



REVIEW

Eosinophilic pancreatitis: a review of the pathophysiology, diagnosis, and treatment

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Abstract

Eosinophilic pancreatitis (EP) is an extremely rare disease caused by purely eosinophilic infiltration of the pancreas. EP is prone to being misdiagnosed as pancreatic cancer, causing unnecessary economic and physical harm to the patient. We report three cases of EP that were cured by steroids without relapse from 2017 to now. The clinical data of the three patients, including clinical manifestations, serological manifestations, imaging (ultrasound, computed tomography, and MRI), pathological diagnosis and treatment, and telephone follow-up of all patients, were retrospectively analysed. In addition, a literature search was conducted on the Web of Science and PubMed databases using key terms related to EP, considering case reports with no restrictions on the date of publication or language. In conclusion, we analysed 19 cases and determined the diagnostic criteria for EP. The diagnostic algorithm for EP can be used to diagnose EP easily. We hope that our standards and algorithm can reduce the rate of misdiagnosis and contribute to clinical diagnosis and treatment. In addition, we expect to evaluate more EP cases to test our diagnostic criteria and design a systematic diagnostic flow chart.

Key words: eosinophilic pancreatitis; rare disease; diagnostic criteria; mechanism diagram; systematic diagnostic flowchart

Background

Eosinophilic pancreatitis (EP) is characterized by a purely eosinophilic systemic infiltrate [1]. It is associated with elevated immunoglobulin E (IgE) levels, hypereosinophilia, and eosinophilic infiltrates in other organs [2]. EP is a rare disorder, with only 16 case reports in 40 years. The incidence of an increased number of eosinophils is <1% in all pancreatic specimens, as described in the files from the John Hopkins Hospital [1]. EP was first described in 1978 by G. Barresi as acute eosinophilic insulinitis [3].

In the pancreas of the newborn of a diabetic mother, an eosinophilic infiltrate surrounding the islets and perivascular and periductular connective tissue was identified [3]. Eosinophil accumulation occurs in human pancreatitis more than with normal pancreatic tissue [4]. Typical presenting symptoms of EP include abdominal or mid-back pain and obstructive jaundice that mimic the presentation of pancreatic cancer [1, 2, 5–11]. Distinguishing between EP and pancreatic cancer is crucial because the treatments and prognoses of the two diseases are

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very different. Manohar et al. [12] showed that eosinophilia is related to the progression of pancreatitis, including fibrosis and malignancy in humans. Pancreatic ductal adenocarcinoma is one of the deadliest malignant tumors with a 5-year survival rate of <6% [13]. Surgery is the cornerstone for decreasing perioperative morbidity and mortality [14], but it is unnecessary for EP patients. In all of the previously reported cases, eosinophilic infiltration of the pancreas was frequently noted after autopsy or pancreatic resection in patients with a suspected pancreatic tumor [1–3, 5–10]. In general clinical work, pancreatic tissue is obtained by surgical resection or biopsy. The disadvantages of both approaches can be divided into several groups: (i) the patient's physical condition is so poor that he or she cannot undergo pancreatic surgery or pancreatic needle biopsy; (ii) some medical institutions do not have the ability to perform pancreatic puncture; and (iii) the patient is not willing to accept any invasive examination. Therefore, there is an urgent need for clinical diagnostic criteria that not only protect patients from surgical trauma, but also improve patient health earlier.

Case presentation

The data for three patients with EP treated at the First Affiliated Hospital of China Medical University (Shenyang, China) between 2014 and 2019 were collected. All cases were confirmed by pathology. All three patients were male, with an average age of 52 years (range, 43–67 years). The average time from onset to diagnosis was 2 months (range, 1–3 months) in three patients, with abdominal pain as the first symptom. One of them had allergic rhinitis. The detailed laboratory studies are available in [Supplementary Tables 1–3](#).

