Eosinophilic pancreatitis: a rare or unexplored disease entity?

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Abstract

Several case reports show accumulation of eosinophils in pancreatitis patients and term the disease as “eosinophilic pancreatitis (EP)”. EP usually presents with a pancreatic tumour and abdominal pain in obstructive jaundice, which is generally not diagnosed until the patient undergoes pancreatic resection. Histologically, EP reveals distinct patterns like diffused, periductal, acinar, and septal inflammatory infiltrates with eosinophils, eosinophilic phlebitis, and localised extreme eosinophilic infiltrates related with pseudocyst formation. EP patients also have elevated serum IgE levels with high eosinophil counts in the pancreas as well as in other organs such as the gastrointestinal tract, which is termed as eosinophilic gastroenteritis. Due to the lack of knowledge based on just a few case reports, it is considered that eosinophilic infiltration is quite rare in the pancreas; therefore, the significance of eosinophils in pancreatitis is not yet established. This review assesses the current understanding of eosinophilic pancreatitis and the important role of eosinophils in promoting pancreatic fibrosis including malignancy.

Introduction

Pancreatitis is a disease defined as an acute or chronic inflammatory process of the pancreas and characterised by the induced pro-inflammatory cytokines, chemokines and tissue recruitment of inflammatory cells, including monocytes, macrophages, and eosinophils [1–5]. Eosinophils are immune cells, and they play a key role in the mucosal immune system of the gastrointestinal tract during normal and inflammatory conditions. In normal conditions, the mucoza of the digestive tract is the only organ harbouring a substantial number of eosinophils that exert several effector and immunoregulatory functions [6]. Eosinophilic pancreatitis is a rare disease during chronic pancreatitis, and it is characterised by local or diffused infiltration of eosinophils into the pancreas. However, pancreatic infiltration with eosinophils has been reported with many aetiologies including lymphoplasmacytic sclerosing pancreatitis (LPSP), pancreatic allograft rejection, pancreatic pseudocyst, inflammatory myofibroblastic tumour, and histiocytosis X [7]. The first case of peripheral blood eosinophilia in a patient with chronic relapsing pancreatitis with pleural effusion was reported in 1955 [8]. Subsequently, several cases reports described eosinophils accumulation in pancreatitis patients and the diseases was termed eosinophilic pancreatitis (EP) [9–13]. Abraham et al. described two different histological patterns in patients with eosinophilic pancreatitis: 1) a diffuse periductal, acinar, and septal eosinophilic infiltrate with eosinophilic phlebitis and arteritis; and 2) localised intense eosinophilic infiltrates associated with pseudocyst formation [7]. Additionally, a case report diagnosed pleural effusion-associated eosinophilia in the pancreas following the execution of pancreatic resection [14]. EP is also more frequently reported in adults with malignancy in humans [15], parasitic infection in dogs [16, 17], nematodes infection in horses [18], and scorpion toxin-induced eosinophilic pancreatitis in rats [19].
Although eosinophil accumulation in the pancreas has been reported in several species including humans, it has not been given much attention by healthcare providers. As per our understanding, most of the human pancreatic cancer biopsies were performed by endoscopic retrograde cholangiopancreatography (ERCP), i.e., endoscopic ultrasound with fine needle aspirate procedure. Notably, these methods did not provide sufficient tissue for pathological examination. Therefore, EP in these patients may not be detected in most hospitals and clinics. Hence, the possibility of the role of eosinophils in pancreaticis pathogenesis is unnoticed and designated as a rare disease.

**Diagnosis of eosinophilic pancreatitis (EP)**

The diagnosis of eosinophilic pancreatitis is important and difficult [20] because it can mimic a pancreatic neoplasm [21] and is associated with eosinophilic gastroenteritis [10, 22–29] and hypereosinophilic syndrome [30]. Eosinophil-associated pancreatic disorders mainly include eosinophilic pancreatitis [31, 32], pancreatic cancer [33], and autoimmune pancreatitis [34]. The real diagnosis of EP is very important and is made after the exclusion of parasitic infections and other gastrointestinal symptoms that exhibit marked eosinophilic infiltration in pathological samples [25, 35]. However, some cases of pancreatic cancer have been associated with marked eosinophilia [21, 33]; therefore, due to several similar clinical symptoms, features, and imaging results, sometimes EP is misdiagnosed as pancreatic cancer and is often treated surgically [14, 17, 36, 37].

There is evidence indicating that eosinophilic pancreatitis is frequently diagnosed only after “false positive” pancreatic resection for suspected pancreatic tumour, and eosinophilic pancreatitis can mimic a pancreatic neoplasm [10, 11, 37].

