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Original Research Article

Relevance of peripheral eosinophilia in chronic pancreatitis

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ABSTRACT

Background: Eosinophilia in peripheral blood has been observed in few patients with chronic pancreatitis (CP) but the clinical significance and the causes are not well understood. The aim was to analyse the features of CP in patients with and without eosinophilia and compare both groups and assess its significance.
Methods: All patients diagnosed to have CP during period June 2009 to July 2012 were included in the study. Patients were divided into two groups based on eosinophil count in peripheral blood. Those with eosinophil count >0.6x109/L (6%) were considered as having eosinophilia. Author had analyzed and compared the clinical features of CP in patients with and without eosinophilia.
Results: There were 28 (24.56%) patients with eosinophilia among 114 CP patients. Mean age at presentation was similar in two groups. The male to female ratio was significantly higher in patients with eosinophilia (p=0.03). Patients with eosinophilia had higher incidence of pancreas enlargement (78.57% vs. 37.2%, p=0.007). Mean intraductal pressures (20.42 vs. 22.52; p=0.05) and average pancreatic ductal diameter (7.85 vs. 8.90; p=0.03) were lower in patients with eosinophilia. The incidence of complications was significantly more in patients with eosinophilia (85.71% vs. 20.93%; p=<0.001). There was no infiltration of eosinophils in all the pancreatic tissue samples analysed in both groups.
Conclusions: Association of eosinophilia with CP is a relatively common entity. It is associated with significantly increased incidence of disease related inflammatory complications, but the exact mechanism is not clear. Whether eosinophilia is a cause or effect of complication is not clear.

Keywords: Autoimmune pancreatitis, Chronic pancreatitis, Eosinophilia, Eosinophilic pancreatitis, Intraductal pressures

INTRODUCTION

Chronic pancreatitis (CP) is defined as a progressive inflammatory disease characterized by irreversible morphologic changes that typically cause pain and/or permanent loss of function.[1] The occurrence of peripheral eosinophilia in CP has been noticed but it is overlooked. The importance of this occurrence is not evaluated. There are few studies in literature which have evaluated the incidence and significance of peripheral eosinophilia in CP.[2,3] Many hypotheses have been suggested. The study by Wang Q et al, concluded peripheral eosinophilia may be related to autoimmune mechanisms, serous membrane response or the progression of pancreatic inflammation

and fibrosis.[2] In a study by Tokoo M et al, peripheral eosinophilia of CP frequently developed in association with severe damage to neighboring organs (pleural effusion, pericarditis, and ascites) as well as in association with pancreatic pseudocyst.[3] They suggest that there is a close correlation between marked eosinophilia and severe tissue injury during acute exacerbations of chronic pancreatitis. A possible explanation for this is that local pancreatic inflammation might induce degranulation of mast cells and release of eosinophilic chemotactic factor A, which would then stimulate the development of eosinophilia. Hence, in this study, author had analyzed all the patients with chronic pancreatitis who presented with peripheral eosinophilia to determine its relevance.

METHODS

All the patients diagnosed to have CP and admitted for surgery during the period June 2009 to July 2012 were included in the study. Demographic characteristics were recorded. Etiology was considered Alcohol if patient consumes alcohol >80g/day for more than 5yrs.[4] Rest were considered as nonalcoholic. Severity of pain was assessed using an established scoring system (Izbicki). Baseline haematological and biochemical investigations were done. Patients were assessed clinically for exocrine and endocrine dysfunction. They were considered to have exocrine dysfunction if they have loose, greasy, foul smelling stools that are difficult to flush which constitutes steatorrhea. No laboratory criteria were used to assess exocrine insufficiency. Endocrine insufficiency was considered if they were diabetic on oral hypoglycemic agents or on insulin therapy. In not diagnosed as diabetes mellitus previously, further assessment was done using Oral Glucose Tolerance Test (OGTT). Patients with abnormal OGTT were considered diabetic. CA 19-9 was considered elevated if it was >37U/ml. Serum amylase was considered elevated if it was more than 3 times the normal laboratory value. Patients were divided into two groups based on eosinophil count in peripheral smear. Those with eosinophil count >0.6x109/L (6%) were considered as having eosinophilia. All patients with peripheral eosinophilia underwent evaluation to rule out common causes eosinophilia by history and stool examination.

