

Eosinophilia and Allergic Disorders in Autoimmune Pancreatitis

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- OBJECTIVES:** In autoimmune pancreatitis (AIP), the prevalence, interrelationships, and significance of peripheral eosinophilia, allergic disorders, and eosinophil infiltration in the pancreas remain unclear.
- METHODS:** From medical records, we obtained data on peripheral eosinophil counts at presentation and follow-up, and clinical diagnoses of allergic disorders in 97 AIP patients (78 type 1 and 19 type 2), which were compared with matched healthy controls. Available pancreatic histologic specimens were graded for eosinophils. Peripheral eosinophilia was defined as counts $>0.5 \times 10^9$ per liter. We examined nature of and association between these parameters in AIP.
- RESULTS:** Among 78 type 1 AIP patients (mean age 62 ± 14 years, 77% men), peripheral eosinophilia at presentation was diagnosed in 12% and allergic disorders in 15% (vs. 0 and 4% in controls, $P=0.0004$ and 0.006 , respectively). Allergic disorders were observed in 27 and 11% of type 1 AIP with and without eosinophilia, respectively ($P=0.08$). Patients with and without peripheral eosinophilia were similar in clinical profile. Moderate-to-severe eosinophil infiltration was present in 67% of pancreas resection specimens and did not correlate with peripheral eosinophilia. Type 2 AIP did not differ from type 1 AIP in any of these parameters.
- CONCLUSIONS:** Peripheral eosinophilia, allergic disorders, and pancreatic eosinophil infiltration are associated with AIP. Eosinophilia in AIP may not reflect an allergic phenomenon, but appears to be consistent with autoimmune mechanism.

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INTRODUCTION

Autoimmune pancreatitis (AIP) is an increasingly recognized chronic fibroinflammatory disorder with systemic involvement (1–3). The classically described pancreatic disease closely mimics pancreatic cancer in presentation. Involvement of several extrapancreatic organs has been described in AIP including salivary glands, bile ducts, retroperitoneum, kidneys, lymph nodes, lungs, and liver among others (3–10). Affected organs have a lymphoplasmacytic IgG4-positive infiltrate and fibrosis (11–13). On the basis of systemic manifestations, Kamisawa *et al.* (14,15) proposed the concept of IgG4-related sclerosing disease. Apart from the extrapancreatic organ involvement, several other associations of AIP have been described, such as inflammatory bowel disease (16), Sjogren's syndrome (7), hypothyroidism (5,17,18), and lymphoma (19). It is important to recognize these associations not only because many of these conditions are typically responsive to steroids but also because of their significance in understanding the pathogenesis of AIP.

Peripheral blood eosinophilia in chronic pancreatitis (CP) was first described in 1955 by Juniper (20), and since then several reports have appeared in the literature (20–23). In a large series of CP patients, Wang *et al.* (21) recently reported prevalence of peripheral blood eosinophilia in 15.6% patients and it was significantly higher in AIP patients. Peripheral blood eosinophilia in patients with AIP has been reported in some additional studies (23–28). Kamisawa *et al.* (23) recently reported high prevalence of allergic disorders in AIP. Allergic disorders including asthma have been observed in AIP patients by other groups as well (28–30). Furthermore, the occurrence of eosinophilic infiltrates in pancreas of AIP patients has been described, though with variable estimates of prevalence and severity, in several studies (27,28,31–36) and has also been noted in extrapancreatic organs involved in AIP (10,24,28,37–39). Mild-to-moderate eosinophilic infiltrate was seen in as many as 79% of patients with lymphoplasmacytic sclerosing pancreatitis (LPSP) in one report (28).

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The significance of these findings is unclear. Do eosinophilia and allergic manifestations represent a different subset among AIP patients? Furthermore, two histologic patterns, namely LPSP and idiopathic duct-centric chronic pancreatitis (IDCP), with distinct clinical profiles (referred to as type 1 and type 2) have been recently noted in AIP (31,40–42). Type 1 AIP is the classically described form of AIP associated with IgG4-associated systemic manifestations whereas type 2 AIP appears to be pancreas-specific disease with no association with IgG4 (40–42). The nature of these subtypes in terms of eosinophilia and allergy is not known.

The aim of this study was to clarify the prevalence of and associations among peripheral blood eosinophilia, allergic disorders and pancreatic eosinophil infiltration in AIP, and to examine their clinical and pathologic significance.

