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ORIGINAL ARTICLE

# Autoimmune Pancreatitis, a Single Centre Experience within the United Kingdom

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**ABSTRACT**

**Objective** Autoimmune pancreatitis is a rare form of chronic pancreatitis characterized by a dramatic response to steroids. We describe our single centre experience of autoimmune pancreatitis over a ten-year period. **Methods** Between 2004 and 2014 seventeen patients were treated for Autoimmune Pancreatitis within our institution. Patterns of recurrence and the use of corticosteroid therapy are described. **Results** Seventeen patients with a median age of 61 (29-81) years were identified from a retrospective clinical database review. Extra-pancreatic involvement was common and was seen in eleven of seventeen patients. Nine patients received steroid therapy, two underwent pylorus preserving pancreaticoduodenectomy for presumed malignant disease and six had spontaneously resolving disease. Six patients suffered from relapsing disease. Extra-pancreatic involvement correlated with disease relapse (P=0.0427) however the use of corticosteroids at presentation failed to correlate with disease relapse (P=0.131). **Conclusion** Autoimmune pancreatitis although rare is becoming increasingly recognised in the United Kingdom. Extra-pancreatic features at presentation were common along with spontaneous resolution of disease among our patients. A multidisciplinary approach is recommended to avoid un-necessary surgical intervention or indeed the misdiagnosis of underlying malignancy.

## INTRODUCTION

Autoimmune pancreatitis (AIP) is a distinct rare form of chronic pancreatitis characterized by a dramatic response to steroids [1]. Although the clinical characteristics of the disease were first described in 1961 [2] the term AIP was not coined until 1995 [3]. There are two categories of AIP: Type 1 and Type 2. Type 1 AIP may mimic pancreatic cancer and presents most commonly with painless obstructive jaundice and pancreatic enlargement [4-6]. Type 1 AIP is the pancreatic manifestation of a systemic IgG4-associated disease which may involve other organs such as the biliary tree, retro-peritoneum, kidney's and salivary glands [7]. Patients with Type 2 AIP are generally younger than those with Type 1 and rarely have an elevated serum IgG4 or extra-pancreatic involvement [8]. Response to steroid therapy in patients with AIP is dramatic and consistently leads to clinical improvement regardless of AIP subtype. Disease relapse is however common and occurs in 30% of patients with Type 1 AIP [9]. The role of maintenance therapy to prevent disease relapse (either steroid or immunomodulator) has yet to be clearly defined. It remains unclear whether maintenance therapy should be used on all patients with AIP or restricted to those who relapse at least once [10]. We report our experience in the management of this condition in a large tertiary referral centre for pancreaticobiliary disease in the North of England.

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## METHODS

All patients who were treated for AIP at St James's Teaching Hospital Leeds, a large tertiary referral centre in the North of England who presented between January 2004 and March 2014 were included. Patients were identified following local ethical approval from a prospectively maintained pancreaticobilliary database. Data including age, sex, date of diagnosis, presenting symptoms, presence of exocrine or endocrine insufficiency, extra-pancreatic involvement, serology (IgG4) and follow up data were collected. Pancreatic exocrine insufficiency was defined as the presence of steatorrhoea or a faecal elastase of < 200 μg/g faeces. Impaired glucose tolerance was diagnosed through glucose tolerance testing (blood glucose 7.9–11mmol/L two-hours following ingestion of 75 grams of glucose). All patients were investigated by either computered tomography (CT) or magnetic resonance imaging (MRI). Baseline IgG4 was available for all patients. Selected patients were further investigated by endoscopic retrograde pancreatography (ERCP) and endoscopic ultrasound (EUS) with fine needle aspiration (FNA) where the diagnosis remained unclear. All patients were discussed in a dedicated pancreaticobiliary multidisciplinary team meeting to ensure correct diagnosis.