All patients underwent contrast CT scan abdomen for evaluation of the pancreas. Imaging characteristics of the gland was noted in terms of size of the gland, diameter of main pancreatic duct (MPD), ductal or parenchymal calcifications. Gland was considered enlarged if the anteroposterior diameter was >3cm in head or the anteroposterior diameter >2.5cm in body and tail.[5] Complications of CP such as duodenal or biliary obstruction, splenic or portal vein thrombosis, pleural effusions and ascites were noted if present. All patients underwent definitive surgery based on the morphology of the gland. Intraoperatively, intraductal pressures were measured by inserting a 24G needle into the main pancreatic duct and connecting it to the saline filled pressure transducer. Pancreatic tissue was sent for histopathology in all patients and specimens were assessed for any eosinophilic infiltration and rule out malignancy. Author had analyzed and compared the clinical features of CP in patients with and without eosinophilia. Continuous variables were expressed as mean±SD. Statistical analysis of differences was assessed by Fisher exact test, Student t-test and the Mann-Whitney U test as applicable. P value of <0.05 was accepted as statistically significant.

RESULTS

A total of 114 patients were included in the study. There were 28 (24.56%) patients with peripheral eosinophilia. The characteristics of the patients treated in each group are shown in Table 1.

Table 1: Patient characteristics.

Characteristics	With eosinophilia	Without eosinophilia	P value
No. of patients	28 (24.56%)	86 (75.43%)	<0.001
Mean age	33.14 (±13.05)	33.44 (±13.99)	0.90
Male:female	24:4 (6.00:1)	46 :40 (1.15:1.00)	0.03
Etiology-alcoholic	14 (50.00%)	24 (27.91%)	0.13
Mean pain scores	51.26 ± 7.28	47.61 ±6.83	0.76
Steatorrhea	6 (21.42%)	16 (18.60%)	0.82
Diabetes mellitus	6 (21.42%)	36 (41.86%)	0.18
Average ductal diameter (mm)	7.85 (±3.03)	8.90 (±2.33)	0.03
Calcifications	28 (100%)	86 (100%)	1.00
Enlargement of pancreas	22 (78.57%)	32 (37.20%)	0.007
Mean intraductal pressures (mm of saline)	20.42 (±5.40)	22.52 (±5.61)	0.05
Elevated CA 19-9	6 (21.42%)	14 (16.27%)	0.65
Elevated amylase	16 (57.14%)	26 (30.23%)	0.07
Complications	24 (85.71%)	18 (20.93%)	<0.001

The male to female ratio was significantly higher in patients with eosinophilia (p=0.03). Patients with eosinophilia had higher incidence of pancreas enlargement on CT scan (78.57% vs. 37.2%, p=0.007). The average ductal diameter (7.85 versus 8.90; p=0.03) and mean intraductal pressures measured intraoperatively (20.42 vs. 22.52; p=0.05) were lower in patients with eosinophilia. The overall incidence of complications in the study group was 36.84% (42/114 patients). Of these, 36 (31.57%) were inflammatory and 6 (5.26%) were malignant. 12 (10.52%) patients had more than one complication. The incidence of disease related complications was significantly more in patients with eosinophilia (85.71% vs. 20.93%; p=<0.001).

Comparison of complications in two groups is shown in Table 2. The incidence of pseudocyst (p=0.007), biliary obstruction (p=0.01), duodenal obstruction (p=0.01), Splanchnic vein thrombosis (p=0.003), pleural effusions (p=0.002) and pancreatic ascites (p=0.002) were significantly higher in patients with eosinophilia. None of the 6 patients with malignancy had associated peripheral eosinophilia.

Table 2: Complications in patients with and without eosinophilia.

Complications	With eosinophilia	Without eosinophilia	P value
Pseudocysts	10 (35.71%)	6 (6.97%)	0.007
Biliary obstruction	8 (28.57%)	4 (4.65%)	0.01
Duodenal obstruction	4 (14.28%)	0 (0.00%)	0.01
SV/PV thrombosis	8 (28.75%)	2 (2.32%)	0.003
Pleural effusion	6 (21.42%)	0 (0.00%)	0.002
Pancreatic ascites	6 (21.42%)	0 (0.00%)	0.002

The mean pain score, etiology of CP, exocrine and endocrine insufficiency, calcifications in the gland, CA 19-9 and amylase values did not differ significantly in two groups. Histopathological assessment of all pathological specimens in patients with eosinophilia showed no evidence of eosinophilic infiltration of pancreas. On assessment of factors affecting eosinophilia, only three factors were found to be significantly associated with (Table 3).

Table 3: Factors affecting eosinophilia.

Factors (n=114)		Eosinophilia (n=28)	P value
Sex	Male (n=70)	24 (34.3%)	0.0009
	Female (n=44)	4 (9.09%)	
Size of the gland	Enlarged (n=54)	22 (40.7%)	0.007
	Atrophic (n=60)	6 (10.0%)	
Compli-cations	Present (n=42)	24 (57.14%)	<0.001
	Absent (n=72)	4 (5.55%)	

Males patients with CP had significantly higher incidence of eosinophilia (p=0.0009). Majority of patients with eosinophilia had their pancreas enlarged rather than atrophy (p=0.007). Inflammatory complications were higher in patients with CP with eosinophilia (p <0.001). On multivariate analysis, only presence of complications was associated with eosinophilia (adjusted odds ratio for presence of complications was 0.07 (95% CI: 0.01, 0.39) (Table 4).