Computed tomography (CT) scan showed a diffusely enlarged pancreas without a pancreatic duct, and the outline of the pancreas was blurred with stripes and multiple nodules surrounding it ([Figure 1A and B](#)). Magnetic resonance cholangiopancreatography (MRCP) analysis showed dilatation of the extrahepatic bile duct above the pancreatic segment, a thickened common-bile-duct wall and a distended gallbladder, and occlusion of the bile duct with tapering within the pancreas. Pancreatography showed a diffusely enlarged pancreas without a pancreatic duct ([Figure 1C–E](#)).

Endoscopic ultrasound (EUS)-guided pancreatic biopsy confirmed eosinophilic infiltration ([Figure 2A and B](#)) in one patient. In the other two patients, eosinophils (EOS) infiltration was also evident in the pancreatic pathology obtained by surgery.

After 7 days of methylprednisolone treatment at a dose of 80 mg per day, the patients' peripheral eosinophil counts, liver-function tests, and serum IgE levels returned to normal ranges. Then, we adjusted the dosage of prednisone to 40 mg orally, reduced the dosage by 5 mg per week, maintained the treatment at 5–10 mg, and discontinued the hormone treatment after approximately half a year. One month later, repeated CT scan from the same patient showed that the pancreas had shrunk and the previous stripes that had been visible around the pancreas could no longer be observed ([Figure 1F](#)). After the patients had been discharged from the hospital for 16 months, a telephone follow-up showed that the patients were in good condition.

Clinical presentations

Since EP is a rare disorder, only 16 cases have been published to date. These cases have varying clinical manifestations. Patients with EP may experience common non-specific symptoms such

as fatigue, nausea, fever, vomiting, diarrhea, anorexia, and weight loss. The typical clinical presentation may include jaundice or different degrees of abdominal pain. In these 19 patients, 17 had clinical symptoms of jaundice and abdominal pain. In addition, patients with jaundice usually have pruritus, acholic stools, and skin and/or scleral icterus. We tried to classify the clinical presentations of EP by the organs affected as pancreatic or extrapancreatic. The pancreatic presentations involve features of acute pancreatitis and obstruction caused by pancreatic enlargement, and thus mimic pancreatic cancer. As such, the common symptoms are abdominal pain with/without posterior radiation that spontaneously disappears within a few hours, obstructive jaundice, recurrent acute pancreatitis without a definite etiology, fever, nausea, vomiting, and weight loss. The extrapancreatic presentations are commonly caused by peripheral eosinophilia, infiltration of eosinophils into other organs, and an obstructive pancreatic mass. Furthermore, gastroenteritis, biliary-tree stricture, or other autoimmune responses are also common in these patients.

Histology

Overall, the histopathological changes in EP can be summarized as the following triad: (i) the pancreas has inflammatory pathologic changes that may be pseudocysts, parenchymal necrosis, atrophy, or fibrosis; (ii) there is no sign of tumor cells; and (iii) idiopathic inflammation with eosinophilia can be found on macroscopic examination of the pancreas.

Macroscopically, most EP cases present as a diffusely enlarged tail or head of the pancreas [1, 2, 5, 8–10]. A cyst in the pancreas that causes pancreatic-duct and common-bile-duct obstruction can be noted at the time of surgery [1, 7–10]. In addition, there are no stones or other materials in the common bile duct [2, 5, 9]. The cyst often shows areas of fibrosis and necrosis [1, 7–10]. The enlarged lymph nodes and infiltration of the lamina propria of neighboring organs such as the gallbladder, duodenum, spleen, and ampulla of Vater may be present in some cases [1, 2, 5, 7–9]. Cases of autoimmune pancreatitis (AIP) often involve 'sausage-shaped' enlargement of the pancreas [15] and EP is accompanied by a 'rock-hard' pancreas [1].

Microscopically, EP usually reveals numerous eosinophilic infiltrates with few other inflammatory cells. The area of the cyst may be marked by diffuse periductal and septal eosinophilic infiltration with intra- and interlobular fibrosis, multiple acinar foci, arteritis and/or phlebitis, and atrophy of the pancreatic parenchyma [1, 2, 5, 8–10]. The pancreas can be infiltrated by eosinophils with no sign of any tumor cells. Apart from the above-mentioned features, EP may present with different variants.