Selected patients were commenced on prednisolone at an initial dose of 40 mg per day and tapered over a period of 4-6 weeks. Clinical response to treatment was monitored through symptomatic, serological (IgG4) and radiological response. Relapse of AIP was defined as the reappearance of pancreatic or extra-pancreatic involvement after steroid withdrawal. For the purpose of this study patients were classified according to the International Consensus Diagnostic Criteria (ICDC) for AIP [1]. The ICDC criteria are based on core cardinal features, namely pancreatic parenchymal imaging (P), pancreatic ductal imaging (D), serology (S), other organ involvement (OOI), histology (H) and response to steroid therapy (Rt). Criteria are defined by level of evidence. Level 1 parenchymal imaging (typical) is defined as diffuse enlargement with delayed (sometimes rim-like) enhancement with Level 2 (indeterminate including atypical) as segmental/focal enlargement with delayed enhancement. Level 1 ductal imaging (through ERCP) is defined as long (>1/3 length main pancreatic duct) or multiple strictures without marked upstream dilation and level 2 ductal imaging segmental/focal narrowing without marked upstream dilation. Patients with raised IgG4 were divided into those with levels >2 times normal (level 1) or those with levels 1-2 times normal (level 2 evidence).

## RESULTS

### Presentation

Autoimmune pancreatitis was diagnosed in 17 patients during the period Jan 2004 to March 2014. The median age at presentation was 61 (range 29-81) years with a median follow-up of 51 (25-108) months. Fourteen patients were male. The most common presentation was jaundice in thirteen (76%) patients. Abdominal pain and exocrine insufficiency were also common presentations. Extra-pancreatic involvement was seen in 11 patients (65%). Cholangiopathy and lachrimal involvement were the most common extra-pancreatic features **(Table 1)**.

## DIAGNOSIS

All patients were investigated by computered tomography (CT) (N=15) or magnetic resonance imaging (MRI) (N=11). Endoscopic retrograde pancreatography (ERCP) was performed in eleven patients and endoscopic ultrasound (EUS) in five. IgG4 levels at presentation were elevated in eleven (65 %) patients **(Table 1)**. According to the ICDC criteria 13 (76%) were classified as definitive Type 1, one patient definitive Type 2, one probable Type 1, one probable Type 2 and one patient AIP of non-specific type **(Table 1)**. Two patients did not fully meet the IDCD criteria (one patient treated as AIP non-specific type and one patient with probable AIP Type 1) as response to steroids could not be assessed due to spontaneous resolution of disease. Both patients remain disease free at 52 and 44 months respectively.

### Medical Management

Nine of seventeen patient (53%) received corticosteroid therapy. Eight patients (seven with definitive Type 1 and one with probable Type 2 AIP) were treated at disease onset with steroid therapy. All eight patients experienced rapid resolution of symptoms along with normalization of IgG4. Early repeat imaging in six patients (MRI N=2, CT N=2, EUS N=1 and ERCP N=1) confirmed resolution of pancreatic parenchyma and biliary tree findings. Five patients suffered disease recurrence at a median of 18 (2-48) months. All were treated with corticosteroids along with a steroid sparing agent and achieved symptomatic relief and resolution of serology and/or imaging **(Tables 1 and 2)**. One patient received a delayed course of steroids following an initial period of palliation for presumed metastatic pancreatic cancer within a referring centre. Upon resolution of hilar lung changes on CT the diagnosis was questioned. A diagnosis of AIP was confirmed through specialist imaging review along with serology findings. Corticosteroid therapy was commenced with good initial response. Hepaticojejunostomy was however later required for metallic biliary stent extraction due to recurring episodes of biliary sepsis. Despite corticosteroid therapy discontinuation at 33-months (with normal pancreatic parenchyma on imaging along with serum IgG4) recurrence (cholangiopathy) occurred at 41-months. Steroid therapy was complicated by a Cushingoid appearance, vertebral wedge fracture and a bleeding duodenal ulcer. A subsequent trial of cyclophosphamide was discontinued due to thrombocytopenia. Follow up continued up-to 68 months when death occurred due to an unrelated cause.

### Surgical Resection

Surgical resection for presumed malignancy was performed in two patients (12%) Neither patient had typical imaging for AIP or a raised IgG4 at presentation. AIP was diagnosed at post-operative histology following pylorus preserving pancreaticoduodenectomy. Both patients remain well and in remission at 48 and 51 months without corticosteroid therapy **(Table 1)**.

### Expectant Management

Spontaneous resolution occurred in six (35%) patients. Median follow up among this cohort lies at 48 (39-82) months. Four patients were classified as definitive Type one, one probable Type 1 and one AIP non-specific type. Of those with spontaneous resolution, four patients were jaundiced at presentation, three had features of extra-pancreatic involvement and three had raised IgG4 at presentation **(Table 1).** One patient with initial spontaneous resolution of disease (who presented jaundiced with features of extra-pancreatic involvement and raised IgG4) suffered from disease relapse at 65 months. This patient was subsequently treated with corticosteroid induction therapy along with maintenance azathioprine and remains in remission at 82 months **(Table 1).**

### Patterns of Recurrence

Disease recurrence occurred in six patients (33%) at a median time of 29 (2-64) months post diagnosis.

