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ORIGINAL SCIENTIFIC REPORT

Differentiation of Autoimmune Pancreatitis from Pancreatic Cancer Remains Challenging

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Abstract

Background Autoimmune pancreatitis (AIP) is an uncommon form of chronic pancreatitis. Whilst being corticosteroid responsive, AIP often masquerades radiologically as pancreatic neoplasia. Our aim is to appraise demographic, radiological and histological features in our cohort in order to differentiate AIP from pancreatic malignancy.

Methods Clinical, biochemical, histological and radiological details of all AIP patients 1997–2016 were analysed. The initial imaging was re-reviewed according to international guidelines by three blinded independent radiologists to evaluate features associated with autoimmune pancreatitis and pancreatic cancer.

Results There were a total of 45 patients: 25 in type 1 (55.5%), 14 type 2 (31.1%) and 6 AIP otherwise not specified (13.3%). The median (IQR) age was 57 (51–70) years. Thirty patients (66.6%) were male. Twenty-six patients (57.8%) had resection for suspected malignancy and one for symptomatic chronic pancreatitis. Three had histologically proven malignancy with concurrent AIP. Two patients died from recurrent pancreatic cancer following resection. Multidisciplinary team review based on radiology and clinical history dictated management. Resected patients (vs. non-resected group) were older (64 vs. 53, $p = 0.003$) and more frequently had co-existing autoimmune pathologies (22.2 vs. 55.6%, $p = 0.022$). Resected patients also presented with less classical radiological features of AIP, which are halo sign (0/25 vs. 3/17, $p = 0.029$) and loss of pancreatic clefts (18/25 vs. 17/17, $p = 0.017$). There were no differences in demographic features other than age.

Conclusion Despite international guidelines for diagnosing AIP, differentiation from pancreatic cancer remains challenging. Resection remains an important treatment option in suspected cancer or where conservative treatment fails.

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Introduction

Autoimmune pancreatitis (AIP) is a form of chronic pancreatitis that invariably responds to corticosteroid treatment with characteristic radiological, serological and histopathological features [1, 2]. The International Consensus Diagnostic Criteria (ICDC) defines type 1 and type 2 AIP [1]. The more common AIP-1 is associated with IgG4-related disease (60% other organ involvement including inflammatory bowel disease in 10%), and usually has raised serum IgG4 levels (over 80%) and histologically prominent IgG4 plasma cell infiltration of the pancreas. This occurs three times more in men than women with a median onset in the seventh decade. AIP-2 is rarer, usually without raised serum IgG4 (<10%), and the absence of other IgG4-related disease. Inflammatory bowel disease occurs more often (around 30%) with histological duct-centric granulocytic epithelial lesions [3]. It occurs equally in men and women and presents earlier (median third decade). Although there are different radiological features for type 1 and 2 AIP, these overlap and it may be difficult to differentiate the two subtypes by imaging alone [1, 3].

Dual-phase computed tomography (CT) findings for AIP are diffuse pancreatic enlargement with loss of pancreatic clefts and the presence of pancreatic ductal strictures [1]. Unfortunately, these specific features are infrequently found, and atypical CT findings share much in common with alternative pancreatic pathologies, notably pancreatic ductal adenocarcinoma [4–6].

Initial presenting symptoms of jaundice and/or abdominal pain combined with similar radiological features to pancreatic neoplasm necessitated exclusion of this more sinister diagnosis. The principal treatment of symptomatic AIP is corticosteroid therapy. Although maintenance treatment with low-dose steroids reduces relapse rates, it does not eliminate them [7, 8]. Surgery in AIP is indicated if pancreatic cancer is unable to be excluded or in the presence of highly symptomatic repeated relapses. The prevalence of AIP (0.82–2.2 per 10^5) is lower than pancreatic cancer (around 10 per 10^5) [9]. Differentiation of AIP from pancreatic cancer is confounded by its coexistence and fivefold increased risk rate in chronic pancreatitis [10, 11].