Serology

An abnormal serum eosinophil count was reported in 11 of our summarized 16 cases ([Table 1](#)) [1, 2, 5–10, 16]. An increased plasma level of eosinophils has been suggested as a characteristic of EP. The efficacy of IgE in the diagnosis of EP is obviously important. This condition is similar to the high plasma level of IgG that is seen in AIP patients and is related to an autoimmune mechanism. Elevated liver-function enzymes including alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase, and alkaline phosphatase are helpful in diagnosing hepatitis or cholestatic hepatitis in the majority of patients, as only small proportions of patients have normal values. In addition, elevated levels of direct bilirubin

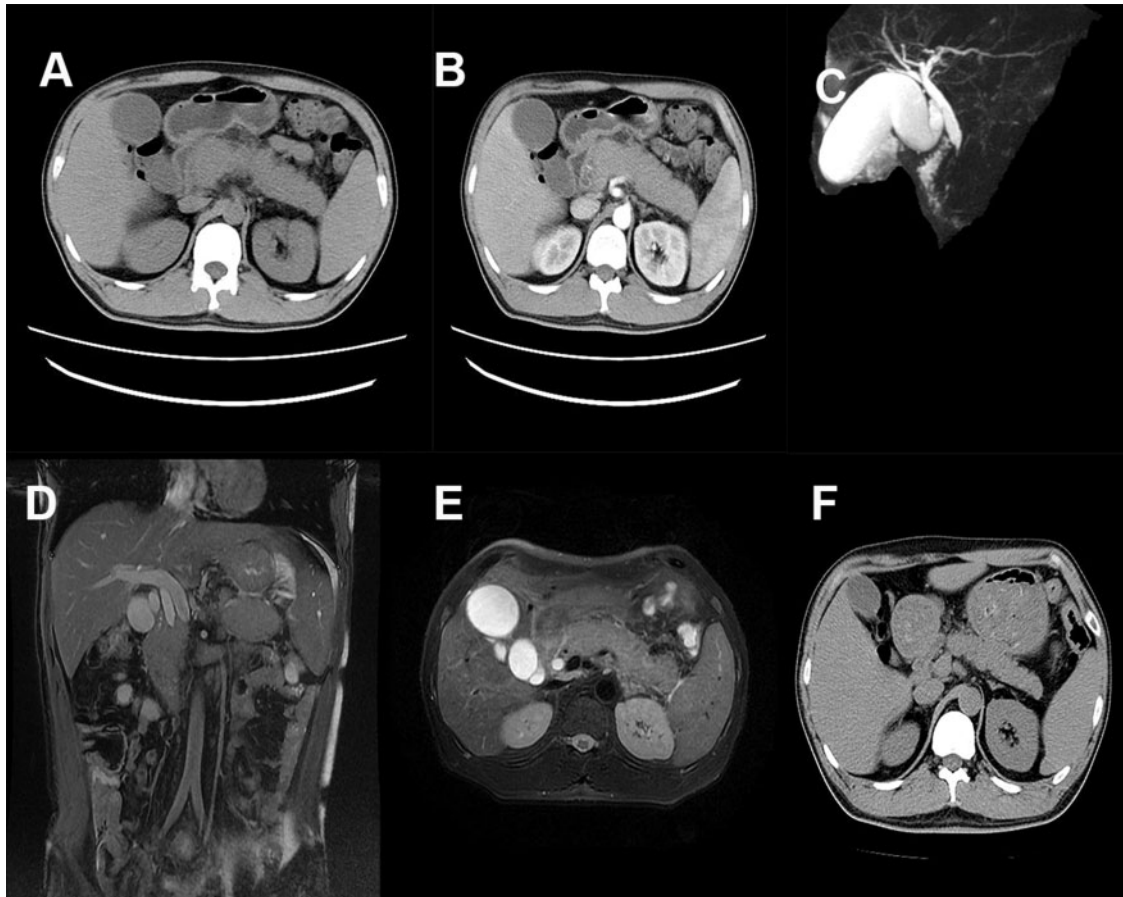


Figure 1. Comparison of pancreatic and ductal imaging before and after steroid treatment. (A) and (B) The computed tomography scans (CT) show a diffusely enlarged