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Original Article

Evolution in the diagnosis and treatment of autoimmune pancreatitis: experience from a single tertiary care center

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Abstract: Background: Autoimmune pancreatitis (AIP) is a recently characterized disease with specific clinical, radiographic, and histological features. These diagnostic features have been codified in the recently revised HISORt criteria. The aim of this study was to determine how the recognition and management of AIP has evolved at our center since the publication of the HISORt criteria in 2006. Methods: We conducted a historical cohort study consisting of patients with AIP based on the revised HISORt criteria seen at our tertiary care center since 1990. Cases were identified from pathology, laboratory, and pancreas clinic databases. The medical records were reviewed to ascertain demographic and clinical characteristics, radiologic and laboratory results, and patient outcomes. When available, prior images and pathology slides were retrospectively reviewed. The clinical outcomes of the patients were assessed following surgical or medical treatment, and compared based on the calendar year of presentation (before or after 2006). Results: Forty-seven cases were identified based on the revised HISORt criteria. Of these, 22 were evaluated before and 25 after January 1, 2006. In the early cohort, the diagnosis was frequently missed, including 15 patients that underwent surgical resections. None from the early cohort had a serum IgG4 drawn or mention of possible AIP in the imaging reports. When histology was obtained, the surgical pathologist did not perform IgG4 or Movat stain to allow a histological diagnosis of AIP. Several patients developed diabetes (n=3), calcific pancreatitis with exocrine insufficiency (n=3), proximal biliary strictures (n=7), and pancreatic cancer (n=1) during follow-up. In contrast, patients in the late cohort were less likely to undergo a surgical resection that the early cohort (36% vs. 68%, p=0.042). They were more likely to have a serum IgG4 drawn (80% vs. 0%) and to undergo a corticosteroid trial (44% vs. 0%, p=0.0003). 10/11 patients (92%) who underwent corticosteroid trials had resolution of their symptoms and improvement in structural abnormalities on imaging. Conclusion: A growing multidisciplinary awareness of AIP has led to improved diagnostic evaluation, prompter diagnosis, fewer surgical resections, and more frequent corticosteroid trials.

Keywords: Autoimmune pancreatitis, IgG4, resection, corticosteroid

Introduction

Autoimmune pancreatitis (AIP) is a recently characterized disorder which may fall within the spectrum of IgG4-related sclerosing disease [1]. It is histologically defined by severe periductal lymphoplasmacytic infiltration of the pancreas, and it is associated with characteristic clinical and morphologic findings. Expeditious diagnosis and treatment of AIP is critical in preventing disease progression that results in parenchymal fibrosis, stone formation, and exocrine insufficiency [2, 3]. Furthermore, having a high clinical index of suspicion and familiarity with imaging features of AIP at initial evaluation may help prevent or reduce morbidity and cost associated with unnecessary pancreatic resection.

In our multidisciplinary pancreas clinic, we have noticed a increasing physician awareness of AIP in the past several years. Our aim for this study was to determine how the recognition and management of AIP has evolved since its initial characterization in the 1990s [4], and what ongoing awareness or clinical pathways need to be implemented. From our pancreas clinic and pathology databases we identified cases of AIP

over the past two decades. Each case was carefully reviewed to determine promptness and accuracy of diagnosis, method of treatment, and patient outcome. When possible, pathological specimens and imaging studies were retrospectively reviewed by subspecialty trained physicians to study the histological and imaging features at the time of initial evaluation.

Methods

Study design and participants

A single-center, HIPAA-compliant historical cohort study was conducted with a waiver of informed consent due to its retrospective nature (Cleveland Clinic IRB 10-779). Potential patients were identified retrospectively from January 1990 to August 2012.

Only patients meeting the revised HISORt criteria for diagnosis of AIP were included [5]. The revised HISORt system is comprised of 5 criteria used to diagnose and distinguish AIP from pancreatic cancer, including histology, imaging, serology, other organ involvement, and response to corticosteroid treatment. Each criterion is stratified as 'highly suggestive/diagnostic of AIP' (e.g. H1, I1, etc.), 'indeterminate/supportive of AIP' (e.g. H2, I2, etc.), and 'highly suggestive/diagnostic of pancreatic cancer' (e.g. I3, etc.). Once the individual criteria are determined, the diagnosis of AIP can be made in 3 ways: 1. Diagnostic histology (H1); 2. Typical imaging (I1) with other supportive features (S1/S2, O1/O2, or H2); and 3. Response to corticosteroids (resolution or marked improvement in pancreatic/extrapancreatic manifestations) in patients meeting criteria for steroid trial.