METHODS

Case ascertainment and acquisition of data

The study was approved by the Mayo Clinic Institutional Review Board. The diagnosis of AIP was based on the HISORt (Histology, Imaging, Serology, Other organ involvement, Response to therapy) criteria. For obtaining data, we used the database of AIP patients seen at our center, which is maintained prospectively by STC. A total of 19 patients in this database were retrospective diagnoses (between 1985 and 2002) based on resection specimen whereas 59 patients were prospectively diagnosed after 2002. All of these patients were on follow-up in our clinic. Further details of this AIP cohort, including details of follow-up, treatment, and relapse, can be found in another report from our group (43). The electronic records of these patients were reviewed to obtain data on demography, clinical characteristics, laboratory data, and imaging findings. Follow-up eosinophil counts were noted and period of follow-up on eosinophil counts was based on this data.

Controls ($N=100$) were randomly selected from a group of healthy individuals presenting between 1999 and 2001 to the Mayo Clinic. This period was selected due to access and availability of data, and to avoid large temporal separation between controls and the study population. Controls were age- and gender matched. In addition, we also reviewed the records of 19 patients with histologically proven type 2 AIP (IDCP). Among these 19, 12 patients were retrospective diagnoses before 2002 previously reported in Notohara *et al.* (40).

Peripheral blood eosinophilia

Eosinophilia in the peripheral blood was defined as eosinophil count greater than 0.5×10^9 per liter. Eosinophil count at presentation was noted. Follow-up peripheral blood eosinophil counts were also recorded to study the course of eosinophilia, occurrence of new eosinophilia, and response of eosinophilia to steroid treatment. The clinical profile, laboratory data, and imaging features of AIP patients with and without peripheral eosinophilia were compared.

Asthma and allergic disorders

Physician-diagnosed asthma and allergic disorders were considered on the basis of review of electronic records. Allergic

disorders included hay fever and allergic rhinitis in addition to asthma. We analyzed whether presence of asthma and allergic disorders was associated with peripheral blood eosinophilia in AIP.

Histology and grading for eosinophils

Available resection (18) and EUS biopsy (6) specimens of pancreas were reviewed by our pathologist for presence of eosinophils. The pathologist was unaware of the clinical parameters or the peripheral blood eosinophil counts of the respective patients. Number of eosinophils per HPF was counted for five fields and average count was taken. Areas with highest density of eosinophilic infiltrate were evaluated. Average counts ≥ 10 were considered as severe eosinophilia (44), and average counts ≥ 5 but less < 10 were considered as moderate eosinophilia. Because there is no well-defined grading for eosinophils on histology specimen, all absolute counts have been noted either in the tables or in the text. The association between peripheral blood eosinophilia and pancreatic eosinophil infiltration in these patients was examined.

Statistics

Quantitative variables were expressed as mean $\pm$ s.d. and compared using Student's *t*-test. Quantitative variables not satisfying normality assumption were expressed as median (range) and compared using Mann–Whitney test. Correlation between two continuous non-normal variables was analyzed using Spearman's rank correlation. Categorical variables were expressed as percentages and χ^2 -test was used for comparisons. Fisher's exact test was used when one or more expected frequencies were less than 5. Two-tailed *P*-values were reported and $P < 0.05$ was considered as statistically significant.

RESULTS

Prevalence of peripheral blood eosinophilia and allergic disorders

The AIP cohort consisted of 78 patients with mean age 62 ± 14 years. Total 77% percent were men. The control group was similar to AIP cohort in terms of age and gender distribution (Table 1). We compared prevalence of peripheral eosinophilia at presentation and of allergic disorders in AIP with that in controls (Table 1). Among AIP patients, nine (12%) had peripheral eosinophilia at presentation whereas none of the controls had peripheral eosinophilia ($P=0.0004$). Allergic disorders had been diagnosed in 12 (15%) in the AIP group compared with 4 (4%) in the controls ($P=0.006$). Of the AIP patients with allergic disorders, nine had asthma and three had other allergic disorders.

The median follow-up on peripheral eosinophil counts of AIP patients was 28 months (range: 0–176). In addition to peripheral eosinophilia at presentation, 13 additional patients developed peripheral eosinophilia on subsequent follow-up. Thus, 28% of AIP patients in our cohort had peripheral eosinophilia at presentation or during follow-up.

