

Autoimmune Pancreatitis: A Systemic Immune Complex Mediated Disease

Vikram Deshpande, MD,* Sonia Chicano, MD,* Dmitry Finkelberg, MD,† Martin K. Selig, BA,*
Mari Mino-Kenudson, MD,* William R. Brugge, MD,† Robert B. Colvin, MD,*
and Gregory Y. Lauwers, MD*

Abstract: Autoimmune pancreatitis (AIP) is a mass forming inflammatory pancreatobiliary-centric disease. Recent reports of multiorgan inflammatory mass forming lesions with increased numbers of IgG4 positive plasma cells suggest that AIP may have a systemic component. In this study, we explore the systemic nature of AIP, investigate the relevance of subtyping AIP, perform a systematic study of tissue IgG4 immunoperoxidase, and ultrastructurally evaluate the presence of immune complexes. Our study group consisted of 36 patients with AIP, 21 of whom underwent a Whipple procedure. On the basis of the pattern of inflammation, pancreatic involvement was subtyped as ductocentric (AIP-D) or lobulocentric (AIP-L). Extrapaneatonic lesions included bile duct (n = 3), salivary glands (n = 3), lung (n = 2), gallbladder (n = 11), and kidney (n = 4). Clinical and radiologic data was recorded. Immunohistochemistry for IgG4 was performed on both pancreatic and extrapancreatic tissues and the numbers of IgG4 positive plasma cells were semiquantitatively scored. A control cohort composed of pancreatic adenocarcinoma (n = 19) and chronic pancreatitis-not otherwise specified (NOS) (n = 14) was also evaluated. Eleven pancreatic specimens, including 2 cases of chronic pancreatitis-NOS and 4 kidneys were evaluated ultrastructurally. The pancreas, bile duct, gall bladder, salivary gland, kidney, and lung lesions were characterized by dense lymphoplasmacytic infiltrates with reactive fibroblasts and venulitis. IgG4 positive plasma cells were identified in all pancreatic and extrapancreatic lesions. The AIP cases showed significantly more pancreatic IgG4 positive plasma cells than chronic pancreatitis-NOS or adenocarcinoma ($P = 0.001$). However, IgG4 positive cells were identified in 57.1% of chronic pancreatitis-NOS and 47.4% of ductal adenocarcinoma. Fifteen of 21 resected cases were classified as AIP-D, and 6 as AIP-L, the latter notably showing significantly more IgG4 positive plasma cells than the former ($P = 0.02$). Additionally, clinical and radiologic differences emerged between the 2 groups. Ultrastructurally, electron dense deposits of immune complexes were identified in the basement membranes of 7 of the 9 AIP

cases and in 3 of the 4 renal biopsies evaluated. AIP represents the pancreatic manifestation of a systemic autoimmune disease. Clinical and immunologic findings justify the recognition of pancreatic lobulocentric and ductocentric subtypes. Documentation of increased numbers of tissue IgG4 positive plasma cells, although not an entirely specific marker for AIP, may provide ancillary evidence for the diagnosis of a IgG4-related systemic disease.

Key Words: autoimmune pancreatitis, pancreatitis, IgG4, ultrastructure

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Autoimmune pancreatitis (AIP) is a chronic, mass forming, inflammatory process, which was first recognized by Sarles²¹ in 1961, but received little attention until the 1990s.^{14,16,19} It has been since extensively studied and recognized worldwide as the etiology of a “mass” lesion, usually mimicking pancreatic adenocarcinoma. The ensuing surgical resections has allowed for the histologic evaluation of large series of specimens, resulting in a better recognition of the characteristic morphologic features of this disease.^{20,28–30}

Elevation of serum IgG4 has been reported as a preoperative tool to distinguish AIP from pancreatic carcinoma.¹⁰ Unfortunately, limited data is available in Western centers and thus the significance of IgG4 outside Japan is unknown. Significantly, increased numbers of IgG4 positive plasma cells have been documented not only within the pancreatobiliary system but in other organs as well.^{4,23,24,26,31,32} Consequently, several authors have alluded to the possibility of a systemic IgG4 disease.^{13,32} Naturally, these reports raise the enticing possibility that an IgG4 tissue immunoperoxidase stain could be used as adjunctive evidence of AIP. Nevertheless, a systematic study of tissue immunohistochemical staining for IgG4 has not previously been performed.

In the current study, our aim was to analyze a large series of AIP and to explore the clinicopathologic features of the disease, specifically with regards to its systemic distribution. Furthermore, to investigate the pathogenesis of this condition we ultrastructurally evaluated a subset of pancreatic and renal biopsies. We also evaluated the value of tissue IgG4 immunohistochemistry as a potential

From the Departments of *Pathology, and †Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA.

Reprints: Gregory Y. Lauwers, MD, Gastrointestinal Pathology Service, Department of Pathology (WRN 2), Massachusetts General Hospital, 55 Fruit St, Boston, MA 02114 (e-mail: glauwers@partners.org).

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marker of AIP, and corroborate the specificity of IgG4 at the tissue level.