Subjects were identified by searching three databases: 1. The surgical pathology database was queried for all pancreatic pathology specimens obtained from 1990 to 2012. All reports were manually reviewed to identify cases in which the original diagnosis was either AIP or usual chronic pancreatitis (CP). The archived slides of all cases of AIP and usual CP were then obtained and screened and confirmed by two GI pathologists (XL, LY) to determine if histological features of AIP were present. Additional sectioning of paraffin embedded tissue blocks was done and used for IgG4 immunohistochemistry and Movat pentachrome staining if not done previously. 2. The laboratory administrative database was queried for all patients that had serum IgG subclasses drawn in the past 10 years. The records of patients with elevated IgG4 levels (>1x ULN) were screened to determine if they met additional HISORt criteria to support the diagnosis. 3. Patients with a clinical diagnosis of AIP were identified from our pancreas clinic database.

Data collection

The electronic and written medical records were reviewed using a standardized data collection form to ascertain demographics, symptom presentation, laboratory and radiographic findings, original clinical and pathological diagnoses, treatment, and condition at follow-up. The social security death index was queried to detect mortality.

Radiographic image interpretation

When available, single portal venous phase or dual pancreas phase CT and MRI imaging at initial presentation and after treatment were reviewed and recorded by a subspecialty trained abdominal radiologist (SNS) and categorized as typical, indeterminate, or atypical features of AIP [6]. Typical imaging features include diffuse pancreatic enlargement with or without rim enhancement and long or multiple strictures without marked upstream dilation. Indeterminate features included focal enlargement and focal strictures without upstream dilation. Atypical features included low attenuation mass and stricture with proximal ductal dilation or atrophy [4].

Histological confirmation

AIP was confirmed in all cases using the following histologic criteria: 1. the presence of a fibroinflammatory process that was duct centric and contained many lymphocytes and plasma cells with variable neutrophils, 2. obliterative phlebitis. 3. The presence of ≥10 IgG4-positive plasma cells per high power field (HPF) [7]. For core biopsies, the diagnosis was further confirmed by more than four of the following six features: granulocytic epithelial lesions (GELs), ≥10 IgG4-positive plasma cells/HPF, ≥10 eosinophils/HPF, cellular fibrosis with inflammation, lymphoplasmacytic infiltration, and venulitis

Table 1. Demographic and clinical characteristics

Variable	Stratum	N (%)
Age	<30	2 (4.3)
	30-49	12 (25.5)
	50-69	22 (46.8)
	≥70	11 (23.4)
Sex	Female	17 (36.2)
	Male	30 (63.8)
Race	White	39 (83.0)
	Black	5 (10.6)
	Hispanic	1 (2.1)
	Asian	1 (2.1)
	Arab	1 (2.1)
Symptoms	Jaundice	26 (55.3)
	Abdominal pain	29 (61.7)
	Acute pancreatitis	19 (40.4)
	Weight loss	28 (59.6)
Medical history	Diabetes	16 (34.0)
	Autoimmune diseases	8 (17.0)
	Inflammatory bowel disease	2 (4.3)

[8]. The subtype of AIP (Type 1 vs. Type 2) was determined according to the criteria described by Zhang L *et al* [9]. Movat pentachrome staining was performed when whole tissue sections were available to evaluate for obliterative venulitis (either obliterative or lymphocytic). Materials were routinely fixed in either formalin or Hollandes, processed, embedded in paraffin, and sectioned at a 4 μm thicknesses for Movat pentachrome staining, as previously described [10]. Lymphocytic and/or obliterative phlebitis was defined as lymphocytic infiltration of the venous wall with elastin fiber destruction and incorporation of connective tissue fibers and ground substance into the vein wall, with or without obliteration of the lumen. For IgG4 staining, pathology materials were routinely fixed in either formalin or Hollandes, processed, embedded in paraffin, and sectioned at a 4 μm thickness. Primary mouse antihuman monoclonal IgG4 antibody (clone HP6025; Invitrogen, Carlsbad, CA, USA) at a 1:500 dilution was applied to deparaffinized and rehydrated tissue sections for 60 min at 37°C followed by a diaminobenzidine basic detection kit (Ventana Medical Systems, Tucson, AZ, USA) and hematoxylin counterstaining on a Benchmark XT automated immunohistochemical stainer (Ventana Medical Systems), as previously described [11]. Appropriate positive and negative controls were run with each batch. Positive IgG4 plasma cells were counted in the areas with highest density of IgG4-positive plasma cells. Three HPFs were selected and an average number of IgG4-positive plasma cells/HPF was calculated [12]. The presence of ≥10 IgG4 positive plasma cells per HPF was considered positive for this feature [7].