This study aims to appraise demographic and radiological features to assess whether we can improve our patient selection for surgery—improving our rate of medical management without missing any malignancies concurrently with AIP in a large tertiary referral pancreatic centre.

Patients and methods

Patients with potential diagnosis of AIP were identified retrospectively from outpatient electronic notes and histological database between January 1997 and December 2016 in a single surgical pancreatic tertiary referral centre. Patients were identified through keyword searching of all electronic letters for “autoimmune pancreatitis” [including variations, historic names and acronyms] and “IgG4”.

Demographic details (including age, sex, co-morbidities and date of diagnosis), serological investigations (including IgG4, Ca19-9, immunoglobulins and other autoimmune serological tests) and radiological investigations (including CT, magnetic resonance imaging (MRI), positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrated with CT (PET-CT), magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiopancreatography (ERCP)) were analysed.

All patients were referred for multidisciplinary team discussion, which made all decisions for either operative or conservative management according to clinical history and radiological findings. Details of management outcomes including success of steroid therapy, type and complications of operative management and histology for AIP and malignancy, were collected.

All initial diagnostic CT imaging, wherever available, was anonymised for blinded radiology review by three independent pancreatic radiologists (FA, FB and PH) for features of AIP as per the ICDC guidelines and features of pancreatic cancer [1]. The radiological factors leading to operative decision-making were analysed.

The combination of clinical history, biochemical, histological and radiological findings was used to retrospectively classify all patients into subtypes according to ICDC criteria [1].

Statistics

Categorical data are presented as frequency and proportions (%) and analysed using Fisher’s exact or the χ^2 test. Medians with interquartile range (IQR) were used to describe continuous data, and analysed using Kruskal–Wallis and Mann–Whitney tests. A two-sided p value < 0.05 was taken as statistically significant. Bonferroni correction was not applied. All statistical analyses were performed using the SPSS v24 for Windows (IBM Ltd).

Table 1 Characteristics of the three AIP subtypes

	AIP-1 $n = 25$	AIP-2 $n = 14$	AIP-ONS $n = 6$	p value
Male (%)	18 (72.0)	10 (71.4)	2 (33.3)	0.177
Median (IQR) age at diagnosis years	62 (56–71)	52 (33–56)	61 (50–69)	0.036
Serology IgG4				
Tested (%)	10 (40.0)	8 (57.1)	4 (66.7)	0.525
Raised (%)	4 (16.0)	0	0	0.365
Treatment				
No treatment with steroid or surgery (%)	3 (12)	1 (7.1)	3 (50)	0.079
Operated (%)	12 (48.0)	9 (64.3)	2 (33.3)	0.359
Treated with steroids (%)	6 (24.0)	4 (28.6)	1 (16.7)	0.498
Steroids and operation (%)	4 (16.0)	0	0	0.365
Responded to steroids	3 (32.0)	3 (21.4)	0	0.249
Associated conditions				
Any autoimmune disease (%)	9 (36.0)	7 (50.0)	0	0.101
IgG4-related disease (%)	1 (4.0)	0	0	0.000
Other autoimmune disease (%)	8 (32.0)	1 (7.1)	0	0.077
Inflammatory bowel disease (%)	0	6 (42.9)	0	0.000
None recorded (%)	16 (64.0)	7 (50.0)	6 (100)	0.349

Other autoimmune diseases: primary sclerosing cholangitis ($n = 4$), autoimmune gastritis ($n = 3$), autoimmune thyroiditis ($n = 1$), autoimmune sialadenitis as part of IgG4-related disease ($n = 1$)

Results

Of the 45 patients diagnosed with AIP during the studied period, 25 (55.5%) were classified as AIP-1, 14 as AIP-2 (31.1%) and 6 as AIP otherwise not specified (AIP-ONS) (13.3%) [1]. The characteristics of the three AIP subtypes are shown in Table 1. Six (42.9%) patients with AIP-2 had inflammatory bowel disease, compared to none with AIP-1 ($p = 0.000$). Eight (32.0%) patients with AIP-1 had other non-IgG4-related autoimmune diseases, compared to one (7.1%) with AIP-2 ($p = 0.077$).