pancreas without a pancreatic duct, and the outline of the pancreas is blurred with stripes and multiple nodules around it. (C) Magnetic resonance cholangiopancreatography (MRCP) shows a normal intrahepatic bile duct, dilated extrahepatic bile duct above the pancreatic segment, distended gallbladder, and occluded bile duct with tapering within the pancreas. (D) MRCP shows the thickness of the common-bile-duct wall. (E) MRCP shows a diffusely enlarged pancreas without a pancreatic duct. (F) Abdominal CT scan at 1-month follow-up reveals the pancreas decreased in size and the previous stripes around the pancreas cannot be observed.

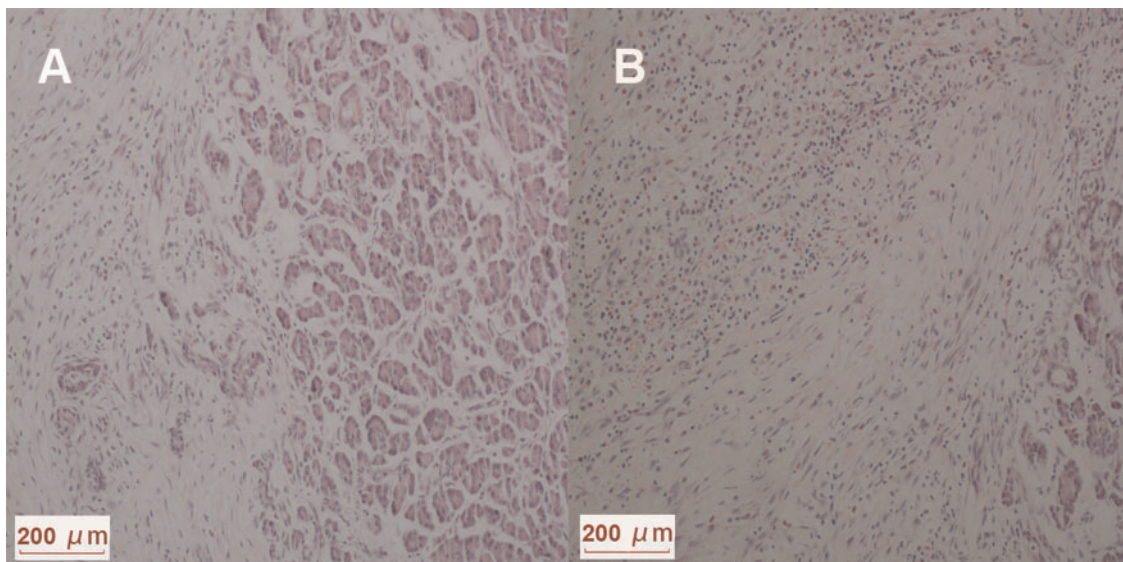


Figure 2. Pancreatic pathology. Significant purely eosinophilic infiltration in a biopsy specimen obtained from the pancreatic tissue (H&E stain).

Table 1. Summary of the presentation and laboratory data of 19 patients with eosinophilic pancreatitis