MATERIALS AND METHODS

Case Selection

Fifty-eight cases of AIP were identified in the files of the Massachusetts General Hospital. Paraffin-embedded tissue blocks from 36 patients formed the core of this study. Paraffin-embedded tissue was not available on the remaining 22 cases. The hospital database was queried for prior and subsequent histopathologic material, clinical reports and imaging studies, operative notes, serological investigations, and follow-up information. Among those we identified 21 patients on whom a pancreatoduodenectomy was performed. The other 15 cases were treated conservatively. The diagnosis of AIP was based on accepted histologic criteria.^{15,28-31} The cardinal features of AIP include a dense lymphoplasmacytic infiltrate of the glandular parenchyma with secondary fibrosis. More precisely, AIP is characterized by the presence of a periductal collar of lymphoplasmacytic inflammation (around both small and large ducts) and lymphocytic phlebitis. Notably, ductal involvement is frequently patchy.

Of the remaining cases, a pancreatic biopsy was available in 7, whereas in 8 cases no pancreatic tissue was available for evaluation. The diagnosis of these cases was based on clinical and radiologic features as well as response to steroid therapy or benign follow-up. In addition, bile duct resections were available for review in 3 patients and cholecystectomy specimens in 11 patients. A review of the clinicopathologic database also revealed resections/biopsies of pulmonary inflammatory mass lesions, and salivary gland lesions in 2 and 3 patients, respectively. Kidney biopsies had also been performed in 4 patients. Sixteen patients from this cohort were initially evaluated with a pancreatic EUS-guided fine needle aspiration biopsy and these formed the basis of a prior report.⁹

Histopathologic Evaluation

Routinely processed and sectioned hematoxylin and eosin slides were available for all 21 pancreatotomy specimens. The pancreatic inflammatory pattern allowed for the subtyping into ductocentric (AIP-D) (Fig. 1) and lobulocentric (AIP-L) (Fig. 2) categories. The former was defined as a fibroinflammatory process confined predominantly to the periductal region with or without pancreatic lobular involvement. The latter showed an almost exclusively lobular involvement by a dense infiltrate of lymphocytes and plasma cells although periductal inflammation was either absent or very limited.

The presence and the distribution of parenchymal neutrophils were documented. Finally, the presence of lobular and interlobular fibroblastic proliferation was evaluated and semiquantitatively graded as 1+ when scant (occupying less than 40 × field) proliferative foci were seen. Pseudotumor formation was categorized as

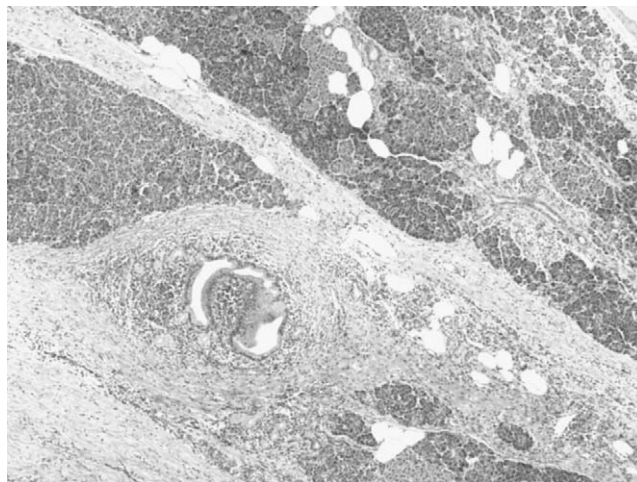


FIGURE 1. AIP-ductal type. Ductocentric inflammation with relative sparing of the pancreatic lobules.

3+, whereas intermediary cases were graded as 2+. Pseudotumors were defined as diffuse proliferations of fibroblast, lymphocytes, and plasma cells, with obliteration of the pancreatic parenchymal architecture.

Immunohistochemistry for IgG4

Immunohistochemistry for IgG4 (Zymed, Carlsbad, CA; dilution 1:50) using the avidin-biotin immunoperoxidase method was performed on 18 pancreatotomy specimens. The IgG4 positive plasma cells were semiquantitatively scored per 20 × field as 0 = 0; 1 = < 10; 2 = 11-30; 3 = 31-50; 4 = > 50. The area with the highest IgG4 score was recorded. To evaluate the specificity and sensitivity of IgG4 immunohistochemistry a control cohort of chronic pancreatitis-not otherwise specified (CP-NOS) and pancreatic ductal adenocarcinoma were also immunostained. The former were consecutive



FIGURE 2. AIP-lobular type. Predominantly pancreatic lobular involvement with relative sparing of ducts.

pancreatoduodenectomy specimens (n = 14) operated between 2001 and 2004 that lacked clinical/radiologic and histologic features of AIP and showed at least focal lymphoplasmacytic infiltrates. The latter consisted of 19 consecutive cases of ductal adenocarcinoma of the pancreas. However, only cases with a moderate to dense intratumoral or peritumoral inflammatory infiltrate were included.

In situ hybridization for Epstein-Barr virus RNA was performed on both lung biopsies to evaluate the possibility of lymphomatoid granulomatosis.