IgG4 serum levels were raised in 2 (7.4%) of 25 patients in the operated group who were tested. Raised IgG levels with normal IgG4 levels were found in three patients, two with AIP-1 and one with AIP-ONS. Serum Ca19-9 levels were measured in 38 (84.4%) patients, and elevated in 12 (44.4%) of 27 patients operated on and two (16.7%) of the 18 patients medically managed ($p = 0.013$).

Fifteen (33.3%) out of the 45 patients were treated with steroids. Eleven (73.3%) of these patients demonstrated symptomatic and radiological response. Twenty-seven (60.0%) patients had surgical resection either for suspicion of malignancy in 26 (55.3%) or intractable pain secondary to chronic pancreatitis in one. Comparison of the operated and non-operated groups is shown in Table 2. Four operated patients (14.8%) had been treated with therapeutic steroid therapy prior to subsequent surgical resection.

Twenty-two (81.5%) had partial pancreatoduodenectomies, three (11.1%) had left pancreatectomies, one (3.7%) had duodenum-preserving pancreatic head resection (Beger procedure), and one (3.7%) had a total pancreatectomy. There were no post-operative deaths, but two patients had re-operations due to post-operative haemorrhage. Sixteen (59.3%) of these operated patients were AIP-1, nine (33.3%) were AIP-2 and two (7.4%) were AIP-ONS ($p = 0.359$). The histology of the resected specimens from all of the 27 patients operated on confirmed the diagnosis of AIP. Concurrent pancreatic malignancy was identified in three (11.1%) patients, two with AIP-1 and one with AIP-2. Two had pancreatic ductal adenocarcinoma, and one had a solid pseudopapillary neoplasm. The individual details of these patients are shown in Table 3. Comparison of these three patients radiological and biochemical findings within the operative and non-operative cohort was insufficiently powered to reach a meaningful conclusion. There were no malignancies identified in the medically managed cohort with a median (IQR) follow-up of 78.5 months (55.75–90.25).

In the resected specimens, lymphoplasmacytic infiltration was described in all. Other histological features of autoimmune pancreatitis were also described: storiform fibrosis (in 11 of 14 recorded cases, 78.6%), extra-pancreatic involvement (in 14 of 24 recorded cases, 58.3%) and obliterative phlebitis (11 of 13 recorded cases, 84.6%).

Table 2 Comparison of the operative and non-operative groups

	Operative	Non-operative	*p* value
Male	19 (70.4)	11 (61.1)	0.519
AIP-1 ($n = 25$)	16 (59.3)	9 (50.0)	0.359
AIP-2 ($n = 14$)	9 (33.3)	5 (27.8)	
AIP-ONS ($n = 6$)	2 (7.4)	4 (22.2)	($\chi^2 = 2.052$, $df = 2$)
Deceased (%)	6 (22.2)	0	0.032
Median (IQR) age at diagnosis years	64 (58–73)	53 (33–61)	0.003
Serology			
IgG4			
Tested (%)	11 (40.7)	12 (66.7)	0.199
Raised (%)	2 (7.4)	2 (16.7)	0.233
Ca19-9			
Tested (%)	26 (96.3)	12 (66.7)	0.007
Raised (%)	12 (44.4)	2 (16.7)	0.013
No treatment with steroid or surgery (%)	0	7 (38.9)	0.000
Treated with steroids (%)	4 (14.8)	11 (61.1)	0.001
Responded to steroids	2 (7.4)	9 (50.0)	0.001
Associated autoimmune disease (%)	6 (22.2)	10 (55.6)	0.022
No associated conditions (%)	21 (77.8)	8 (44.4)	0.082

IgG4 immunohistochemistry was performed on 8 (29.6%) patients, of which three were positive, all within the AIP-1 cohort ($p = 0.004$) (Table 4).

