months and a maintenance therapy (5 mg/day) for at least 6 months is recommended to prevent relapse (44). It is important to realise that corticosteroids can induce a temporary clinical amelioration in an initial stage of pancreatic malignancy. In a prospective outcome study of Moon *et al.* it is shown that a 2-week steroid trial after an initial negative investigation for malignancy could differentiate AIP from pancreatic cancer (45). The exact role of other immunosuppressive agents such as azathioprine (especially for maintenance therapy) has to be determined yet (5,24). A surgical intervention is only necessary in a minority and can be mandatory when there is a persisting doubt about a possible underlying malignancy. When a biliary stenosis does not decrease after initiating a therapy with steroids, one should take the placement of a biliary prothesis into consideration.

Evolution – prognosis

In up to 25-40 percent of the cases, a recidive is present with a risk for the development of pancreatic lithiasis and – more rare – also an evolution to exocrine or

endocrine pancreatic insufficiency is possible (3,7,20, 24). Recently, a steroid therapy up to 1 year is recommended (6 months induction therapy with reduction to a maintenance therapy of 5 mg prednisolone/day for a period of 6 months). If a complete remission is present after one year, the maintenance therapy can be stopped (44). It is unknown which factor could determine or even predict the occurrence of a recurrence and what the exact long term prognosis of AIP is because most case series do not report long-term follow-up data (20,21). In the subgroup of patients with IgG4-related sclerosing cholangitis, the presence of proximal strictures predisposed to having a relapse. Hence, in this group, a longer treatment regimen can be mandatory (35). It is not certain whether AIP holds a risk for the development of a pancreatic carcinoma, but at this moment no case control studies are available (25). It seems that the subgroup of patients who develops obstructive jaundice, has more advantages of an early start of corticoid treatment. Moreover, in this subgroup this early treatment could have a protective role for the further evolution to sclerosing cholangitis and avoiding the necessity to place a biliary stent (35,43,46-48). If the placement of a biliary stent is necessary, a quicker resolution of the symptoms can be achieved. In this cases, the stent can be removed 2 to 4 weeks after the start of steroids (24).

B. *Extrapancreatic manifestations of IgG4-related sclerosing disease*

Introduction

The subdivision of the five main classes of antibodies dates of the 1960's, in which the numbering of the IgG subclasses accords to the time of discovery (49). In general, the level of IgG4 can be elevated in allergy, atopic dermatitis and astma bronchiale, but also in parasitic infections or pemhigus vulgaris, pemphigus foliaceus and pemphigoid disease (3). Despite this well-known associations, the IgG4 antibodies remain to be a more mysterious subgroup with poorly defined characteristics (49). IgG4 is the least abundant IgG-isotype (3 to 6 percent). It has bispecifical, but functional monovalent properties as it behaves as having a single antigen-binding site (2,49-51). IgG4 production is regulated by Th2 cells and indicates that anti-inflammatory, tolerance-inducing mechanisms have been activated. Moreover, IgG4 seems to appear after a prolonged immunization (49). IgG4 cannot activate the classic complement pathway since it cannot bind with complement C1q (28,52). Although IgG4 could play a role in immune complex mediated reactions, there are no typical clinical manifestions of immune complex-disease such as arthritis or glomerulonephritis (28).

IgG4-related sclerosing disease : 'tip of the iceberg' ?

The new clinicopathologic entity of IgG4-related sclerosing disease (IgG4-SD, see Figure 1) as suggested by Kamisawa *et al.* in 2003, has received growing attention in recent years. Levels of serum IgG4 and immunohistopathology with anti-IgG4 antibodies can be used in making the diagnosis. It is not sure what the exact pathophysiologic role of IgG4 is in this disease entity (a secondary response to an unknown primary trigger ?). IgG4 does not seem to be just an innocent bystander (49).

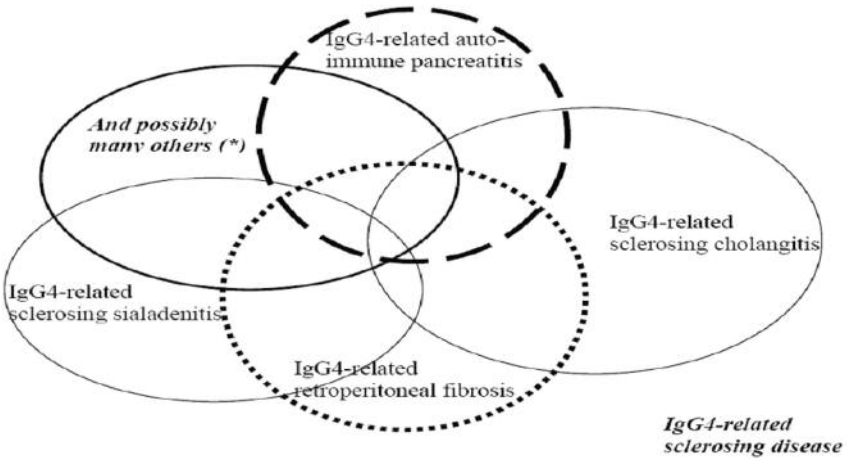
Heterogenous disease localisation : autoimmune pancreatitis and extrapancreatic manifestations