Electron Microscopy

Ultrastructural evaluation was performed on 9 cases of AIP, 2 cases of chronic pancreatitis, and all 4 renal biopsies. Briefly, representative areas were removed from the paraffin block. Paraffin was extracted by an overnight soak in xylene and successive, decreasing (100%, 95%, 70%, 50%, and 25%) ethanol treatments followed by a buffer wash and glutaraldehyde (2.5% glutaraldehyde, 2.0% paraformaldehyde, 0.025% CaCl₂ in a 1.0 M sodium cacodylate buffer, pH 7.4) fixation step. From this point, tissues retrieved from paraffin and freshly fixed tissue samples were treated identically. Briefly, after fixation, tissues were dehydrated in a graded ethanol series, infiltrated with propylene oxide epoxy mixtures, and embedded in pure epoxy resin. Thin sections were cut, stained, and examined in a Philips 301 (Eindhoven, The Netherlands) and imaged with an AMT (Advanced Microscopy Techniques, Danvers, Massachusetts) digital CCD camera.

RESULTS

Demographic Data

There were 26 males and 10 females with a mean age of 55 years (range 17 to 80 y).

Presenting symptoms included obstructive jaundice (n = 20, 55.5%), abdominal pain (n = 17, 47.2%), weight loss (n = 20, 55.5%), and nausea and vomiting (n = 7, 19.4%).

Radiologic Features

Computerized tomographic (CT) and EUS findings were available in 27 and 22 cases, respectively. Radiologically both focal (EUS n = 9 and CT n = 8) and diffuse pancreatic enlargement (EUS n = 10 and CT n = 13) was identified. Lesions identified on endoscopic retrograde pancreatocolangiography included diffuse narrowing of the main pancreatic duct (n = 10), focal strictures (n = 7), strictures of the distal common bile duct (n = 16), and dilatation of main pancreatic duct (n = 1).

Clinical Features-AIP-L versus AIP-D (Table 1)

Fifteen cases were classified as AIP-D and 6 as AIP-L. The clinical, radiologic, histologic, and immunologic findings of these subtypes are compared in Table 1.

Extrapancreatic Manifestations of AIP "Syndrome"

We defined systemic manifestations as involvement of the bile duct, kidney, salivary gland lung, and inflammatory bowel disease. Fourteen cases (38.9%) showed at least one of these systemic manifestations.

Associated Immune-mediated/allied Diseases

Various associated conditions within this cohort of patients included diabetes (n = 10), and rheumatoid arthritis (n = 2). Additionally one case each of amyotrophic lateral sclerosis and bullous pemphigoid was identified.

TABLE 1. Clinicopathologic Features: AIP-D versus AIP-L

	AIP-D (n = 15)	AIP-L (n = 6)	P*
Mean age	52	50	NS
M:F	8:7	6:0	0.04
Obstructive jaundice	4 (26.7)	4 (66.7%)	NS
Ulcerative colitis	4	1	NS
Other autoimmune diseases	Rheumatoid arthritis (2)	Sjögren (3) Bullous Pemphigoid (1)	NS
CT*			
Focal enlargement	5/12 (41.7%)	0	NS
Diffuse enlargement	4/12 (33.3%)	3/4 (75%)	NS
Granulocytic epithelial lesions	12 (80%)	1 (16.7%)	0.006
Lobular neutrophilic infiltrate	5 (33.3%)	1 (16.7%)	NS
Fibroblastic proliferation†			
1+	4 (26.7%)	4 (66.7%)	0.002
3+	0	2 (33.3%)	
Ductocentric granulomas	5 (33%)	1 (16.6%)	NS
Tissue IgG4 in pancreas‡ > 50/20 × field	1/13 (7.7%)	5/5 (100%)	0.0001
Immune deposits in pancreas basement membranes	3/5 (60%)	4/4 (100%)	NS

*CT findings were available in 16 cases.

†Fisher exact test.

‡Immunohistochemistry performed in 18 cases.

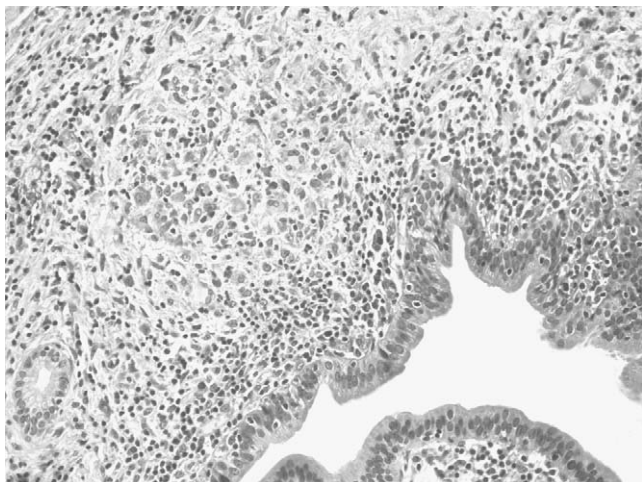


FIGURE 3. AIP with ductocentric granulomas.