Allergic disorders and eosinophilia in AIP: are they related?

Allergic disorders were present in 6 of 22 (27%) AIP patients with peripheral eosinophilia compared with 6 of 56 (11%) in patients without peripheral eosinophilia ($P=0.08$; Table 2). Among AIP

Table 1. Peripheral blood eosinophilia at presentation and allergic disorders in AIP

	AIP (n=78)	Controls (n=100)	P value
Age (years)	62±14	61±9	>0.5
Gender (M/F)	60/18	76/24	>0.5
Eosinophilia at presentation	9 (12%)	0 (0%)	0.0004
Allergic disorders	12 ^a (15%)	4 (4%)	0.006

AIP, autoimmune pancreatitis; F, female; M, male.

^aNine patients had asthma and three other allergic disorders (allergic rhinitis, hay fever).**Table 2.** Demography and clinical profile of AIP with and without peripheral eosinophilia

	Patients with peripheral eosinophilia (n=22)	Patients without peripheral eosinophilia (n=56)	P value
Age (years)	64.8±11.7	60.7±15.0	0.249
Males/females	16/6	44/12	0.583
AP at presentation	3	9	0.99
Imaging at presentation			0.517
Diffuse swelling	10	21	
Focal features ^a	12	35	
Serum IgG4 elevation	11/15	36/44	0.712
Allergic disorders	6	6	0.087
Diabetes (at last FU)	10	24	0.841
Steatorrhea (at last FU)	9	20	0.671
IAC	20	50	0.99
Proximal BD only	8	22	0.806
Non-IAC other organ involvement	6	22	0.319
Relapse of AIP (stratified by eosinophilia at presentation)	3/9	34/69	0.486

AIP, autoimmune pancreatitis; BD, bile duct; FU, follow-up; IAC, IgG4-associated cholangitis.

^aFocal features included dense focal mass, low-density mass and nonspecific focal findings.

patients with allergic disorders, the absolute eosinophil count at presentation (median (range)) was 0.4×10^9 per liter (0.06–1.08) compared with 0.19×10^9 per liter (0–2.38) in AIP patients without allergic disorders ($P > 0.5$). Hence any likely association between peripheral eosinophilia and presence of allergic manifestations did not reach statistical significance in our cohort.

AIP with and without peripheral blood eosinophilia

We observed no difference between the profiles of AIP with and without peripheral eosinophilia (Table 2). In addition, no correlation was observed between absolute IgG4 counts and peripheral

Table 3. Pancreatic eosinophilia in AIP with and without peripheral blood eosinophilia

	Mean eosinophil counts in examined resection specimens	Moderate-severe eosinophilic infiltrate in pancreas (%)	Mann-Whitney test P value
AIP with peripheral eosinophilia (n=7)	2, 2, 10, 9, 2, 5, 8 (median count: 5)	57	0.39
AIP without peripheral eosinophilia (n=11)	0, 33, 15, 8, 3, 24, 9, 7, 3, 6, 7 (median count: 7)	73	

AIP, autoimmune pancreatitis.

Histology was available for 11 patients with peripheral eosinophilia and was reviewed for presence of pancreatic eosinophilia; histology was also reviewed for 13 AIP patients without peripheral eosinophilia.

blood eosinophil counts at presentation (Spearman's rank correlation $r_s = 0.22$, $P = 0.11$). We did not see any association between peripheral eosinophilia at onset and subsequent relapse (Table 2) even when the comparison was restricted to 53 patients who did not receive surgical treatment (3 of 5 vs. 29 of 48, respectively, among patients with and without peripheral eosinophilia, $P = 0.99$).

Pancreatic eosinophil infiltration in AIP and relationship with peripheral blood eosinophilia