Table 4: Multivariate analysis of factors affecting eosinophilia.

Factors	Odds ratio	Std. error	Z	P>|Z|	(95% CI)	
Sex	0.423744	0.4095945	-0.89	0.374	0.0637272	2.817617
Enlargement	0.3484486	0.2962777	-1.24	0.215	0.0658237	1.844571
Complications	0.0685971	0.0606219	-3.03	0.002	0.0121357	0.3877438

DISCUSSION

Eosinophilia is defined as an increase in the eosinophil count or an increase in the eosinophil percentage in the peripheral blood. Common causes of eosinophilia include allergic disease, infectious disease (especially parasitic infection), haematological disease, drug induced and tumors.[6] Several pancreatic diseases are reported to have association with peripheral eosinophilia which includes chronic pancreatitis, acute pancreatitis, autoimmune pancreatitis, eosinophilic pancreatitis and malignancy.[2,7-10] Peripheral eosinophilia in chronic pancreatitis can be classified as two types. In the first instance, peripheral eosinophilia is associated with infiltration of pancreatic gland with eosinophils (eosinophilic pancreatitis). It is a very rare form with only few cases reported in literature.[11,12] In the second instance, which is a more common form, peripheral eosinophilia is not associated with eosinophilic infiltration of pancreas.

Eosinophilic pancreatitis (EP) is a rare form of chronic pancreatitis characterized by localized or diffuse eosinophilic infiltration of the pancreas. It is associated with elevated serum immunoglobulin (Ig) E levels. The mechanism has not been elucidated. It is postulated that the eosinophils may cause pancreatitis due to a direct toxic effect via cytotoxic and proinflammatory mediators. 13 EP is usually associated with eosinophilic gastroenteritis or hyper-eosinophilic syndrome.[11] It is difficult to distinguish from pancreatic cancer and autoimmune pancreatitis (AIP) by clinical or radiological findings.[12] EP can be differentiated from malignancy based on tumor markers preoperatively and postoperatively by histopathology. AIP can be differentiated by histopathology and serological tests based on HISORt criteria.[14] In EP, inflammatory infiltrate of pancreas mainly consists of eosinophils whereas in AP it is mainly lymphocytes. EP is associated with an increase in IgE levels in the peripheral blood, whereas patients with AP exhibit elevated IgG4 levels. Management of a diagnosed case of EP is mainly medical with steroids. Surgery is indicated only in complicated EP such as biliary obstruction or pancreatic head mass. Association of peripheral eosinophilia with chronic pancreatitis without obvious eosinophilic infiltration of pancreas is a more common entity. Eosinophilia in these

patients may be more of a secondary phenomenon due to serous membrane response due to stimulation of serosa by pancreatic fluid causing inflammatory response.[2] It may also be due to severe injury to adjacent organs.[3] Another hypothesis is that local pancreatic inflammation might induce degranulation of mast cells and release of eosinophilic chemotactic factor A, which would then stimulate the development of eosinophilia.[15] In this study, nearly one fourth of patients with CP had peripheral eosinophilia which was higher than other reported studies (15.6% and 17.2%).[2,3] Higher incidence in the present study may be due to inability to completely rule out other causes of peripheral eosinophilia. Males with CP had higher incidence of eosinophilia, whereas alcohol had no association.

Pancreatic gland characteristics in patients with eosinophilia were different from those without eosinophilia. Pancreas was enlarged rather than atrophic, ductal dilatations was less and mean intraductal pressures were low in patients with eosinophilia. The incidence of inflammatory complications was significantly high in patients with eosinophilia. The incidence of pseudocyst (p=0.007), biliary obstruction (p=0.01), duodenal obstruction (p=0.01), splanchnic vein thrombosis (p=0.003), pleural effusions (p=0.002) and pancreatic ascites (p=0.002) were significantly higher in patients with eosinophilia. None of the patients with eosinophilia had malignancy.

Almost similar findings were reported in the study by Wang Q et al, where none of the 28 patients with eosinophilia had malignancy.[2] In the study by Tokoo et al, only pseudocysts, pleural effusion and ascites are more common among eosinophilic patients.[3] Only pancreatic ascites (p=0.009) and jaundice (p=0.001) were more common among eosinophilic patients in the study by Wang Q et al.[2] As all patients had disease related complications at the time of presentation, it was not possible to assess whether eosinophilia preceded the complication or followed the complication.

CONCLUSION

Association of peripheral eosinophilia with chronic pancreatitis is a relatively common entity. It is associated with significantly increased incidence of disease related inflammatory complications but the exact mechanism by which this phenomenon occurs was not clear. Whether eosinophilia was cause or effect of inflammatory complications was not clear and needs further studies.

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