Statistical methods

Continuous variables were expressed as mean values with ranges and standard deviation. Categorical variables were expressed as a percentage. Continuous data were compared using student *t* test and categorical data analyzed using Fisher's exact test. A *p* value of less than 0.05 was considered statistically significant.

Results

Revised HISORt diagnosis

Forty-seven patients were identified who met the revised HISORt criteria for diagnosis of AIP. The demographic and clinical data for the group are shown in **Table 1**. The diagnosis was established from confirmatory histology in 38 patients, typical imaging with supporting serology, other organ involvement, or compatible histology in 6 patients, and response to corticosteroids with supportive serology, imaging, or compatible histology in 3 patients. Similar to previous report, our AIP cohort showed a male predominance (63.8%) with peak in the seventh decade. Jaundice and acute pancreatitis were common presentations as seen in previous reports. Unlike previous reports, over 60% in our cohort presented with abdominal pain.

The HISORt definitions observed in our sample are shown in **Table 2**. Histological material was available for review in 39 patients (24 from resection; 15 from core-biopsy). Examples of typical histological features of type 1 and type 2 AIP are shown in **Figures 1-3**. Although prospective review and staining of all histological specimens confirmed AIP, the original diagnosis from the pathology report was AIP in only 19 patients (48.7%). The remaining patients were originally diagnosed with unspecified chronic pancreatitis.

Table 2. Revised HISORt classification

Histology		Available	N=39
	Definition	Highly suggestive/diagnostic (H1)	38 (97.4)
		Indeterminate/supportive (H2)	1 (2.6)
	Subtype	Type 1	29 (74.3)
		Type 2	7 (17.9)
		AIP NOS	3 (7.7)
Imaging		Available	N=23
	Definition	Highly suggestive/diagnostic of AIP (I1)	10 (43.5)
		Indeterminate/supportive of AIP (I2)	6 (26.1)
		Highly suggestive of cancer (I3)	7 (30.4)
Serology	IgG4	Available	N=21
		0-139	10 (47.6)
		140-279 (S2)	4 (19.0)
		≥280 (S1)	7 (33.3)
	CA19-9	Available	N=30
		>150 IU/ml (S3)	6 (20.0)
Other organ involvement	Definition	Typical histology or IgG4 stain (O1)	2 (4.3)
		Radiographic evidence (O2)	6 (12.8)
Response to corticosteroid treatment		Treated	N=15
	Definition	Resolution or marked improvement (Rt1)	13 (86.7)
		No improvement in mass/stricture (Rt3)	2 (13.3)

Results depicted as numbers with (percentages).

A serum IgG4 was drawn in only 21 of the patients (44%). Only 7 of these had elevations greater than 2 times the upper limit of normal.

Review of the medical record showed that all patients had either CT or MRCP imaging done at the time of their initial evaluation; however, films were available for prospective review in only 23 patients (13 with contrast enhanced CT, 2 with MRI/MRCP, 8 with both) (**Table 3**). Examples of characteristic radiographic findings are shown in **Figure 4**. Among the 16 patients with typical or supportive imaging features identified on retrospective review, none of the original radiology reports mentioned AIP as a diagnostic consideration. Several patients had calcifications, atrophy, and ductal enlargement, suggestive of chronic pancreatitis.

Other organ involvement from IgG4-related sclerosing disease was suspected in 8 patients. Two had confirmatory histology (HISORt 'O1'). One had a biopsy of a lung nodule which revealed IgG4 positive plasma cells. Another had a salivary gland biopsy showing fibrotic replacement of the normal acinar tissue consistent with IgG4-related sclerosing disease and proximal biliary strictures identified on imaging. Six patients had indeterminate or supportive features of other organ involvement (HISORt 'O2'), including 1 with increased IgG4 positive plasma cells on ampulla biopsy, 2 with retroperitoneal fibrosis on imaging, and 3 with proximal biliary strictures.

To examine the natural history and outcomes of the disease, the patients were categorized based on whether they were initially treated with surgical resection, corti-costeroids, or neither:

Surgical resections

Surgical resections were performed based on a clinical suspicion of cancer in 24 cases, without a trial of corticosteroids. Pylorus-preserving pancreaticoduodenectomy was done in 10 patients and distal pancreatectomy in 14 patients. Preoperative EUS-FNA was performed in 7 patients. Cytology was negative in 6 cases and showed atypical ductal cells in 1 case. The preoperative CA19-9 was <100 U/L in 10 of 15 patients in which it was drawn. A preoperative serum IgG4 was drawn in only 7 patients (28%), of whom 3 had IgG4 >139 mg/dl.