A total of 24 specimens (18 resection, 6 biopsy) of pancreas of AIP patients (11 with peripheral blood eosinophilia and 13 without) were reviewed, blinded to data on peripheral eosinophil counts, for presence of eosinophilic infiltrate and were graded as described in the Methods section (Table 3). The eosinophil counts in the biopsy specimens (mean eosinophil counts in successive biopsies examined: 0, 0, 0, 1, 0, 5) were significantly less than counts obtained from resection specimens (median count 0 vs. 7, $P = 0.003$). This could be potentially related to the nature of EUS biopsies limiting the number of fields available for examination compared with the surgical resections. Moderate-to-severe eosinophilic infiltrate was seen in 13 of 24 (54%) of AIP patients of all specimen examined. However, the prevalence of moderate-to-severe eosinophil infiltration was 12 of 18 (66.7%) in resection specimen. There was no significant difference in eosinophil counts in the resection specimens of patients with and without peripheral eosinophilia (median counts: 5 vs. 7; Table 3). In addition, we did not see any significant correlation between absolute counts for eosinophils in peripheral blood at onset and in resection specimens of pancreas (Spearman's rank correlation $r_s = 0.07$, $P = 0.77$). Also 2 of 12 (17%) patients with moderate-to-severe pancreatic eosinophil infiltration had diagnoses of allergic disorders whereas among 6 patients with no or only mild pancreatic eosinophil infiltration, 1 had allergic disorder (17%) and this was not significant ($P = 0.99$). Figure 1a illustrates severe eosinophil infiltration in the pancreas of a patient with AIP (LPSP).

Response of peripheral eosinophilia to steroid treatment

In our cohort, 13 patients with peripheral eosinophilia received steroid treatment and the course of eosinophilia after steroid

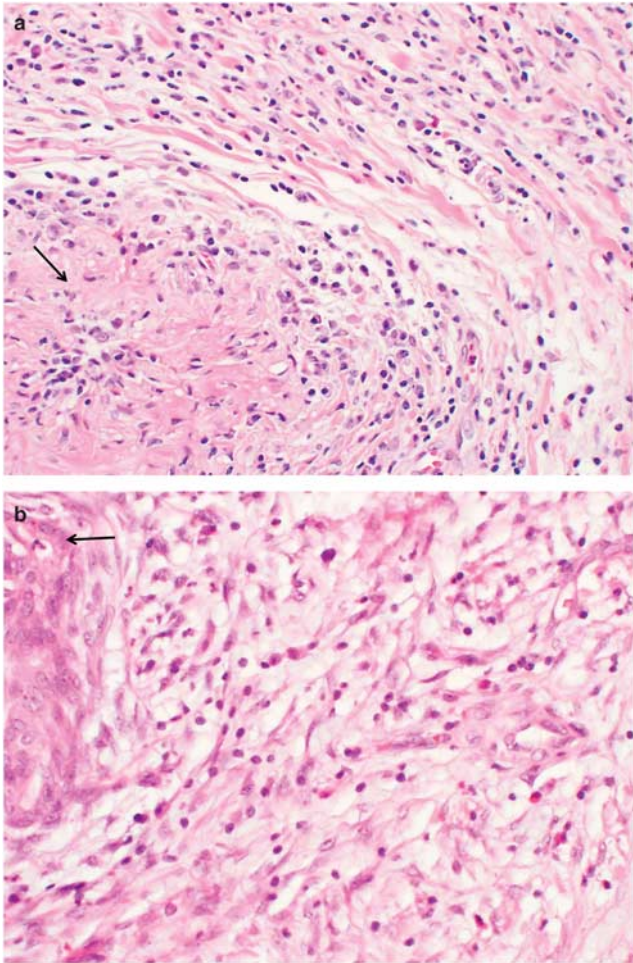


Figure 1. Eosinophil infiltration in the pancreas in autoimmune pancreatitis (AIP). **(a)** Histologic examination of pancreas of a patient with type 1 AIP (lymphoplasmacytic sclerosing pancreatitis, LPSP) showing severe eosinophilic infiltration. Note the presence of lymphoplasmacytic infiltrate in the background and obliterative phlebitis (arrow). **(b)** Histologic examination of pancreas of a patient with type 2 AIP (idiopathic duct-centric chronic pancreatitis, IDCP) showing moderate-to-severe eosinophilic infiltration. Note the granulocytic epithelial lesion (GEL, arrow).

treatment in these patients is summarized in **Table 4**. Of these, in four patients peripheral eosinophilia was observed just before starting steroid therapy. In this group, the eosinophil count normalized in two whereas in one patient, the count decreased but did not normalize. In five patients with peripheral eosinophilia who also received steroid therapy, peripheral eosinophilia was observed for first time after steroid therapy. Among these, four had persistently elevated counts for more than 1 year after stopping steroid therapy.