Author	Year	Age (years)	Sex	Presentation	Peripheral eosinophilia (10 ⁹ /L)	IgE (U/mL)	Pancreatic imaging	Histology of the pancreas
Barresi et al. [3]	1978	0	F	Spontaneous tremors, cyanosis	NA	NA	NA	Marked infiltration of EOS
Bastid et al. [5]	1990	21	M	Epigastric pain	0.72	NA	Enlarged tail of the pancreas	Area of necrosis with an abscess rich in EOS
Barthet et al. [8]	1998	18	M	Epigastric pain, jaundice, weight loss	0.623	204	Mass in the head of the pancreas	Lobular fibrosis and atrophy with infiltration by EOS
		64	M	Jaundice, weight loss	0.38	Normal	Enlargement of the pancreas mostly in the head	Fibrous tissues only in the pancreatic biopsy before surgery
Wagniet et al. [16]	2000	21 months 4	M	Eczema, fever, acholic, stools	0.7-1.3	NA	Enlarged pancreas	NA
			F	Abdominal pain, fever, acholic stools, jaundice, weight loss	2.5	NA	Enlarged pancreas	NA
Euscher et al. [9]	2000	36	M	Epigastric pain, nausea, anorexia, weight loss, fatigue	0.156	NA	Enlarged pancreatic head with a mass	Fibrotic pancreas with a diffuse inflammatory infiltrate of mainly EOS
Abraham et al. [1]	2003	60	M	Abdominal pain, jaundice	1.46	NA	Diffusely enlarged pancreas and a 4 × 3.5 cm mass of the pancreatic head	Infiltration of the pancreas mainly by EOS
		36	F	Abdominal pain	1.75	NA	Cystic pancreatic mass of the pancreatic head	Infiltration of the pancreas mainly by EOS
		41	M	NA	1.18	NA	Pancreatic pseudocyst of the pancreatic head	Infiltration of the pancreas mainly by EOS
Cay et al. [7]	2006	14	M	Abdominal pain, vomiting, jaundice	NA	1,767	Larger-than-normal pancreatic head and a mass in the head of the pancreas	Significant eosinophilic infiltration in the pancreatic mass
Kakodkar et al. [6]	2015	39	M	Epigastric pressure, pruritus, diarrhea, acholic stools, jaundice	0.9	135	Mass in the head of the pancreas and a diffusely enlarged pancreas, especially in the head and neck	Significant eosinophilic infiltration on core biopsy samples of the enlarged pancreatic head
Tian et al. [10]	2016	39	M	Jaundice	0.69	Elevated	Diffusely enlarged pancreatic head	Diffuse inflammatory infiltration of the pancreas primarily by EOS and fibrous-connective-tissue hyperplasia with collagenation
		46	M	Abdominal pain, jaundice	0.62	NA	Diffusely enlarged pancreas and a mass in the pancreatic head	Diffuse inflammatory infiltration of the pancreas primarily by EOS and fibrous-connective-tissue hyperplasia with collagenation
		41	F	Abdominal pain, jaundice, fatigue, anorexia, nausea, vomiting	0.19	Normal	NA	Diffuse inflammatory infiltration of the pancreas primarily by EOS and fibrous-connective-tissue hyperplasia with collagenation
Reppucci et al. [2]	2017	44	M	Epigastric pain, nausea, vomiting	0.6	NA	Coarse calcification of the pancreatic head	Diffuse inflammatory infiltration of the pancreas primarily by EOS and fibrous-connective-tissue hyperplasia with collagenation
Present patient 1	2018	46	M	Epigastric pain, fever, weight loss	0.82	307.2	Diffusely enlarged pancreas	Extensive eosinophilic infiltration and fibrosis of the pancreas
Present patient 2	2018	67	M	Epigastric pain, nausea, vomiting, weight loss	0.3	432	Enlarged pancreatic tail with calcification	Diffuse inflammatory infiltration of the pancreas primarily by EOS and lymphoid-tissue hyperplasia
Present patient 3	2018	43	M	Epigastric pain increased after oily-food intake	0.23	297	Mass in the body of the pancreas	Area of necrosis with a fibrous capsule rich in EOS
								Marked infiltration of EOS

F, female; M, male; NA, details not available; IgE, immunoglobulin E; EOS, eosinophils.