All patients survived surgery and were discharged from the hospital. After a mean follow-up of 35 months (range 1-198 months), three had died of unrelated causes. Among the remaining 21 patients, 12 were without disease recurrence or diabetes mellitus. Three patients developed post-operative diabetes mellitus that was difficult to control. There were four patients who had recurrent AIP. One patient with recurrent acute pancreatitis in the remnant pancreatic head was recognized in a timely manner and treated successfully with corticosteroids. Three patients developed proximal biliary strictures, two of whom were clinically

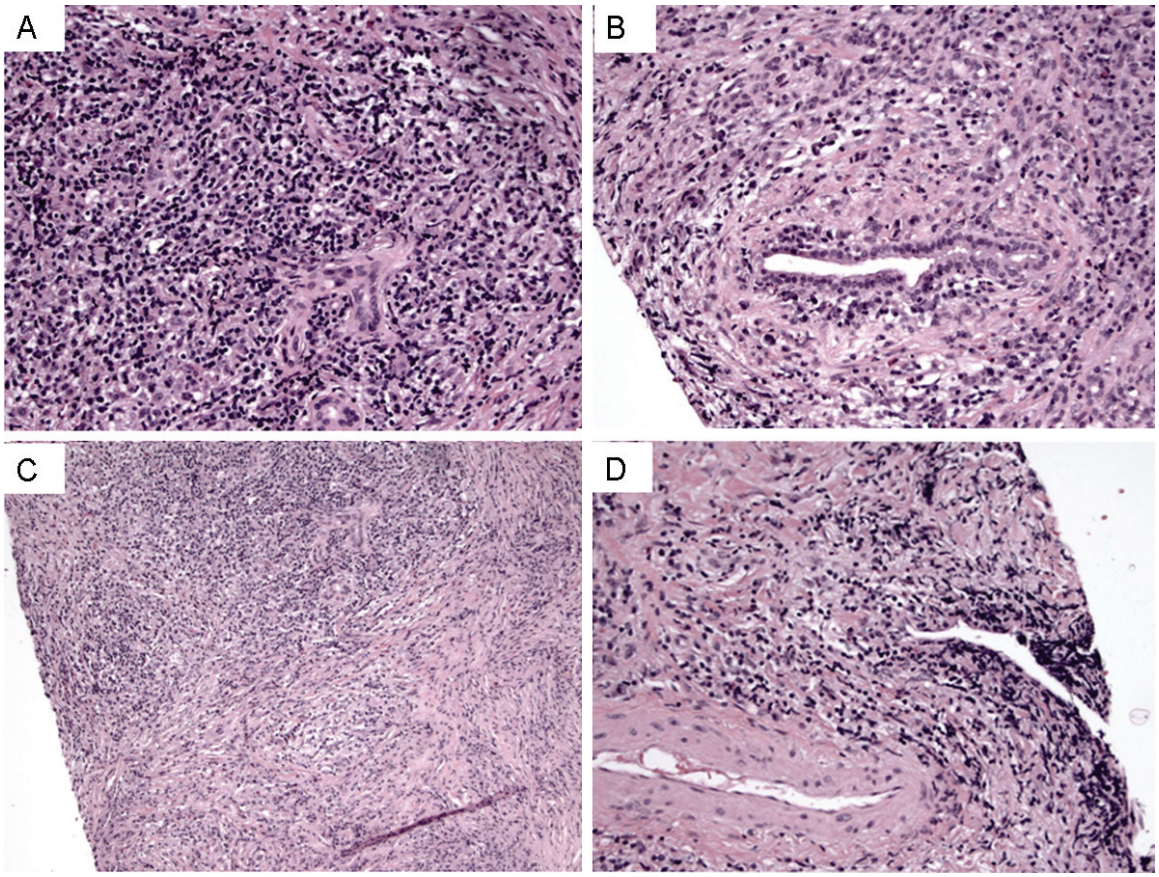

Figure 1. Histologic features of type 1 AIP include peri-ductal lymphoplasmacytic inflammation (A: H&E stain, 200X), periductal fibrosis (B: H&E stain, 200X), storiform and cellular fibrosis in the stroma (C: H&E stain, 100X) and lymphocytic phlebitis (D: H&E stain, 200X).

diagnosed with autoimmune cholangiopathy and effectively treated with corticosteroids.