Histopathology

Pancreatectomy Specimens

Grossly the glands were firm to rock hard without a dominant mass. All cases showed a diffuse lymphoplasmacytic infiltrate and at least focal periductal lymphocytic cuffing and obliterative venulitis. The ductal involvement was patchy. Two cases had significantly less inflammation and instead were characterized by periductal edema.

By definition the AIP-L cases had minimal periductal inflammation but significant lobular and septal inflammation. Two AIP-D cases were exclusively ductocentric without lobular inflammation whereas the other 13 cases had at least focal lobular inflammation. The morphologic differences between the 2 subtypes are tabulated in Table 1.

Neutrophilic infiltration of pancreatic ducts (granulocytic epithelial lesions) were identified in 13 cases (AIP-D:12, AIP-L:1) and notably in all 3 patients with ulcerative colitis. Neutrophils, either single or in clusters, were also identified in 6 cases within the lobules; however, only one of these patient had ulcerative colitis. Eosinophils were identified in 14 cases, with a marked infiltrate in 2 samples (> 15 eosinophils/high-power field).

Non necrotizing ductocentric epithelioid cell granulomas were present in 6 cases (Fig. 3). Granulomatous lymphadenitis was conspicuously absent.

An interlobular fibroblastic proliferation was seen in both groups. However, the AIP-L cases showed a significantly more prominent fibroblastic proliferation ($P = 0.002$) (Fig. 4). Both pancreatic pseudotumors observed in this series developed in the background of a predominantly lobular AIP. Ductal mucinous metaplasia (PanIN1) was noted focally in 7 cases and diffusely in another 7 cases. However, PanIN 2 and 3 were not seen.

Ultrastructural Evaluation

Ultrastructural evaluation showed electron dense immune deposits within periacinar pancreatic basement



FIGURE 4. AIP-associated pseudotumor. The pancreatic parenchyma is replaced by fibroblasts, lymphocytes, and plasma cells.

membranes in 7 of the 9 cases evaluated (Fig. 5). Both cases of chronic pancreatitis-NOS were negative for immune deposits.

IgG4 Immunohistochemistry

AIP cases showed significantly more IgG4 plasma cells than chronic pancreatitis-NOS and ductal adenocarcinoma (Figs. 6A–C). AIP cases showed at least greater than 5 plasma cell per $\times 20$, whereas 57.1% (8/14) of CP-NOS and 42.1% (8/19) of carcinoma

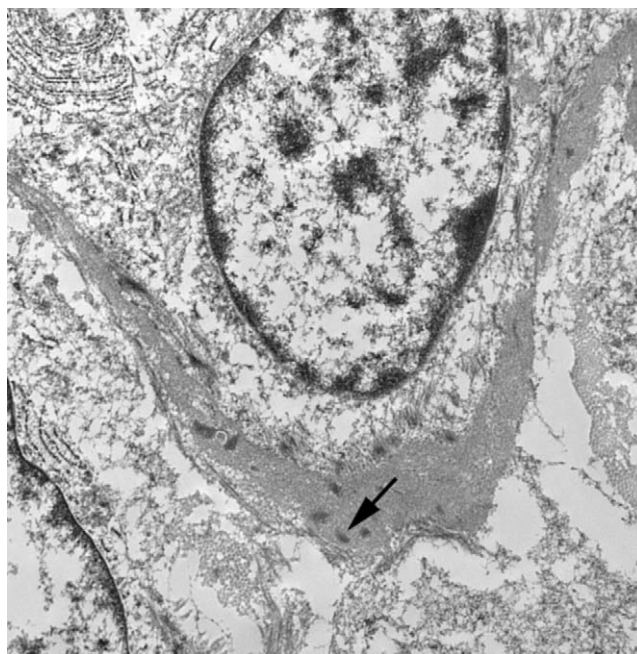


FIGURE 5. Electron dense deposits (arrow) within pancreatic basement membrane.