**Table 1.** Epidemiological and clinical findings of patients classified by the international consensus diagnostic criteria.

| Patient Number | Age (Yrs) | Sex | Igg4 | CT/MRI Pancreatic Parenchyma | Pancreatic Duct | Histology | Extra-Pancreatic Manifestation | Treatment | Recurrence (Mths) | Follow-Up (Mths) | ICDU Criteria |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 66 | M | Level 1 | Level 1 | Level 1 | - | Lachrymal, cholangiopathy | Steroids | 18 + 46 | 84 | Definitive type 1 |
| 2 | 44 | M | Level 1 | Level 1 | Level 1 | - | Lachrymal, cholangiopathy | Steroids | 48 + 98 | 108 | Definitive type 1 |
| 3 | 73 | M | Level 1 | Level 1 | - | - | - | Steroids | - | 32 | Definitive type 1 |
| 4 | 42 | F | Level 1 | Level 1 | - | - | Retro-orbital | Steroids | 18 | 25 | Definitive type 1 |
| 5 | 64 | M | Level 1 | Level 1 | Level 1 | AIP | Lachrymal, cholangiopathy | Steroids | 41 | 68 | Definitive type 1 |
| 6 | 77 | M | Level 1 | Level 1 | - | - | Cholangiopathy, retroperitoneal | SR | 65 | 82 | Definitive type 1 |
| 7 | 49 | M | Level 2 | Level 1 | - | - | - | SR | - | 39 | Definitive type 1 |
| 8 | 74 | M | Normal | Level 1 | Normal | - | Cholangiopathy | Steroids, hepaticojejunostomy | - | 68 | Definitive type 1 |
| 9 | 47 | F | Normal | Level 1 | Normal | - | Cholangiopathy | SR | - | 44 | Definitive type 1 |
| 10 | 67 | M | Level 1 | Level 2 | - | - | Lachrymal, cholangiopathy | Steroids | 2 | 45 | Definitive type 1 |
| 11 | 61 | M | Level 1 | Level 2 | Normal | - | Cholangiopathy | Steroids | - | 38 | Definitive type 1 |
| 12 | 81 | M | Level 1 | Level 2 | Level 1 | - | Hilar and mediastinal | SR | - | 81 | Definitive type 1 |
| 13 | 63 | F | Normal | Atypical | Normal | AIP | Lachrymal | Resection (PPPD) | - | 48 | Definitive type 1 |
| 14 | 40 | M | Normal | Atypical | Normal | AIP | - | Resection (PPPD) | - | 51 | Definitive type 2 |
| 15 | 36 | M | Level 1 | Level 2 | - | - | - | SR | - | 44 | Probable type 1 |
| 16 | 29 | M | Normal | Level 1 | Level 1 | - | - | Steroids | - | 51 | Probable type 2 |
| 17 | 30 | M | Normal | Level 1 | Level 1 | - | - | SR | - | 52 | AIP NOS |

AIP autoimmune pancreatitis; ICDU international consensus diagnostic criteria; PPPD pylorus preserving pancreaticoduodenectomy; SR spontaneous resolution

Patients with extra-pancreatic manifestations of disease at presentation were more likely to suffer from disease recurrence (P=0.0427) along with those presenting with a raised IgG4 (P=0.0427). The administration of corticosteroids following diagnosis failed to reach statistical significance for relapse prevention (P=0.131) **(Table 2)**. All six patients with recurrent disease were commenced on a further course of corticosteroid therapy along with an additional agent **(Table 3).** Azathioprim was the choice agent in four patients. Cyclophosphamide and mycophenalate were used in an additional two patients respectively. Two patients with recurrent disease treated with azathioprim at 18 and 48 months experienced a second recurrence at 46 and 96 months respectively.