Corticosteroid treatment

Eleven patients were treated with corticosteroids regimens consisting of 40-50 mg prednisone for 4-8 weeks followed by a slow taper (5 mg decrease every 1-2 weeks), and had CT or MRI imaging repeated after 4-8 weeks of treatment. In 10 patients (91.0%) there was a dramatic response characterized by complete or near-complete resolution of pancreatic enlargement or strictures. In 7 of 8 patients with biliary strictures, complete resolution was noted at the follow-up ERCP and the biliary stent was removed. One patient's focal pancreatic enlargement and biliary stricture failed to improve. This patient underwent a pancreaticoduodenectomy, and surgical pathology revealed AIP with no evidence of cancer.

After a mean follow-up of 16 months (range 3-44 months), all patients remained alive. Nine patients were off corticosteroids at the time of last follow-up. Three patients developed relapses during the follow-up period and required retreatment with corticosteroids. Two of these were started on steroid-sparing agents (azathioprine and methotrexate).

Neither resection nor corticosteroids

There were 12 patients that underwent neither surgical resection nor corticosteroid treatment. In 11 cases (91.7%), AIP was not considered in the differential diagnosis by the evaluating clinician. One patient was clinically diagnosed with AIP based on the incidental finding of diffuse pancreatic enlargement and elevated IgG4, but was not treated because she was asymptomatic. Another patient presented with acute recurrent pancreatitis and calcific pancreatitis on imaging; this patient underwent a

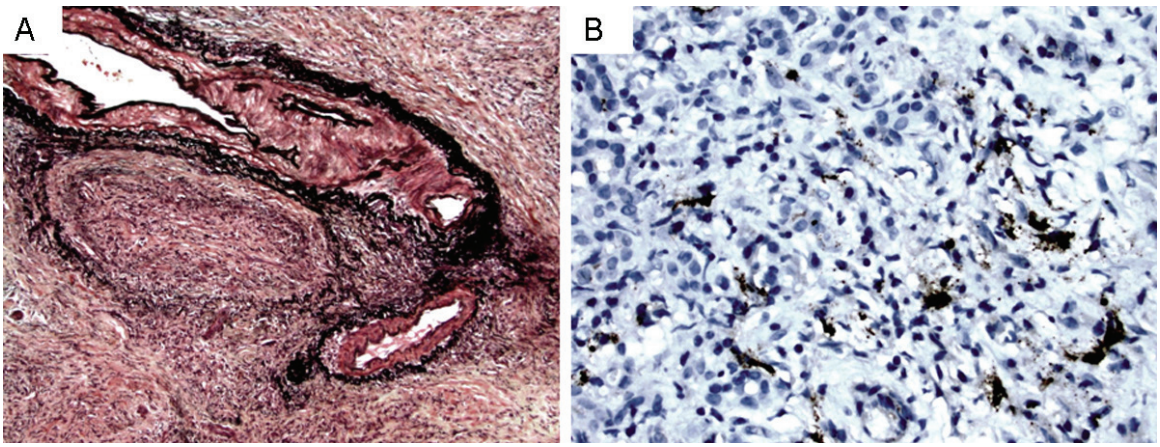

Figure 2. Pathological staining in type 1 AIP. Complete venous lumen obliteration (A: Movat stain, 200X), and increased IgG4 positive plasma cell infiltration (B: immunoperoxidase stain, 400X).