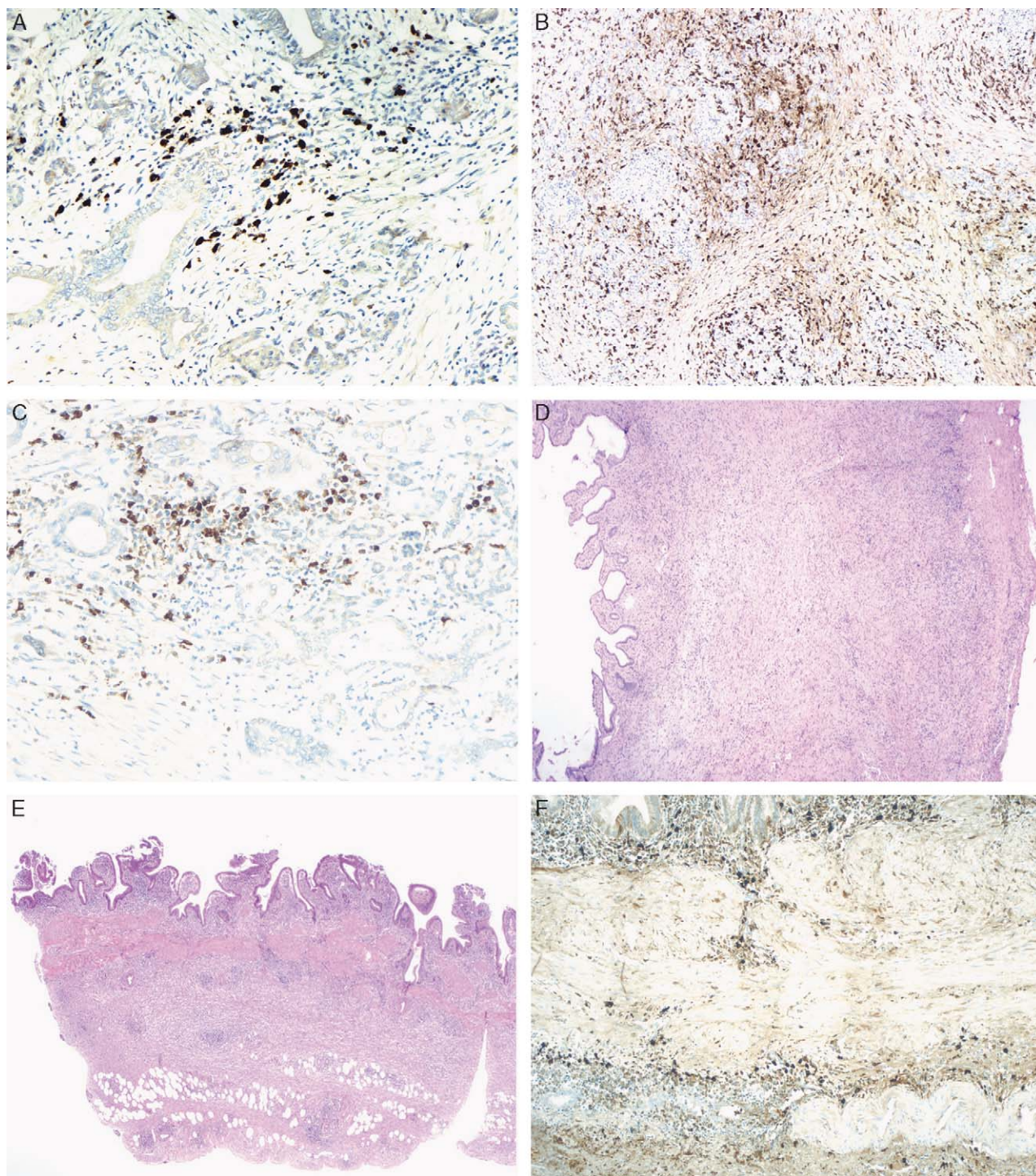


FIGURE 6. AIP-ductal type with periductal aggregates of IgG4 positive plasma cells (A). AIP-lobular type with large numbers of intralobular IgG4 positive plasma cells (B). Ductal adenocarcinoma of the pancreas with aggregates of IgG4 positive plasma cells (C). Extrahepatic bile duct with transmurular lymphoplasmacytic inflammation and fibrosis (D). AIP associated lymphoplasmacytic cholecystitis (E) with transmurular IgG4 positive plasma cells (F).

pancreas cases were entirely negative for IgG4 plasma cells (P 0.001) (Fig. 7).

All 5 (100%) of the AIP-L cases showed 4+ IgG4 plasma cells, compared with only 1 AIP-D cases (7.7%)

(Table 1). Predictably the IgG4 positive plasma cells were predominantly within the lobules in the AIP-L group, whereas among the AIP-D cases the immunoperoxidase stain highlighted periductal plasma cells.

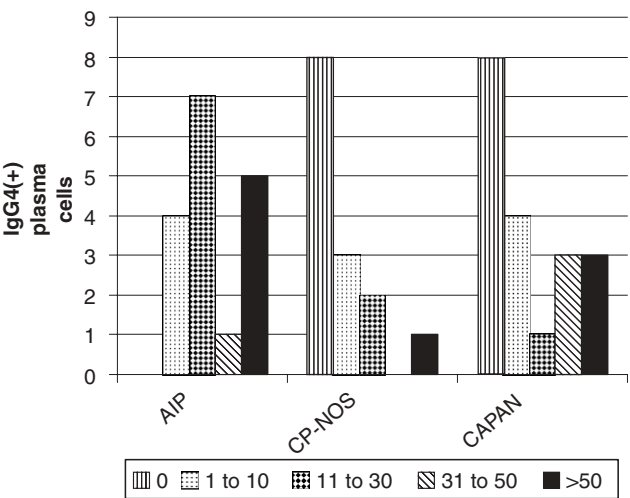


FIGURE 7. Semiquantitative analysis of IgG4 immunohistochemistry in AIP versus Chronic pancreatitis-NOS and carcinoma pancreas. CA PAN indicates carcinoma pancreas.