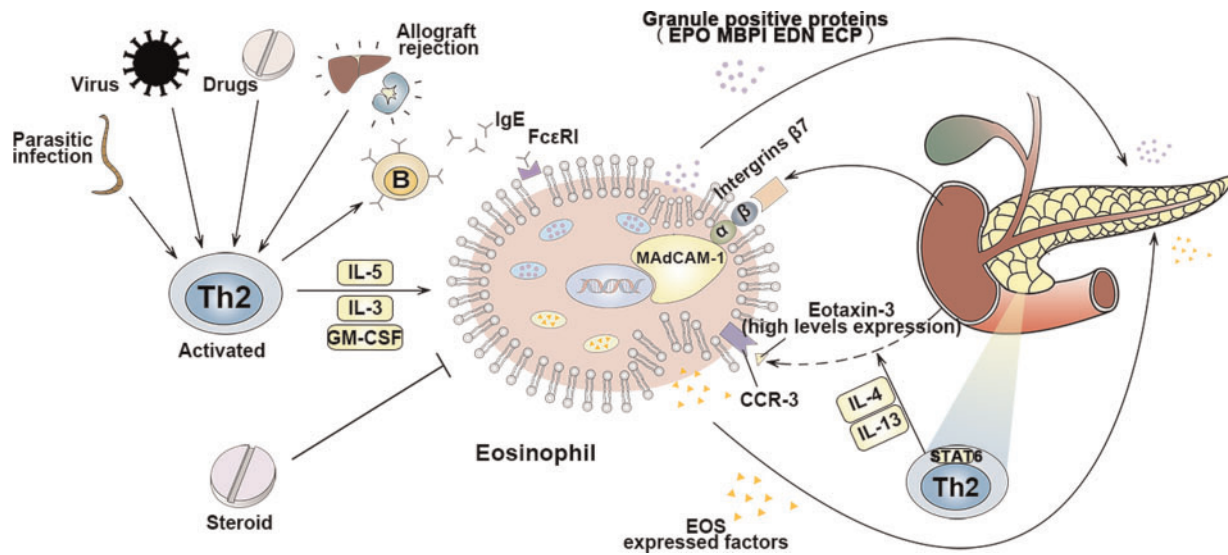


Figure 3. Mechanism of EP pathogenesis. Th2, T-helper 2 cell; B, B-cell; IgE, immunoglobulin E; IL-5, interleukin-5; IL-3, interleukin-3; GM-CSF, granulocyte-macrophage colony-stimulating factor; FcεRI, Fc receptor for IgE; MAdCAM-1, mucosal addressin cell-adhesion molecule-1; EPO, eosinophil peroxidase; MBP1, major basic protein-1; EDN, eosinophil-derived neurotoxin; ECP, eosinophil cationic protein; CCR-3, cell chemokine receptor-3; IL-4, interleukin-4; IL-13, interleukin-13; STAT6, single transducer and activator of transcription 6.

and total bilirubin are usually reported in cases that are complicated by obstructive jaundice. An elevated sedimentation rate, C-reactive protein level, and triglyceride level have also been reported in EP patients [2, 7, 8, 16].

Imaging and EUS-FNA

On CT scans of EP patients, the pancreas is diffusely enlarged, especially in the head and tail, and it sometimes has a hypochogenic or heterogeneous mass that usually shows dilatation of the main duct and the intra- and extrahepatic bile ducts. These features may lead to a misdiagnosis of a pancreatic tumor and AIP. Occasionally, EP may present with coarse calcification of the pancreas on CT scan [2].

MRI/MRCP has some advantages in evaluating the morphology and anatomical structure of the bile duct. MRCP is useful for providing high-resolution images of the biliary tree and pancreatic duct in multiple planes of sections, and a maximum signal-intensity projection can be helpful when overall 3D views are needed [17]. In 2018, the Japanese Clinical Diagnostic Criteria for AIP supplemented MRCP as a complement to endoscopic retrograde cholangiopancreatography (ERCP) to some extent [18]. Therefore, MRCP can achieve similar images to cholangiopancreatography and can obtain similar effects to ERCP or percutaneous transhepatic cholecystography (PTC).

ERCP is used to observe the normality of the bile ducts and the main duct. Using this technique, it is possible to identify a double-duct stricture that is located at the level of the pancreas in patients with EP. In addition, the common bile duct with/without the main duct is usually dilated up to the level of stenosis. Similar technologies include EUS and PTC. These technologies are three minimally invasive methods for pancreatic biopsy.