Forty-two out of 45 patients' CT imaging were re-reviewed by independent radiologists, and the details are shown in Table 5. Biliary duct dilatation (18 vs. 4, $p = 0.028$) and biliary duct stricture (17 vs. 2, $p = 0.004$) were found more frequently in AIP-1 than AIP-2. Pancreatic duct strictures (3 vs. 1, $p = 0.046$) were found more commonly in AIP-2 than AIP-1. All other radiological findings were non-significant between AIP subtypes.

Differences in CT imaging between operative and non-operative groups were found for four features: halo sign (0 vs. 3, $p = 0.029$), loss of pancreatic clefts (18 vs. 17, $p = 0.017$), pancreatic duct stricture (5 vs. 0, $p = 0.049$) and biliary duct dilatation (18 vs. 7, $p = 0.046$). Double duct sign was identified only in three cases, all in the operated group. Six patients presented with solid lesions on CT scans, of whom four (16.0%) were operated on. Three of these four patients had cancer on histopathology within the resected specimens. The pancreatic masses of the two non-operated patients were deemed to be inflammatory at the multidisciplinary meeting, and were treated conservatively with interval CT surveillance.

Sixteen patients (35.6%) had MRI/MRCP as part of their diagnostic workup; of which only one scan report altered management. Four had PET-CT. This was diagnostic in 2 (50%) and grossly normal in 2 patients. ERCP was performed in 22 (44.4%), although often out of area and with comment only on therapeutic procedures including stenting and brushings/biopsy. Of the EUS-FNA biopsies performed in our department, none confirmed or suggested AIP.

Six patients from the whole study group died during the course of the study period, and were all within the operated cohort. Two deaths were due to recurrent pancreatic cancer following resection. One of these patients also had rectal cancer. Another death was due to an ischaemic cerebrovascular accident, and the causes for other three patients were unknown.

There was no symptomatic relapse in those operatively managed requiring hospitalisation or attendance at our outpatient clinics during the study duration.

Discussion

The distribution of clinical, biochemical and radiological features of patients in this study reflects the classification of AIP into two main subtypes with a similar pattern of features to another European study [12]. The general proportion of patients with AIP that need to go forward to surgery, either because of concerns about the diagnosis of underlying pancreatic cancer or highly symptomatic relapse, is difficult to determine because of uncertainty of diagnosis and ascertainment biases. The data from large multi-centre

Table 3 Individual characteristics of the three patients diagnosed with concurrent malignancy

	Patient 1	Patient 2	Patient 3
Diagnosis	AIP-1	AIP-1	AIP-2
Year of diagnosis	2009	2010	2014
Age at diagnosis (years)	56	83	76
Sex	Female	Male	Male
AIP ICDC evidence	Typical histology with IgG4 staining with typical imaging	Typical histology with typical imaging	Typical histology + typical imagine + ductal strictures
IgG4	Positive	Positive	Not performed
Ca19-9 (KU/L)	3	45	65
Associated conditions	None	None	None
Histology	Pancreatic pseudopapillary tumour	Pancreatic ductal adenocarcinoma	Pancreatic ductal adenocarcinoma
Radiology			
Mass	Yes	Yes	No
Lymphadenopathy	No	No	No
Double duct	No, biliary only	No, biliary only	Yes
Mortality	Deceased, pancreatic and rectal cancer 17 months post-operative	Deceased, recurrence 61 months post-operative	Alive as of 15/1/18 30 months post-operative, no recurrence

Table 4 CT and histopathological findings from resected specimens from patients with AIP [35]