Extrapancreatic Manifestations

Biliary Lesions

Cholecystectomy specimens were available in 11 cases. Four were devoid of inflammation; and 3 cases displayed mild to moderate inflammation with predominantly periluminal lymphocytes and plasma cells. Four cases showed marked inflammation, thickening of the gall bladder wall, and a dense transmural inflammatory infiltrate accompanied by a diffuse fibroblastic proliferation, that is, lymphoplasmacytic sclerosing cholecystitis (Fig. 6E). Two of these gall bladders were associated with gallstones.

All 3 cases of lymphoplasmacytic cholecystitis evaluated showed diffuse and transmural IgG4 positive plasma cells, with greater than 50 cells per 20 × field (Fig. 8F). In the 3 cases with mild to moderate inflammation, 0 to 20 positive plasma cells were identified per 20 × field.

Segmental resection of the bile ducts was performed in 3 patients. The clinical and radiologic features were

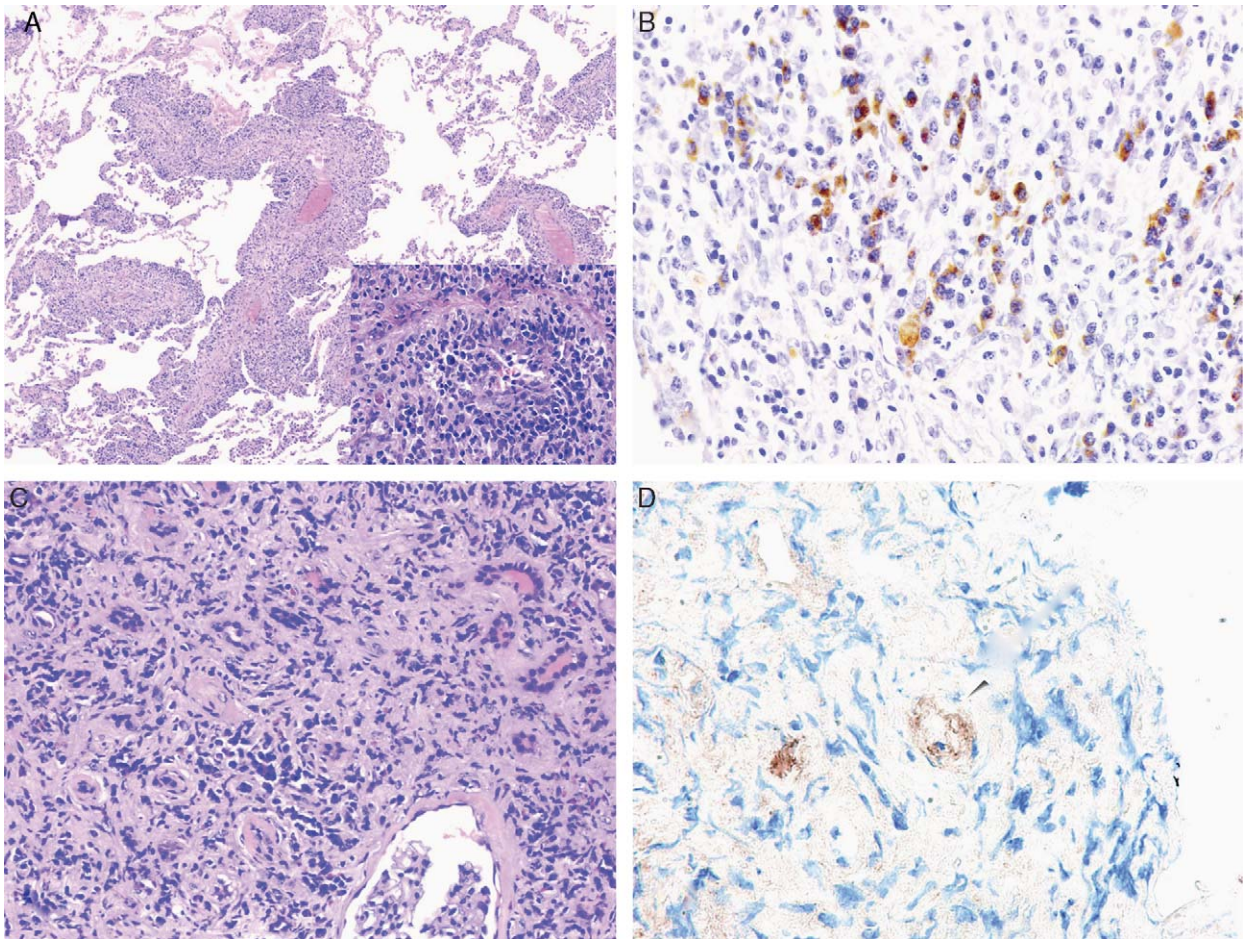


FIGURE 8. Pulmonary manifestation of AIP—interstitial lymphoplasmacytic inflammation with venulitis (A) and numerous IgG4 positive plasma cells (B). Renal manifestation of AIP. Aggressive interstitial lymphoplasmacytic nephritis with marked tubular atrophy (C). IgG4 deposits (arrow) within the tubular basement membrane (D).