## DISCUSSION

Autoimmune pancreatitis is becoming increasingly recognised worldwide. This is reflected by the largest series to date, which includes 1064 patients from 23 different institutions [9, 10]. Despite increased recognition worldwide, AIP in the Western hemisphere was rarely reported up until recent times [11]. Within the UK only two case series have been published to date [12, 13]. Church *et al*. (2007) reports eleven male cases of AIP. Extra-pancreatic involvement was apparent in all patients with intra-hepatic strictures seen in eight patients. Severn had elevated IgG4 at presentation. All eleven patients responded to steroid therapy within four weeks. Six patients relapsed within an 18-month follow up [12]. Chatterjee *et al*. (2014) reported twenty-two cases of AIP. IgG4 was elevated in fourteen patients at presentation. Fifteen patients suffered from extra-pancreatic involvement with fourteen presenting with biliary tree (nine intra-hepatic) strictures. Steroids were commenced in eighteen patients with four having self-limiting disease. Relapse was seen in five patients after steroid withdrawal [13].

In keeping with other UK series, extra-pancreatic involvement was common among our cohort of patients. Eleven of seventeen (65%) of patients suffered extra-pancreatic involvement with cholangiopathy being most common. A lower proportion of our patients (53%) were treated with steroid therapy when compared with large series [9]. Six patients (35%) had spontaneously resolving disease and were managed conservatively. Two patients underwent surgical resection for presumed malignant disease. Both patients remain disease free at 48 and 58 months follow up without steroid therapy. It is of interesting note that of 127 subjects with Type 1 AIP treated by surgical resection in a large multi-center series, 125 (98%) achieved remission [9]. Among our cohort of patients with spontaneously resolving disease only one patient experienced disease relapse at 65-months. The use to steroid therapy failed to reach statistical significance for the prevention of disease relapse (P=0.131) among our patients. This is in contrast to findings from a large multicenter study who report that the percent of subjects achieving remission is higher among Type 1 subjects who receive intervention (either steroids or surgery) (99.2%) compared with those managed conservatively (55.2%, p<0.001) [9]. Based on these findings we would

**Table 2.** AIP disease relapse risk according to initial disease presentation.

| Initial AIP presentation | AIP relapse n (%) | AIP no relapse n (%) | P |
|---|---|---|---|
| Age (mean) | 60 | 53 | 0.432 |
| Jaundice | 4 (67) | 9 (82) | 0.584 |
| Abdominal pain | 2 (33) | 5 (45) | 1 |
| Exocrine insufficiency | 2 (33) | 5 (45) | 1 |
| Weight loss | 2 (33) | 6 (54) | 0.612 |
| Raised IgG4 | 6 (100) | 5 (45) | 0.0427 |
| Extra-pancreatic manifestations | 6 (100) | 5 (45) | 0.0427 |
| Initial corticosteroid therapy | 5 (83) | 4 (36) | 0.131 |
| Spontaneous resolution | 1 (17) | 5 (54) | 0.333 |
| Mean follow-up (mths) | 69 | 50 | 0.0919 |

**Table 3.** Management of AIP relapse and duration follow-up.

| Patient number | AIP relapse (mths) | First AIP relapse treatment | Second AIP relapse treatment | Follow-up (mths) |
|---|---|---|---|---|
| 1 | 18 + 46 | Steroids + azathioprim (not tolerated) | Cyclophosphamide pulse + mycophenalate | 84 |
| 2 | 48 + 96 | Steroids + azathioprim | Steroids | 108 |
| 4 | 18 | Steroids + azathioprim | - | 25 |
| 5 | 41 | Steroids + cyclophosphamide pulse | - | 68 |
| 6 | 65 | Steroids + azathioprim | - | 82 |
| 10 | 2 | Steroids + mycophenalate | - | 45 |

not recommend withholding steroid therapy from patients in favor of conservative treatment. Our study sample is indeed small and there was a tendency towards longer follow up among the disease relapse cohort (69 versus 50 months) although this did not reach statistical significance (P=0.0919).

Autoimmune pancreatitis in recent years is becoming increasingly recognized among the UK population. Extra-pancreatic involvement appears as a common presenting feature. The condition is often difficult to diagnose due to overlapping clinical presentation with pancreatic cancer and multi-disciplinary involvement is required to facilitate early diagnosis and limit un-necessary surgical intervention. A clear consensus agreement with regards to steroid and immunomodulation for both induction and maintenance therapy is urgently needed to minimize morbidity.

## Conflicting Interest

The authors had no conflicts of interest

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