	AIP-1			AIP-2			*p* value
	Present	Absent	Not recorded	Present	Absent	Not recorded	
	Radiology *N* (%) = 25 ()			*N* (%) = 11 ()			
Diffuse enlargement (%)	15 (60.0)	9 (36.0)	1 (4.0)	4 (36.4)	7 (63.6)	0	0.150
Halo sign (%)	2 (8.0)	22 (88.0)	1 (4.0)	1 (9.1)	10 (90.9)	0	0.941
Loss of clefts (%)	20 (80.0)	4 (16.0)	1 (4.0)	8 (72.7)	3 (27.3)	0	0.466
Mass (%)	3 (12.0)	21 (84.0)	1 (4.0)	1 (9.1)	10 (90.9)	0	0.769
Lymphadenopathy (%)	5 (20.0)	19 (76.0)	1 (4.0)	1 (9.1)	10 (90.9)	0	0.392
Double duct (%)	1 (4.0)	23 (92.0)	1 (4.0)	2 (18.2)	9 (81.8)	0	0.169
Pancreatic duct dilatation (%)	1 (4.0)	23 (92.0)	1 (4.0)	2 (18.2)	9 (81.8)	0	0.169
Pancreatic duct stricture (%)	1 (4.0)	23 (92.0)	1 (4.0)	3 (27.3)	8 (72.7)	0	0.046
Biliary duct dilatation (%)	18 (72.0)	6 (24.0)	1 (4.0)	4 (36.4)	7 (63.6)	0	0.028
Biliary duct stricture (%)	17 (68.0)	7 (28.0)	1 (4.0)	2 (18.2)	9 (81.8)	0	0.004
Focal distal pancreatic enlargement (%)	6 (24.0)	18 (72.0)	1 (4.0)	3 (27.3)	8 (72.7)	0	0.886
Focal proximal pancreatic enlargement (%)	3 (12.0)	21 (84.0)	1 (4.0)	1 (9.1)	10 (90.9)	0	0.769
	Histology *N* (%) = 15 ()			*N* (%) = 9 ()			
Lymphoplasmacytic infiltrate (%)	15 (100)	0	0	9 (100)	0	0	n/a
Obliterative phlebitis (%)	8 (53.3)	2 (13.3)	5 (33.3)	3 (33.3)	0	6 (66.7)	0.217
Storiform fibrosis (%)	8 (53.3)	1 (6.7)	6 (40.0)	3 (33.3)	2 (22.2)	4 (44.4)	0.448
IgG4 staining (%)	3 (20.0)	0	12 (80.0)	0	5 (55.6)	4 (44.4)	0.004
Extra-pancreatic involvement (%)	10 (66.7)	5 (33.3)	0	4 (44.4)	5 (55.6)	0	0.285
Malignancy present (%)	2 (13.3)	13 (86.7)	0	1 (11.1)	8 (88.9)	0	0.873

Table 5 CT features identified by blinded radiological review of the operative and non-operative groups

	Operative (n = 25)	Non-operative (n = 17)	p value
Autoimmune pancreatitis			
Diffuse enlargement (%)	14 (56.0)	9 (52.9)	0.952
Halo sign (%)	0	3 (17.6)	0.029
Loss of clefts (%)	18 (72.0)	17 (100)	0.017
Malignant features			
Mass (%)	4 (16.0)	2 (11.8)	0.700
Lymphadenopathy (%)	4 (16.0)	3 (17.6)	0.888
Double duct (%)	3 (12.0)	0	0.138
Other			
Pancreatic duct dilatation (%)	3 (12.0)	0	0.138
Pancreatic duct stricture (%)	5 (20.0)	0	0.049
Biliary duct dilatation (%)	18 (72.0)	7 (41.2)	0.046
Biliary duct stricture (%)	15 (60.0)	8 (47.1)	0.569
Focal distal pancreatic enlargement (%)	5 (20.0)	5 (29.4)	0.482
Focal proximal pancreatic enlargement (%)	1 (4.0)	4 (23.5)	0.055

series are based on retrospective data submitted against study-specific entry criteria, with wide variations in the rates of resection being reported [8, 12–15]. In a series of 327 patients from five Asian countries, the rates of resection ranged from 11 to 72% (total patients 25–137) [13]. In a series from 15 institutes in eight countries, 183 (25.0%) out of 731 AIP cases were resected, again with wide variation in resection rate by country [15]. In the histologically confirmed cases, the resection rates were 60.3% of 204 AIP-1 cases and 78.1% of 64 AIP-2 cases [15]. In the present series, 27 (60.0%) of 45 patients referred had surgery. To some extent, the relatively higher resection rate will represent ascertainment bias, as milder forms of AIP will more likely have been successfully treated in referring units and only those with a high degree of suspicion for pancreatic malignancy will be referred into our MDT. Compared to retrospective multi-centre studies, this single-centre study will depict a more accurate representation of the challenges of clinical practice.