TABLE 2. Pulmonary Lesion Associated With AIP

Age/sex	Presenting Symptoms	Radiology	Other Organs Involved	Endoscopic Retrograde Pancreaticholangiography Data	Response to Steroids	Outcome
72/M	Obstructive jaundice, cough	3 × 2 cm lingular mass with lymphangitic spread, enlarged mediastinal lymph nodes	Nephritis, sialadenitis, pancreatic pseudotumor	Diffuse narrowing of main pancreatic duct, narrowing of distal and right hepatic duct	Lung mass and pseudotumor responded to steroids	A&W
64/M	Obstructive jaundice	5 cm lung mass with interstitial septal thickening and ground glass opacities, consistent with local lymphangitic spread of tumor	Sialadenitis, remote history of nephritis, Lymphadenopathy	Long stricture of pancreatic duct	Lung mass and jaundice responded to steroids	A&W

A&W indicates alive and well.

suspicious for cholangiocarcinoma. One patient showed characteristic histologic features of AIP on a pancreatectomy specimen. A second showed clinical and EUS features of chronic pancreatitis. All cases showed full thickness infiltration of the wall by a moderate to dense infiltrate of lymphocytes and plasma cells associated with a fibroblastic proliferation (Fig. 6D). Venulitis was observed in all cases. IgG4 immunoperoxidase was performed on 2 cases, and showed 20-30 positive plasma cells per 20 × field.

Extragastrointestinal Lesions

Lung

The clinicopathologic profiles of the 2 patients with lung masses are shown in Table 2. On CT scan both showed mass lesions with septal thickening, suggestive of a lymphangitic tumor spread. Video-assisted thoracoscopic biopsies showed a dense interstitial lymphoplasmacytic infiltrate forming uniformly spaced tiny nodular aggregates and prominent obliterative phlebitis (Fig. 8A). Airway involvement was minor and there was no vascular or parenchymal necrosis. One case (case 1) also showed focal fibroblastic proliferation intermixed with lymphocytes and plasma cells reminiscent of a pseudotumor. On both biopsies lymphomatoid granulomatosis was the leading pathologic diagnosis. However, clonal rearrangements of the immunoglobulin heavy chain gene, light chain gene, and the β and γ T-cell receptor genes were absent. Additionally by in situ hybridization for Epstein-Barr virus encoded RNA was negative. Significant numbers of IgG4 positive plasma cells ($> 50/20 \times$) were identified in the sole case evaluated (case 1) (Fig. 8B).

Salivary Gland

The 3 submandibular salivary glands available for review showed a dense lobular lymphoplasmacytic infiltrate with focal periductal inflammation. Focal phlebitis and a diffuse fibroblastic proliferation were present in both cases. Numerous IgG4 positive plasma

cells (30-0 per 20 ×) were recognized in the sole case evaluated.

Kidney

Three renal biopsies were performed to investigate multiple low attenuation mass lesions detected on CT scan ($n = 2$) and 1 was performed to evaluate rising creatinine levels. A partial nephrectomy was performed on a mass forming lesion. All biopsies or specimens showed marked effacement of the parenchyma by an interstitial lymphoplasmacytic infiltrate, myofibroblastic/fibroblastic proliferation, and scattered eosinophils (Fig. 8C). The glomeruli were unremarkable on light microscopy. Two cases showed focal endotheliitis. Tubular basement membrane granular IgG deposits, predominantly of the IgG4 subclass, were detected in 3 of 4 cases by either immunofluorescence or immunohistochemistry. IgG4 positive plasma cells were noted on all 4 biopsies. Ultrastructural evaluation showed electron dense deposits within the tubular basement membranes in 3 of the 4 cases (Fig. 9) and an IgG4 stain confirmed the presence of deposits within the tubular basement membranes (Fig. 8D).

DISCUSSION

AIP is characterized by the simultaneous presence of a periductal collar of inflammation and phlebitis. Obliterative phlebitis is frequently recognized. We recognize AIP-D and AIP-L types of AIP. This classification is modeled on a prior classification proposed by Yadav et al.²⁹ However, our subtyping of AIP, focused primarily on the predominant site involvement (ductal vs. lobular) is likely to be biologically more relevant, given that the ducts and lobules display distinct antigenic profiles. In addition we document clinical, radiologic, immunologic, and histopathologic differences between these subtypes. The AIP-L patients were exclusively male, frequently presenting with obstructive jaundice and diffuse pancreatic enlargement. The AIP-D cases were more frequently

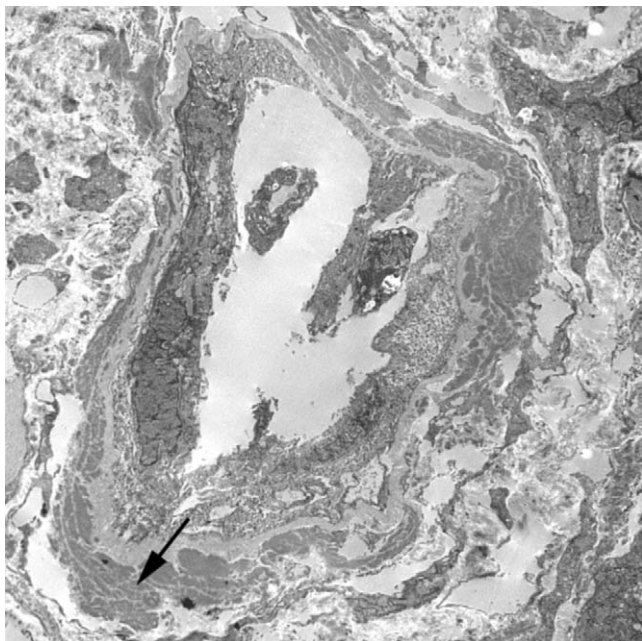


FIGURE 9. Massive deposition of electron dense deposits (arrow) within the renal tubular basement membrane.