**Eosinophilic infiltration in acute pancreatitis and its association with eosinophilic gastroenteritis**

Eosinophil accumulation in the human pancreas is reported along with eosinophilic gastroenteritis (EG) [22–24] and idiopathic hypereosinophilic syndrome (IHS) [29, 30]. A case report of 38-year-old woman revealed peripheral eosinophilia in association with acute pancreatitis [38]. Baek et al. [28] reported a 68-year-old patient with EG presenting with concurrent acute pancreatitis. Notably, the laboratory findings also indicated increased peripheral blood eosinophil count (18.4%) along with high serum level of amylase and lipase. After treatment with oral prednisolone and montelukast, the eosinophil count normalised and the upper abdominal pain was reduced [28]. Food allergy is implicated one of the reasons for EP-associated EG, and clinical reports indicate eosinophilic gastroenteritis-associated EP is due to egg [39] and cow’s milk allergy [27]. However, several case reports also suggest that EP occurs without peripheral or any other gastrointestinal segment eosinophilia. A case report of 44-year-old man showed eosinophilic pancreatitis after pancreatic resection for recurrent attack of acute pancreatitis. Lab testing after 8 h indicates an eosinophil count of 8.5% (reference: 0–8%) and an absolute eosinophil count of \(0.53 \times 10^3/\mu l\) (reference: \(0.3–0.46 \times 10^3/\mu l\)). The patient has only minimal peripheral eosinophilia, no reported history of symptoms related to elevated eosinophilia or immunoglobulin (Ig) E, and only mild eosinophilic infiltrates in his gallbladder [13]. Therefore, EG may be considered in the differential diagnosis of unexplained acute pancreatitis, especially in a patient with duodenal oedema on imaging or peripheral eosinophilia.

**Eosinophil infiltration in human chronic pancreatitis**

The association between chronic pancreatitis and increased number of eosinophils in peripheral blood was first reported in 1955 [8], followed by several case reports that implicated eosinophil accumulation during the pathogenesis of chronic pancreatitis [40–42]. Interestingly, an earlier report showed the presence of large numbers of eosinophils in the peripheral blood of chronic pancreatitis. The study included 122 patients with chronic pancreatitis, in which 17.2% patients (21 patients) had marked blood eosinophilia [41], and most importantly all of these patients were males; whereas, no females were found to be affected. Notably, these eosinophilic pancreatitis patients had marked exocrine pancreatic dysfunction but normal endocrine pancreatic function. The eosinophilic of chronic pancreatitis patients frequently led to severe damage to the neighbouring organs (pleural effusion, pericarditis, and ascites), as well as in association with pancreatic pseudocyst [41]. This study indicates that there may be close correlation between marked eosinophilia and severe tissue injury during acute exacerbations of chronic pancreatitis. Another study of 180 chronic pancreatitis patients revealed 28 (15.6%) patients with eosinophilia and the ratio of male to female patients was 8.3 : 1. Both these reports indicate that eosinophilic pancreatitis is a male dominated disease. Interestingly, no significant difference in the incidence of eosinophilia between alcoholic and nonalcoholic pancreatitis patients was observed [42]. Notably, the role of eosinophils has
been ignored and overlooked in promoting chronic pancreatitis. Nevertheless, the incidence of eosinophilia in autoimmune pancreatitis (AIP) patients was significantly higher than that in non-AIP CP patients. The occurrence of eosinophils was also reported in autoimmune pancreatitis, and reports indicated peripheral eosinophilia, allergic disorders, and pancreatic eosinophils associated with AIP [34, 43]. Recently, a study reported three eosinophilic pancreatitis patients who underwent pancreateoduodenectomy due to a preoperative diagnosis of cancer of the pancreatic head or choledochal cancer [17]. Therefore, the occurrence of eosinophils during the course of CP might be responsible for pancreatic inflammation, fibrosis, and the progression of pancreatic cancer and need further attention.

**Eosinophilic pancreatitis in the infants of diabetic mothers**

Eosinophilic pancreatitis is reported even in infants born from diabetic mothers [44–46]. EP was reported in the newly born infant of a diabetic mother for the first time in 1965 [45]. EP is reported in a premature female infant born to a diabetic mother who died from progressive respiratory distress [44]. Furthermore, eosinophils in the pancreas were also reported in the 34-week-old fetus of a type I diabetic mother. The pancreas of the foetus was grossly remarkable, and histological inspection demonstrated an eosinophilic infiltrate in the fibrous septae and islets of Langerhans along with hypertrophy and hyperplasia of the pancreatic islets [46], which was mechanistically reported to the formation of maternal IgG autoantibodies against insulin.