EUS-guided fine-needle aspiration (EUS-FNA) has been generally used to sample pancreatic tissues since 1992 [19]. EUS-FNA is superior to other methods such as ERCP in terms of tissue acquisition and safety [20]. Furthermore, EUS-FNA for tissue samples is fundamental to avoiding unnecessary surgeries [21]. Clinically, EUS-FNA is an essential procedure for patients with

suspected pancreatic cancer and AIP [20, 22]. The combination of a histologic diagnosis of EP with the other findings specified in our criteria improved the diagnostic accuracy, but EUS may reveal false-negative results.

Pathophysiology

The mechanism of EP is variable but often includes an abundant eosinophilic infiltrate in the pancreas (Figure 3). In past years, elevated numbers of eosinophils have been associated with asthma, helminth infections, and acute anaphylaxis [23]. Recent studies suggest that eosinophils can damage tissues and cause disease by eosinophilic cytotoxic and pro-inflammatory mediators [2, 23]. In addition, eosinophils are pleiotropic multifunctional leukocytes and play a role in the initiation and propagation of numerous inflammatory responses, including parasitic infections, bacterial and viral infections, tissue injury, tumor immunity, and allergic disease [24]. Many factors influence the mechanism of eosinophilic regulation that induces an increase in eosinophils [25]. IgE-mediated mechanisms are commonly known to facilitate the degranulation of mast cells and basophils, and to promote Th2 immunity; these mechanisms not only protect against parasitic worms and noxious substances, but also trigger allergic reactions [26]. Greater amounts of IgE are found in eosinophils with higher levels of serum IgE [27]. Therefore, IgE is an important serological indicator for patients with EP, similar to the association between IgG4 and AIP. Hence, in patients with EP, healthcare providers should note whether the patient has a concomitant parasitic infection, pancreatic allograft rejection, drug reaction to carbamazepine, chronic pancreatitis, myeloproliferative disease, tumor, or other eosinophil-elevating conditions. These known causes can help us to better treat EP.

Differentiation of progenitor cells into eosinophils is induced by IL-5, IL-3, and granulocyte-macrophage colony-stimulating factor (GM-CSF), which are secreted by activated Th2 cells [28]. Eosinophilia is a phenomenon in which the number of eosinophils is increased, likely because many eosinophilic inflammatory diseases suppress the apoptosis of eosinophils [29]. In

Table 2. Criteria for EP

Criterion	Pathological feature
Pancreatic imaging	Diffuse or segmental/focal enlargement with delayed enhancement
Ductal imaging	Stricture or upstream dilatation
Serology	IgE elevated and peripheral eosinophils elevated
Other organ involvement	1. Histology of extrapancreatic organs mainly infiltrated with eosinophils 2. Radiological evidence such as bile-duct stricture, enlarged lymph nodes, or retroperitoneal fibrosis
Histology of the pancreas (core biopsy/resection)	1. Pseudocyst, parenchymal necrosis, atrophy, and fibrosis infiltrated by mainly eosinophils 2. Eosinophilic phlebitis
Response to steroids	Rapid (≤ 2 weeks) radiologically demonstrable resolution or marked improvement in manifestations

EP, eosinophilic pancreatitis; IgE, immunoglobulin E.