Eosinophilia and allergic disorders in type 2 AIP (IDCP)

Among 19 patients with histologically proven IDCP, 4 (21%) had peripheral eosinophilia at presentation and 3 (16%) had diagnosis of allergic disorders (compared with 78 LPSP patients, $P=0.77$ and 0.99 , respectively). Pancreatic histology for eosinophils could

Table 4. Course of peripheral eosinophilia following steroid treatment (13 of 22 patients with peripheral eosinophilia received steroids)

Peripheral eosinophilia	n=13	Course during follow-up
Documented just before starting steroid therapy	4	• Normalized in 2 • ↓ But did not normalize in 1 • No follow-up on 1
New following steroid therapy	5	• Persistently ↑ >1 year after stopping steroids in 4 (1 also received azathioprine) • No follow-up on 1
No temporal association with steroid therapy	4	—

be reviewed for eight IDCP patients (all surgical resection specimens). Moderate-to-severe eosinophil infiltration in pancreas was noted in four (50%) patients (mean eosinophil counts were 4, 3, 7, 11, 2, 9, 4, and 6) which is similar to that observed in resection specimens of type 1 patients ($P=0.66$). Of these four patients with moderate-to-severe eosinophilic infiltrates in pancreas, peripheral eosinophilia was observed in two. **Figure 1b** depicts moderate-to-severe eosinophil infiltration in pancreas in a patient with type 2 AIP (IDCP).

DISCUSSION

As the recognition of AIP has increased, several important associations have become apparent. Recently there have been observations made in several independent studies regarding presence of peripheral eosinophilia (21,23–28), allergic disorders (23,28–30), and eosinophilic infiltrates in pancreas (27,28,31–36) and other involved organs (10,24,28,37–39) in patients with AIP. Though these observations have been variably interpreted among studies, the associations between eosinophilia, allergy, and AIP have remained elusive and the clinical and pathologic significance of these findings is not clear. In this study, on the basis of a large cohort of AIP patients seen at our center, we report prevalence of peripheral blood eosinophilia in 28% patients and allergic disorders in 15%. The clinical profile of AIP with and without peripheral eosinophilia appears to be similar. Allergic disorders may not always be present in AIP patients with peripheral blood eosinophilia. Interestingly, moderate-to-severe eosinophilic infiltrates were observed in 66.7% of pancreatic resection specimen examined in our AIP cohort. These however, did not correlate with presence of peripheral blood eosinophilia. Furthermore, the effect of steroid treatment on the course of peripheral eosinophilia in AIP seems to be variable among patients.

When compared with age- and gender-matched control group comprising healthy individuals, AIP patients have significantly higher prevalence of peripheral blood eosinophilia and clinical diagnoses of asthma and allergic disorders. We report the prevalence of peripheral eosinophilia in 28% of AIP patients. In a nationwide survey of AIP in Japan (25), peripheral blood eosinophilia

(>0.5×10⁹ per liter) was prevalent in 21% of AIP patients. Similarly, Abraham *et al.* (28) reported peripheral eosinophilia in 4 of 13 (31%) LPSP cases whereas the prevalence was 5 of 45 (11%) in the Kamisawa *et al.* study (23) and 6 of 14 (43%) in the Wang *et al.* study (21).

We found that AIP patients with peripheral eosinophilia are similar in demography, clinical presentation, laboratory and imaging parameters, and disease relapse to patients without peripheral eosinophilia. Thus, peripheral eosinophilia in AIP is not representative of a distinct subgroup of disease. Moreover, moderate-to-severe eosinophilic infiltrates in pancreas were present in two-thirds of the resection specimens examined. However, presence of eosinophils in the pancreas did not correlate with presence of eosinophilia in the peripheral blood. Lack of correlation between pancreatic eosinophil infiltration and peripheral blood eosinophilia was also noted by Abraham *et al.* (28) and recently by Wang *et al.* (21). Though the reason is unclear, one likely explanation may be temporal separation between histologic sample collection and measurement of eosinophils in the blood. It is likely that the course of peripheral blood eosinophilia is variable in AIP with fluctuations in the absolute counts. A longer follow-up of peripheral eosinophil counts in AIP may reveal higher prevalence of peripheral eosinophilia. This was evident in our study in which only 12% patients had peripheral eosinophilia at presentation whereas the prevalence increased to 28% when data from follow-up were taken into consideration.