Retrospective histological reviews in two studies have suggested that AIP may be more common in resected cases of chronic pancreatitis than previously supposed [16, 17]. Two other retrospective surgical studies have also suggested that fewer patients might need to go forward to surgery [18, 19]. Our experience suggests that greater vigilance is required in early intervention in those suspected of having pancreatic cancer. Of the three patients who were found to have a pancreatic cancer histologically, two died of recurrent cancer during the follow-up period.

It is well known that chronic pancreatitis is a risk factor for pancreatic cancer [20]. Based on our experience, the risk of pancreatic cancer in AIP would seem to be similar as in other forms of chronic pancreatitis. The risk of malignancies in AIP is probably increased although the data are variable [21–23]. In our series, we had four cancers in 47 patients, three with pancreatic cancer and one also with rectal cancer. Hirano et al. found 14 patients with 15 malignancies (including pancreatic cancer in two patients) in 113 patients with IgG4-related disease (95 patients with AIP) with a standardised incidence ratio of 1.04 (95% confidence interval, 0.57–1.75) at a mean follow-up of 73 months [22]. Shiokawa et al. found 18 cancers in 15 patients (13.9%) during a median follow-up period of 3.3 years in 108 AIP patients with a standardised incidence ratio of 2.7 (95% confidence interval, 1.4–3.9), with the highest risk of cancer in the first year after AIP diagnosis [23].

Diagnostic difficulties in differentiating pancreatic malignancy from focal AIP are well documented [5, 24]. Takahashi et al. showed 15.2% of patients with pancreatic malignancy were incorrectly diagnosed as AIP and 36.0% incorrectly diagnosed AIP as malignancy by at least one of three independent radiologists [5]. These difficulties are evidenced in our comparison of radiological masses. Of 6 patients with masses in this patient cohort, 3 (50%) were malignant. Whilst classical radiological findings for AIP predisposed to medical management and features suspicious for occult pancreatic/biliary neoplasm predisposed to surgical management, caution is advised when using these in isolation to guide management especially given the overlap of features between management cohorts. Looking to the future, PET-CT may complement the existing

diagnostic pathway [25]. Although there may be a role in utilisation of MRCP/MRI pancreas to complement CT scan as part of the AIP diagnosis, the inconsistent use of this modality in our series precluded us from making a meaningful conclusion. Advances in endoscopic ultrasonography with both fine-needle aspiration and biopsies may increase the accuracy of diagnosing AIP [26–29]. At present, FNA has significant issues with sensitivity for level 1 histological evidence as low as 7.8% and a significant false positive rate [30, 31].

Only 7.4% of our AIP patients had elevated serum IgG4 levels, which is lower than other series [12, 14, 15, 24, 32]. Although other studies have suggested that elevated IgG4 is a potential differentiating factor between AIP and pancreatic adenocarcinoma, our findings do not support this conclusion [33–35]. Increasing awareness of AIP over the time frame of this study has affected utilisation of biochemical testing and histological staining for IgG4 [35].

This study is limited by ascertainment bias as many patients were identified histologically after resection for suspected pancreatic malignancy and also patients without severe symptoms or complication of chronic pancreatitis may have been managed without referral to our specialist service. Over the time course of this study, there have been advances in both the histological and radiological diagnosis of AIP; therefore, not all patients were exposed to the same diagnostic tests; in particular, earlier patients did not undergo IgG4 serological testing or MRI and PET-CT imaging.

In conclusion, although AIP is a rare pathology that may be more common than previously supposed, it is increasingly recognised and can present as suspected pancreatic malignancy. We would endorse the outcome of the international guidelines that a steroid diagnostic trial for AIP should be used sparingly and with considerable caution [8]. Surgery remains an important treatment option for symptomatic chronic pancreatitis, including AIP that fails to respond to steroid therapy, and for suspected pancreatic cancer [7, 8, 20, 36].

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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