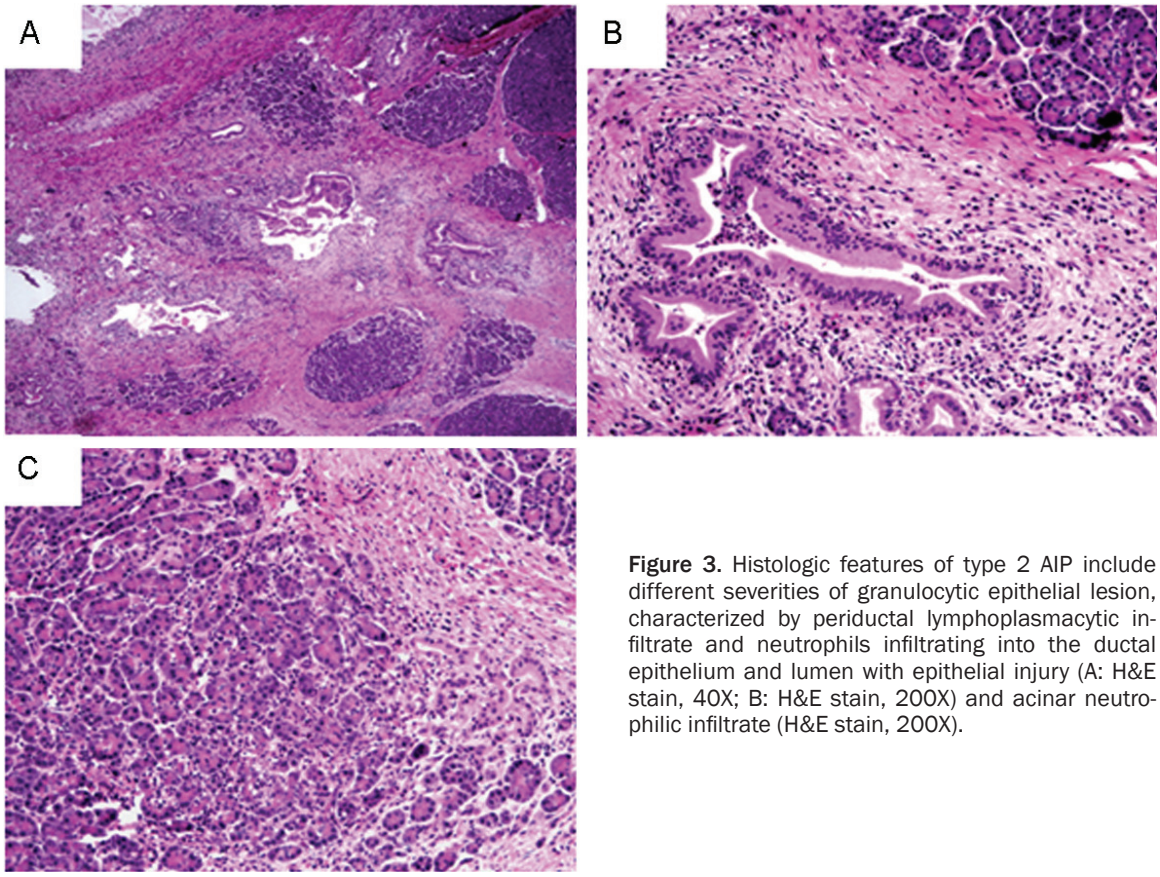

Figure 3. Histologic features of type 2 AIP include different severities of granulocytic epithelial lesion, characterized by periductal lymphoplasmacytic infiltrate and neutrophils infiltrating into the ductal epithelium and lumen with epithelial injury (A: H&E stain, 40X; B: H&E stain, 200X) and acinar neutrophilic infiltrate (H&E stain, 200X).

lateral pancreaticojejunostomy and wedge biopsy that revealed AIP. Ten patients were suspected of having pancreatic cancer. Of these, 8 presented with obstructive jaundice. One had a percutaneous transhepatic choledochostomy (PTHC) drain for palliation. The other 7 cases were found to have an 'unresectable mass' at attempted surgical resection. In all 7, a biliary bypass was performed, and a core or wedge biopsy revealed benign chronic inflammation.

After a mean follow-up of 79 months (range: 1-198 months), three patients developed calcific chronic pancreatitis and exocrine insuffi-

Table 3. Radiographic findings on prospectively reviewed imaging tests

	Feature	Number (%)
Number with imaging available for prospective review		23
Parenchymal features	Diffuse pancreatic enlargement	9 (39.1)
	Focal enlargement	9 (39.1)
	Loss of contour	11 (47.9)
	Capsule like rim	4 (17.4)
	Delayed enhancement	19 (82.6)
	Calcifications	8 (34.8)
	Atrophy	6 (26.1)
Ductal features	Diffuse or multiple strictures	2 (8.7)
	Focal pancreatic duct stricture	6 (26.1)
	Ductal dilation	3 (13.0)

ciency. Four patients developed proximal biliary strictures, two of whom were misdiagnosed with primary sclerosing cholangitis (PSC) and managed with PTHC, and one of whom underwent liver transplantation for presumed PSC. Two patients were diagnosed with autoimmune cholangiopathy and successfully treated with prednisone. One patient died of metastatic pancreatic cancer 168 months after surgical biopsy showed AIP.

Evolution in diagnosis and management

The cohort was divided based on whether their initial evaluation was before or after 2006, the year the HISORt criteria were published (**Table 4**). Several encouraging temporal trends were noted: 1. Serum IgG4 was drawn more commonly in the later cohort. 2. Radiology reports more commonly listed AIP as a leading diagnostic consideration in the later cohort. 3. Fewer patients in the later cohort underwent surgical resections (**Figure 5**). 4. All of the corticosteroid trials were administered to patients in the later cohort. 5. In those who had histologic material obtained, the original diagnosis was AIP in none of the patients in the early cohort and 89% of those in the later cohort. Also, Movat and IgG4 staining was initially done in none of the early patients and most of the late patients.