**Eosinophilic pancreatitis (EP) versus autoimmune pancreatitis (AIP)**

Autoimmune pancreatitis is difficult to distinguish from EP because of their similar clinical symptoms. The most important features that may be used for differential diagnosis of EP and AIP are histopathological changes like diffused eosinophilic infiltration of the pancreatic ducts, acini, and interstitium; the inflammatory infiltrate of the pancreas is mainly composed of eosinophils in EP whereas the lesions of autoimmune pancreatitis are mainly infiltrated by the presence of lymphocytes rather than eosinophils [7]. EP is generally associated with high IgE levels in serum, whereas patients with AIP have elevated IgG4 levels. Patients with AIP generally give a positive test for autoimmune and antinuclear antibodies and have an enlarged (sausage-like) pancreas rather than enlargement of the pancreatic head or tail [17].

**Mechanism of eosinophil accumulation during pancreatitis**

Eosinophil infiltration and accumulation is reported in pancreatitis; however, the mechanisms underlying eosinophilic infiltration are not understood and are yet to be explored. A study has shown the involvement of STAT6 signalling pathway in the activation of eosinophil specific chemokine eotaxin-3 in human pancreatic myofibroblasts. Eotaxin-3 expression was induced by T helper type 2 (Th2) cytokines interleukin-4 (IL-4) and IL-13, which play an important role in inducing the expression of eotaxin-3. Therefore, pancreatic myofibroblasts may be a cellular source of eotaxin-3 in the pancreas [47]. We recently reported induced eosinophil accumulation and degranulation followed by increased mast cells and acinar cell atrophy in the pancreas of a caerulein-induced murine model of pancreatitis. Additionally, our report also demonstrates induced transcript and protein levels of pro-inflammatory and pro-fibrotic cytokines (IL-5, IL-18) and chemokines (eotaxin-1 and eotaxin-2) in experimental pancreatitis in mice. Mechanistically, we showed a critical role of eosinophils using eosinophil-deficient GATA1 and endogenous IL-5-deficient mice that were protected from the induction of proinflammatory and profibrotic cytokines, chemokines, and tissue eosinophilia in a caerulein-induced murine model of pancreatitis [31]. Furthermore, our extended studies in human pancreatitis and malignant patients indicated the induced accumulation and degranulation of eosinophils, and mast cells in the progression of pancreatic malignancy [33]. In conclusion, these experimental and translational studies suggest that the occurrence of eosinophilia during the course of chronic pancreatitis is related to the progression of pancreatitis pathogenesis including fibrosis and malignancy in human.

**Current treatment options for EP**

There are very few cases of EP reported in the literature, despite the fact that the appropriate diagnosis of EP is very important to treat it properly. The non-invasive treatment options should be preferred for EP, which preserve pancreatic function and minimize the impact on the patients’ quality of life. Current treatment options for EP are based on a steroidal approach, i.e. 40–60 mg daily, can prevent recurrent attacks, and avoiding unnecessary surgical interventions. However, these steroidal approaches may have some adverse effects. Therefore, several non-steroid drugs can be used as a treatment option for EP, such as cromolyn, montelukast, hydroxyurea, azathioprine, and ketotifen [10, 13]. Proper treatment of EP can restrict the progression
of other associated disease conditions such as eosinophilic gastroenteritis and hypereosinophilic syndrome. Furthermore, it is very important to follow up these EP patients with their eosinophil count, immunoglobulin E levels, and biopsies of other gastrointestinal sites may be warranted.

Conclusions and future prospects
The current review provides available details on the significance of eosinophils in the pathogenesis of pancreatitis, which is termed as a rare disease. This summarised report indicates that EP may not be a rare disease but rather an ignored or unexplored entity. Several clinical reports indicate that induced eosinophil infiltration in pancreatic patient pancreatic biopsies and suggest that eosinophilic pancreatitis mimics the pancreatic neoplasia because a number of eosinophils are detected in pancreatic tumours. We state that the possibility of eosinophil accumulation in the pancreas may not be noticed because most pancreatic biopsies are performed using endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound with fine needle aspirate, with the purpose of detecting only pancreatic malignancy. We feel that fine needle aspirate procedures do not provide sufficient tissue for pathological examination; therefore, EP is not detected and is ignored. Our recent findings indicate: (i) the role of eosinophils in the progression of chronic pancreatitis and fibrosis in an experimental mouse model [31]; and (ii) eosinophils degranulation promotes human pancreatic malignancy [33] indicating that indeed eosinophilic pancreatitis may be an independent disease entity that needs further investigation. Therefore, EP requires appropriate attention to understand the mechanism of eosinophil accumulation during pancreatitis and pancreatic fibrosis including malignancy.

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Conflict of interest
The authors declare no conflict of interest.

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