We found clinical diagnoses of allergic disorders in 15% of patients in our cohort, which was significantly higher than in the control group. The prevalence of allergic disorders in the control group was 4%, which is expected to be lower than actual population prevalence (estimated 12-month prevalence of self-reported or current asthma was 6.7% in adults in 2004 (45)) due to selection of healthy individuals in the control group with higher proportion of male gender. Nevertheless, AIP is clearly associated with increased prevalence of allergic disorders although the prevalence of 15% of clinician-diagnosed allergic manifestations in our cohort is lower than estimates in other studies, namely Kamisawa *et al.* (23), 20 of 45 (44%) and Abraham *et al.* (28), 10 of 24 (41%). The diagnosis of allergic disorders in both these studies was based on data from patient interview in addition to definitive clinician diagnoses. Both studies (23,28) had a higher proportion of non-asthma allergic manifestations, such as hay fever, that are subject to greater regional and racial variability. In our cohort, 9 of 12 patients with allergic manifestation had asthma.

Blood eosinophilia of extrinsic origin (pathology outside the eosinophils) or reactive eosinophilia is driven by cytokines, most commonly IL-5 (46,47). Allergic disorders are common cause of reactive eosinophilia where allergen-activated T_H2 response is responsible for IL-5 release (46–48). The association of AIP with allergic disorders and peripheral eosinophilia points to a possible relationship between these two manifestations in AIP. In fact, Kamisawa *et al.* (23) found that peripheral eosinophilia was significantly more common in AIP with allergic manifestations

(25 vs. 0% in AIP without allergy, $P=0.013$) and seasonality was observed in the occurrence of “allergic type” AIP. However, in our cohort we could not show significant association between presence of allergic disorders and peripheral eosinophilia or pancreatic eosinophilia.

Kamisawa *et al.* in their study (23) concluded that allergic mechanisms may be closely related to AIP pathogenesis and the “true” autoimmune nature of AIP and ISD was debated. Allergic pathogenesis in AIP was further supported by two arguments (i) findings of upregulated T_H2 cytokine response in tissues of patients with AIP as well as patients with other IgG4-related systemic disease by Zen *et al.* (49), and (ii) association of AIP and ISD with IgG4, which is also seen in atopic diseases (50).

The nature of T_H1/T_H2 balance in AIP is not clear at present although most classical autoimmune diseases show a predominant T_H1 immune response. In contrast to the findings of the Zen *et al.* study (49), Okazaki *et al.* (51) reported increased circulating T_H1 cells and serum level of T_H1 cytokines in AIP. Similarly, Yamamoto *et al.* (52) found higher IFN- γ /IL-4 ratio (IFN- γ and IL-4 are T_H1 and T_H2 cytokines, respectively) in Miculicz’s disease (an IgG4-related lesion) compared with classical Sjogren’s syndrome. Recently, Park *et al.* (41) suggested that T_H1 response induced by self-autoantigens is responsible for initiation of AIP and this response also activates regulatory T cells (Tregs). In this paradigm, evolution of AIP involves activation of T_H2 immune response by Tregs and this response is important for progression of disease.

Tregs secrete IL-10, which is known to switch B cells to IgG4 antibody production (53). IgG4 antibodies, a rare IgG subclass, are seen in addition to AIP, in atopic diseases such as bronchial asthma (50) and some autoimmune diseases such as pemphigus (54). However IgG4 appears to be protective in asthma as evidenced by induction of IgG4 by antigen induction immunotherapy for allergic diseases (50,53). In addition, Tregs are implicated in suppressing allergen-induced T_H2 response in allergic diseases (53). Protective role of Tregs and IgG4 in allergic disorders (in contrast to possible Tregs-induced T_H2 response in AIP) and presence of IgG4 in other nonallergic diseases argues against drawing similarities between pathogenesis of AIP and allergic disorders based on current evidence. Nevertheless, T_H2 response in AIP may be responsible for eosinophilia in blood and tissues.