AIP is not only a kind of pancreatitis, but a pancreatic lesion of the IgG4-related systemic disease with several possible extrapancreatic manifestations (4,22,53-55). As IgG4-positivity is not only found in the pancreas, but also at the level of the extrahepatic biliary ducts, gallbladder, lungs, salivary and lacrimal glands, breasts, retroperitoneal tissue and aorta, ureters, prostate, meninges and lymph glands, much attention raised for a possible hyper-IgG4 disease (50,54,56-61). There is growing evidence that IgG4-SD could be the link between a subgroup of autoimmune hepatitis and sclerosing cholangitis (the latter being different from the primary sclerosing cholangitis) and in this way being an explanation for one of the overlap syndromes in hepatology (34,62-67). Pulmonary involvement with IgG4-related interstitial lung disease and inflammatory pseudotumor or plasma cell granuloma have been described (68-70). There is a possible correlation with IBD : IgG4-related colitis is seen as another possible entity in the spectrum of IgG4-SD (71). Recently, there was a report about a possible IgG4-related sclerosing pachymeningitis (72). Within the group of retroperitoneal fibrosis and aortitis, IgG4-related aortitis seems to be an interesting subgroup in inflammatory abdominal aortic aneurysm (73).

With specific interest to renal involvement, there are 3 patterns of renal involvement in IgG4-SD : first, extraparenchymal involvement with hydrouretero-nephrosis, second diffuse and third, focal tubulointerstitial nephritis (74,75). The latter are characterized by dense lymphoplasmacytic infiltration of the renal interstitium, often with interstitial fibrosis and tubular atrophy (74-78). Only rarely, IgG4-related glomerulonephritis has been reported but membranous nephropathy can be one of the renal features of IgG4-SD (79,80). Macroscopically, the renal lesions can be wedge-shaped or nodular and in the latter, they can mimick metastatic tumours (39,51,78,81-83). The lesions are often multiple and at the level of the renal cortex (81). Especially in an early stage there seems to be little effect on renal function and renal insufficiency is not always present (51,81). The renal involvement is more common than presumed : in a study of Takahashi *et al.* up to 35% of the patients have parenchymal or extraparenchymal involvement (51,53,78,81).

Unclear pathogenesis

IgG4 is the most likely pathophysiologic key between AIP and all possible extrapancreatic manifestations (25). Except for the role of IgG4 earlier mentioned, the precise



(*) These are :

Liver	IgG4-related autoimmune hepatitis
Gallbladder	IgG4-related sclerosing cholecystitis
GIT	IgG4-related IBD
Salivary gland	IgG4-related sclerosing sialadenitis *(Kuttner's tumor or chronic sclerosing sialadenitis: submandibular > other salivary glands / Mikulicz disease or IgG4-related plasmacytic exocrinopathy: salivary and lacrimal glands)*
Lymph glands	IgG4-related lymphadenopathy
Eyes	Orbital pseudotumor
Lacrimal glands	IgG4-related ocular adnexal disease
Thyroid gland	Riedel's thyroiditis, IgG4-related thyroiditis
Breast	IgG4-related mastitis
Aorta	IgG4-related aortitis (see retroperitoneal fibrosis)
Kidney	IgG4-related tubulointerstitial nephritis
Lung	IgG4-related interstitial pneumonia, inflammatory pseudotumor (plasma cell granuloma)
Prostate	IgG4-related prostatitis
CNS	IgG4-related pachymeningitis

Fig. 1. — IgG4-related sclerosing disease with several manifestations and some overlap with other disease entities (RF, AIP)

pathogenesis and pathophysiology of IgG4-SD remains a mystery.

Conclusion

We discussed IgG4-related sclerosing disease with specific interest for autoimmune pancreatitis and show the possibility of an 'overlap syndrome' with several possible localisations. IgG4 may be one answer to a lot of questions about this entity and seems to play an important pathophysiologic role. Moreover, it may be a clue for several overlap syndromes in medicine. In further optimizing diagnostic and therapeutic strategies, it is important to come to international consensus about diagnostic criteria (especially concerning autoimmune pancreatitis).

It remains a mystery what the exact role of IgG4 is. The data collected all over the world could improve understanding, diagnosing and treating this interesting systemic disease. At this point, it is very likely that further research will outline the importance of IgG4-related overlap diseases and will lead to the development of new treatment strategies for this disease entity that is more frequently recognized in recent years.

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