associated with ulcerative colitis and showed granulocytic epithelial lesions, an association previously reported.³⁰ However, other than a distinct sex distribution, the other clinical and radiologic differences did not achieve statistical significance. Although the AIP-L cases demonstrate a significantly greater degree of fibroblastic proliferation, the AIP-D cohort showed ductocentric granulomas. We also demonstrated a higher number of IgG4 positive plasma cells in AIP-L compared with AIP-D.

There are similarities between this classification and the 2 animal models of AIP. One developed by the immunization of neonatally thymectomized mice with carbonic anhydrase (an antigen mainly located on duct pancreatic epithelium) and later the transfer of CD4⁺ lymphocytes results in a duct centric pattern of pancreatitis.²⁵ The second model involves the adoptive transfer of amylase-specific (an antigen mainly located in acinar cells) CD4(+) T cells, results in pancreatitis in naive syngeneic recipient animals.⁸ Notably, the histologic lesions of this model mimic the lobulocentric inflammatory reaction seen in the AIP-L subgroup. Of interest, a recent study showed that patients with elevated IgG4 were males and presented with cholestasislike in our AIP-L cohort.⁵ Conversely, cases with an elevated carbonic anhydrase demonstrated a clinical profile more akin to the AIP-D subgroup.

In contrast to the limited North American experience,⁶ Japanese authors report the elevation of serum IgG4 level is a reproducible marker of AIP.^{10,11} Furthermore, several reports have documented an increased numbers of tissue IgG4 positive plasma cell.^{4,31} We provide evidence that organ-based infiltration by IgG4

positive plasma cells is also of relevance in Western patients. However, overlaps between AIP, chronic pancreatitis and adenocarcinoma preclude the use of immunolabeling as a diagnostic tool, particularly when evaluating pancreatic biopsies. Nevertheless, on resection specimens, although the absence of IgG4 positive plasma cells would weigh against a diagnosis of AIP, the presence of large numbers of immunoreactive plasma cells would support this diagnosis.

IgG4 immunoperoxidase could also play a role in the evaluation of extrapancreatic lesions. Lymphoplasmacytic cholecystitis associated with AIP closely resembles cholecystitis associated with primary sclerosing cholangitis (PSC) and other forms of biliary obstruction.² Increased IgG4 positive cells could help distinguish AIP-associated lymphoplasmacytic sclerosing cholecystitis from PSC and similar appearing lesions caused by long standing biliary obstruction. However, this study did not directly compare AIP-associated cholecystitis with gall bladders associated with other forms of biliary obstruction. A definitive statement on the use of IgG4 on gall bladder resections will have to await the results of such a study. Our study also provides further evidence that there exists a small cohort of patients usually diagnosed as PSC, that may have overlapping features with AIP.^{22,31} Distinction of this entity from classic PSC is particularly important because AIP-associated biliary lesions are responsive to steroids, indicating that steroid responsive cases of PSC may belong to this subgroup.^{17,22} Another value of IgG4 immunolabeling of plasma cells is the appropriate diagnosis of pulmonary^{3,12,18,24,27} and renal^{7,23,26} manifestations of the disease which can simulate a lymphoproliferative disorder.

We identified electron dense immune deposits within the basement membranes of the pancreas and kidney. A tissue IgG4 stain confirmed the presence of IgG4 deposits within the renal tubular basement membranes. This novel observation provides further proof of both the systemic and the autoimmune nature of this disease.

IgG4, the least common of the 4 IgG isoforms, produces bispecific antibodies that in most situations behave as functionally monovalent antibodies. This unique bispecificity greatly decreases the pathologic potential and the antibodies' main function is to interfere with immune-mediated inflammation.¹ Thus, it seems likely that although large numbers of IgG4 plasma cells are one of the hallmarks of AIP, it may merely represent a secondary response to a yet unidentified primary trigger of this inflammatory process.

In conclusion, our experience suggests that AIP is a heterogeneous entity with 2 distinct patterns of pancreatic inflammatory damage. The previously unreported demonstration of electron dense deposits in the pancreas and other tissues, in conjunction with immunologic data and the described animal models imply that this disease is immunologically mediated. Thus, we propose that the nomenclature of AIP be upheld instead of lymphoplasmacytic sclerosing pancreatitis, a mere descriptive term used by some authors. Finally, given the frequency

of extrapancreatic involvement we offer that AIP and the myriad of associated lesions should be seen as the manifestations of a systemic IgG4 positive plasma cell disease.

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