Discussion

In this observational study, we evaluated our single-center experience of patients with AIP. The HISORt criteria were employed to accurately identify subjects with AIP, and the clinical, imaging, and histological data were reviewed to assess diagnostic accuracy, treatment and clinical follow-up and outcome. Our aim was to assess temporal trends in the management of this disease.

The year 2006 was used to temporally divide the cohort, because we hypothesized that the publication of the HISORt criteria coincided with a greater awareness of the disease amongst physicians who manage digestive diseases. In the 'pre-HISORt' years, we found frequent misdiagnosis by the gastroenterologist, surgeon and imagers alike. Even the surgical pathologist failed to recognize the unique type of pancreatitis characterized by severe lymphoplasmacytic infiltrate and fibrosis, and conduct the proper staining to confirm the diagnosis. Subsequently, many patients underwent futile pancreatic resection. This contrasts with the 'post-HISORt' period, when the work-up was more expeditious and thorough, with therapy oriented toward an initial corticosteroid trial.

Currently, clinicians are more likely to consider AIP in patients with focal or diffuse pancreas enlargement, and order serum IgG4 and core biopsies for confirmation of the HISORt criteria. Radiologists have also begun to recognize and report the typical features of AIP as well [13]. At our institution, most patients with suspicion of AIP now undergo a contrast enhanced MRI with MRCP or dual phase pancreas CT with review by subspecialty abdominal radiologists. If imaging findings are not typical and serum IgG4 is not markedly elevated, a percutaneous or EUS-guided core biopsy is usually obtained. In this series, we found that pathologists have also become more adept at recognizing the histological pattern of AIP and performing confirmatory IgG4 and Movat pentachrome staining. Indeed, AIP requires a multidisciplinary approach for timely diagnosis.

The importance of prompt corticosteroid treatment is illustrated by our follow-up data. In our study, not only did we many patients undergo futile pancreatic resection, but several other detrimental outcomes were seen in those patients in whom a corticosteroid trial was