Eosinophilia is also seen in a number of other autoimmune diseases without clear association with allergy or T_H2 predominant response, such as, systemic sclerosis, eosinophilic fasciitis, primary biliary cirrhosis, Riedel’s thyroiditis, and pemphigus (47). It is possible that other autoimmune mechanisms promoting activation of IL-5-producing T cells may exist in these diseases. However, in the study by Wang *et al.* (21), peripheral eosinophilia was also observed in 22 of 166 non-AIP CP patients (13.2%) and was associated with ascites and pleural effusion, leading the authors to propose serous inflammation due to pancreatic fluid possibly causing eosinophilia. Similarly, in 1992, when AIP was still not recognized, Tokoo *et al.* (22) reported peripheral eosinophilia in 17% of 122 CP patients, which in

retrospect may include AIP cases. We also observed peripheral eosinophilia in 21% of type 2 AIP (IDCP) in our study. This variant of AIP has recently been recognized as a separate clinical entity with a distinct pathogenesis likely not involving IgG4 as in the classical form of AIP (type 1 AIP) (40–42). It may be that exposure of some common pancreatic antigen due to tissue damage in classical AIP and other forms of CP (21,22), including IDCP, may be responsible for peripheral eosinophilia.

A rare cause of eosinophilic infiltration of the pancreas, eosinophilic pancreatitis (EP), with only a few case reports in literature (28,55,56), deserves a mention at this point. Pure eosinophilic infiltration in the absence of the typical lymphocytes observed in AIP is a characteristic of this disease. Unlike AIP, frequent eosinophilic involvement of adjacent organs including biliary tree, duodenum, and other parts of the gastrointestinal tract is observed in EP (28,55–57). The peripheral eosinophil counts in EP are much higher than that observed in our series. Though some overlap between the descriptions of EP and AIP cannot be ruled out, EP does not appear to be a variant of AIP but may be a manifestation of eosinophilic gastroenteritis with multivisceral fibrosis (56,57). None of the AIP patients with eosinophilic involvement in our cohort fits the description of EP.

Our study did not show a definite responsiveness of peripheral eosinophilia to steroid treatment. Though therapy-related eosinophilia cannot be ruled out in five patients in whom fresh peripheral eosinophilia was noted after steroid therapy, it seems unlikely. Only one among these five patients received azathioprine with no demonstrable temporal relationship with occurrence of eosinophilia. In addition, four of these five patients had persistent elevation of eosinophil counts for more than a year, which points against a possible drug-induced reaction. Furthermore, lack of a clear temporal association with steroid treatment in some patients (Table 4) indicates a variable course of peripheral eosinophilia in AIP and that the observed new eosinophilia after steroid treatment in a few patients may be an incidental finding. However, a larger study will be required to assess the effects on peripheral eosinophilia and its responsiveness to steroids in AIP patients.

In conclusion, peripheral eosinophilia and allergic disorders are associated with AIP, with prevalence of about 28 and 15%, respectively. Eosinophil infiltration in the pancreas is common in AIP, seen in two-thirds of resection specimens. Eosinophilia in AIP may not reflect allergic phenomena and may be consistent with an autoimmune mechanism.

CONFLICT OF INTEREST

Guarantor of the article: Suresh T. Chari, MD.

Specific author contributions: Study concept and design: Suresh T. Chari and Raghuwansh P. Sah; statistical analysis, interpretation of data, and paper drafting: Raghuwansh P. Sah and Suresh T. Chari; acquisition of data and review of manuscript: Raghuwansh P. Sah, Rahul Pannala, Suresh T. Chari, and Aravind Sugumar; pathology review: Lizhi Zhang and Rondell P. Graham; administrative support: Suresh T. Chari.

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Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ With increasing recognition of autoimmune pancreatitis (AIP) worldwide, many associations of this disease are becoming evident.
- ✓ Understanding the significance of various associations of AIP will improve our knowledge of the pathogenesis of this disease, which is obscure at present.
- ✓ Isolated reports of peripheral eosinophilia and allergic disorders in AIP and variable accounts of observation of eosinophilic infiltrate in the pancreas combined with our own observation led us to study and characterize these associations in AIP.
- ✓ The possibility of eosinophilic and allergic manifestations in AIP has important implications in our current understanding of pathogenesis of AIP and of autoimmune diseases in general.

WHAT IS NEW HERE

- ✓ AIP is associated with peripheral eosinophilia and allergic disorders, with prevalences of 28 and 15%, respectively.
- ✓ Patients with and without peripheral eosinophilia have similar clinical profiles.
- ✓ Moderate-to-severe eosinophil infiltration in the pancreas is common in AIP, observed in two-thirds of resection specimens.
- ✓ Eosinophilia in AIP may not reflect an allergic phenomenon, and appears to be consistent with an autoimmune mechanism.

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