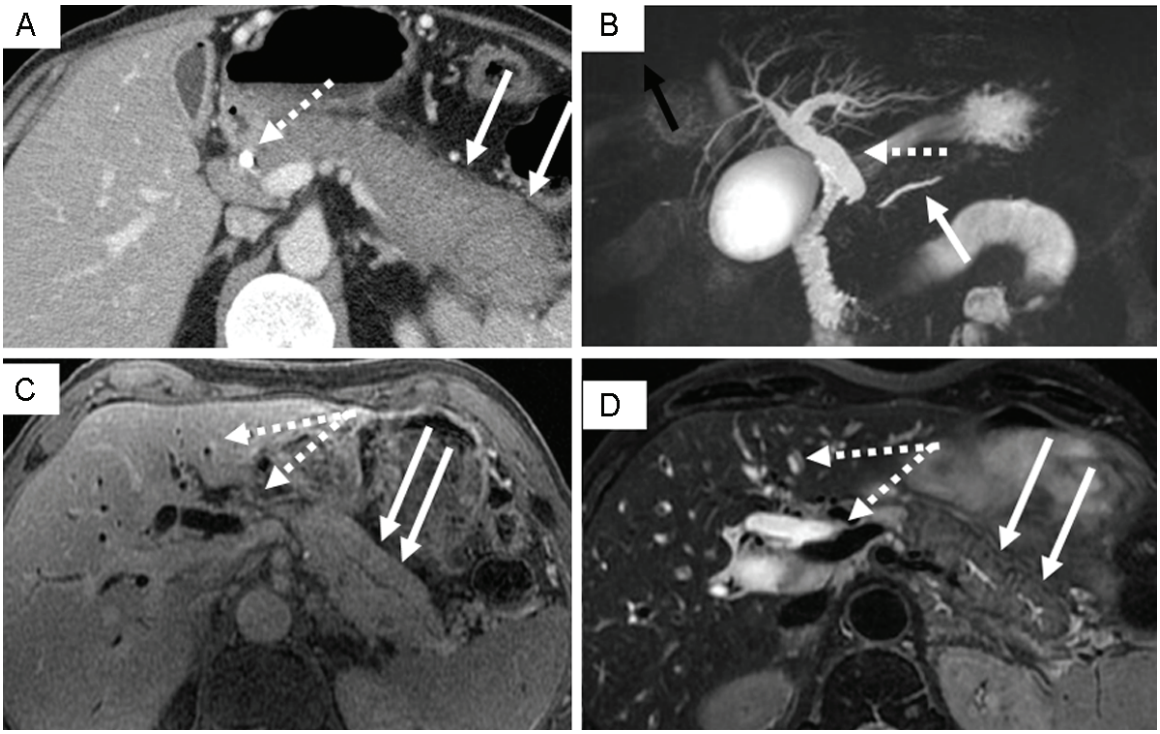

Figure 4. Panel A. Contrast enhanced CT demonstrates diffuse enlargement of the pancreas ("sausage pancreas") with loss of normal contour and diminished enhancement (solid white arrows). An internal biliary stent is present (dashed white arrow). Panel B-D are MRI images. Panel B. Coronal MIP HASTE image from MRCP demonstrates a diffuse pancreatic duct stricture in the head and tail with a mildly dilated isolated duct segment in the body (solid white arrow). Note extra- and intra-hepatic biliary dilatation from CBD stricture (dashed white arrow). Panels C and D. T1W and T2W axial MR images show diffuse enlargement of the pancreas with loss of contour consistent with autoimmune pancreatitis. Note diffuse irregularity of the main pancreatic duct due to stricture (solid white arrows) and biliary dilatation (dashed white arrows).

Table 4. Temporal trends in diagnosis and management of AIP

	Before 2006 N=22	2006-2012 N=25	*p*-value*
Serum IgG4 drawn	0/22 (0)	20/25 (80)	0.0001
Radiology report mentions AIP as diagnostic consideration	0/22 (0)	7/25 (28)	0.0104
Original pathological diagnosis of AIP	0/22 (0)	17/19 (89)	0.0001
Surgical resection performed without trial of corticosteroids	15/22 (68)	9/25 (36)	0.0415
Steroid trial given	0/22 (0)	11/25 (44)	0.0003

Results expressed as number/total with (percent). **P* value based on Fisher's exact test.

delayed. For example, several patients developed worsening structural and functional changes of the pancreas indicating progression to chronic pancreatitis. In fact, there was a relatively high prevalence of atrophy, calcifications, and ductal enlargement on imaging tests, suggesting a 'burnt out' phase of untreated AIP in the group of AIP patients received neither surgical resection nor corticosteroid treatment. The failure to recognize AIP resulted in a missed opportunity to prevent irreversible pancreatic fibrosis with resulting exocrine insufficiency. Additionally, several patients developed proximal biliary strictures, but were not given corticosteroids due to a failure to recognize autoimmune cholangiopathy. These additional missed opportunities for effective medical therapy resulted in long term percutaneous drains and even a cadaveric orthotopic liver transplantation. Another interesting outcome was a case of

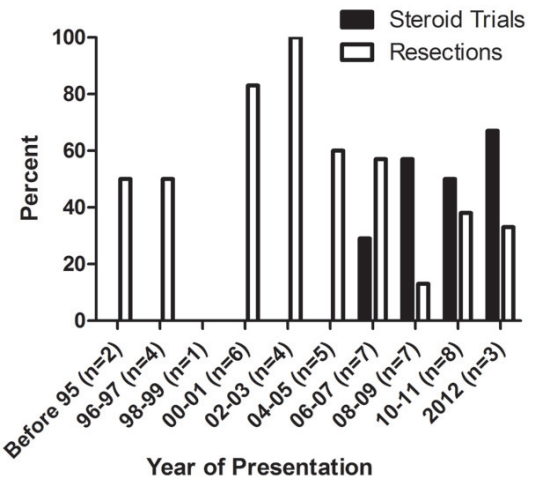

Figure 5. Temporal trends in the treatment of AIP.

pancreatic cancer that developed 14 years later; this is one of few such cases reported in the literature [14]. It suggests the possibility that untreated AIP increases the long term risk of pancreatic cancer in a similar fashion as conventional chronic pancreatitis. Another possibility is that caner develops independently of AIP as precursor lesions of pancreatic ductal adenocarcinoma, pancreatic intraepithelial neoplasia (PanIN) are also noted in the pancreas involved by AIP (unpublished observation). For all these reasons, AIP should be considered carefully in the differential diagnosis of all patients with acute and chronic pancreatitis, pancreatic mass, and those presenting with obstructive jaundice.

In summary, this retrospective study shows a favorable trend in a more prompt and accurate detection, diagnosis and management of AIP at our center. We expect that these encouraging practice trends are also replicated at other tertiary care centers across the world. Further education regarding the typical clinical, imaging, and pathological features of this unusual variant of pancreatitis is needed among physicians of all related disciplines.

Disclosure of conflict of interest

None.

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