many allergic disorders, overexpression of IL-5 is crucial for delayed eosinophil apoptosis [30]. In addition, animal experiments have demonstrated that IL-5-deficient mice show reduced pancreatic eosinophilia [4]. Eosinophils are non-dividing terminally differentiated cells that die rapidly and undergo spontaneously apoptotic death without survival factors [31]. In addition to these missing survival factors, apoptogenic factors can induce eosinophil apoptosis. The latter may be useful for triggering the resolution of unwanted eosinophilic inflammatory responses to compounds such as steroids [30]. The bone marrow contains a pool of eosinophils, and the gastrointestinal tract is a gathering place for eosinophils outside of the circulation [25]. Integrins belong to the cell-adhesion receptor superfamily and are transmembrane $\alpha\beta$ heterodimers that bind to extracellular matrix ligands, cell-surface ligands, and soluble ligands [32]. The integrin $\beta 7$ /MAdCAM-1 pathway is responsible for the migration of leukocytes into the pancreas [33–35]. $\beta 7$ integrins can be expressed by eosinophils and can mediate the diverse functions of eosinophils, such as rolling, firm adhesion, and migration [36]. Eotaxin-3 is the predominant CCR3 ligand and is markedly induced by IL-4 and IL-13, which are secreted by Th2 cells, and its expression is dependent on the transcription factor STAT6. In addition, CCR3 can recognize the levels of CC chemokines, including MCP-2, MCP-3, MCP-4, RANTES, eotaxin-2, and eotaxin-3 [37, 38]. However, the interaction between eotaxin-3 and CCR3 is an important mechanism in eosinophil transepithelial migration [39]. The CCR3 agonists that are secreted by epithelial cells of the digestive tract, in addition to VLA-4 (CD 99d/CD 29), have a homing effect on eosinophils [40]. Isolated human pancreatic myofibroblasts show high levels of eotaxin-3 expression that is induced by IL-4 and IL-13 [41]. IgE can activate eosinophils through the Fc ϵ RI signaling pathways [26].

Predominant eosinophilic infiltration of the pancreas is the common pathological feature of patients who vary widely in their radiographic features and clinical manifestations. EP can also be diagnosed when eosinophils are the predominant inflammatory cell type in the pancreatic resection [9].

Differential diagnosis

The definition of AIP is a distinct form of pancreatitis characterized clinically by frequent presentation with obstructive jaundice with or without a pancreatic mass, histologically by a lymphoplasmacytic infiltrate and fibrosis, and therapeutically

by a dramatic response to steroids [42]. These features may lead to misdiagnosis of EP and AIP. The efficacy of IgG in the diagnosis of AIP is obviously important, and is similar to the high plasma level of IgE that is seen in EP patients. Patients with AIP generally have positive test results for autoimmune and antinuclear antibodies [10]. The imaging findings of AIP often involve ‘sausage-shaped’ enlargement of the pancreas [15] and EP is accompanied by a ‘rock-hard’ pancreas [1]. Compared with AIP, EP is caused by pure eosinophilic infiltration of the pancreas. International consensus diagnostic criteria for AIP established in 2011 formally defined criteria for the diagnosis of type 1 and type 2 AIP [42]. Type 1 AIP is considered an IgG4-related disease. Some typical major histopathological features associated with IgG4-related disease have been identified, particularly the presence of a dense lymphoplasmacytic infiltrate, storiform-appearing fibrosis, and obliterative phlebitis [43]. Type 2 AIP is histologically characterized by a neutrophilic infiltrate associated with duct destruction and obliteration, and this form of inflammation has been termed idiopathic duct-centric pancreatitis [44].

Supplementary tables show that many patients with EP have eosinophilic infiltration in the gastrointestinal tract and gallbladder. Eosinophils are multifunctional leukocytes that are normal constituents of the gastrointestinal tract and protect against pathogenic parasites and bacteria [45]. All eosinophilic gastrointestinal diseases are defined as an excess of eosinophils in the mucosa, serosa, or muscular layer of the gastrointestinal tract, and often the cause is unknown [46]. The mechanism of eosinophilic esophagitis involves a Th2 immune response that is frequently driven by food allergy, which is believed to play a central role in recruiting eosinophils to the gastrointestinal tissue [47]. Eosinophilic gastrointestinal disorders represent a group of diseases characterized by eosinophil-driven inflammation in specific locations in the gastrointestinal tract.

Treatment

Overall, the key to the successful treatment of EP is steroids without a laparotomy. However, owing to the high rate of malignant tumors, it has been proposed that surgery should be considered for patients with EP. The preoperative diagnosis of EP is difficult to establish; thus, there have not been many reports on pure steroid treatment of patients with EP. It is generally accepted that EP patients have a favorable prognosis. In our statistical analysis of 19 patients, 12 were cured and 1 died; the

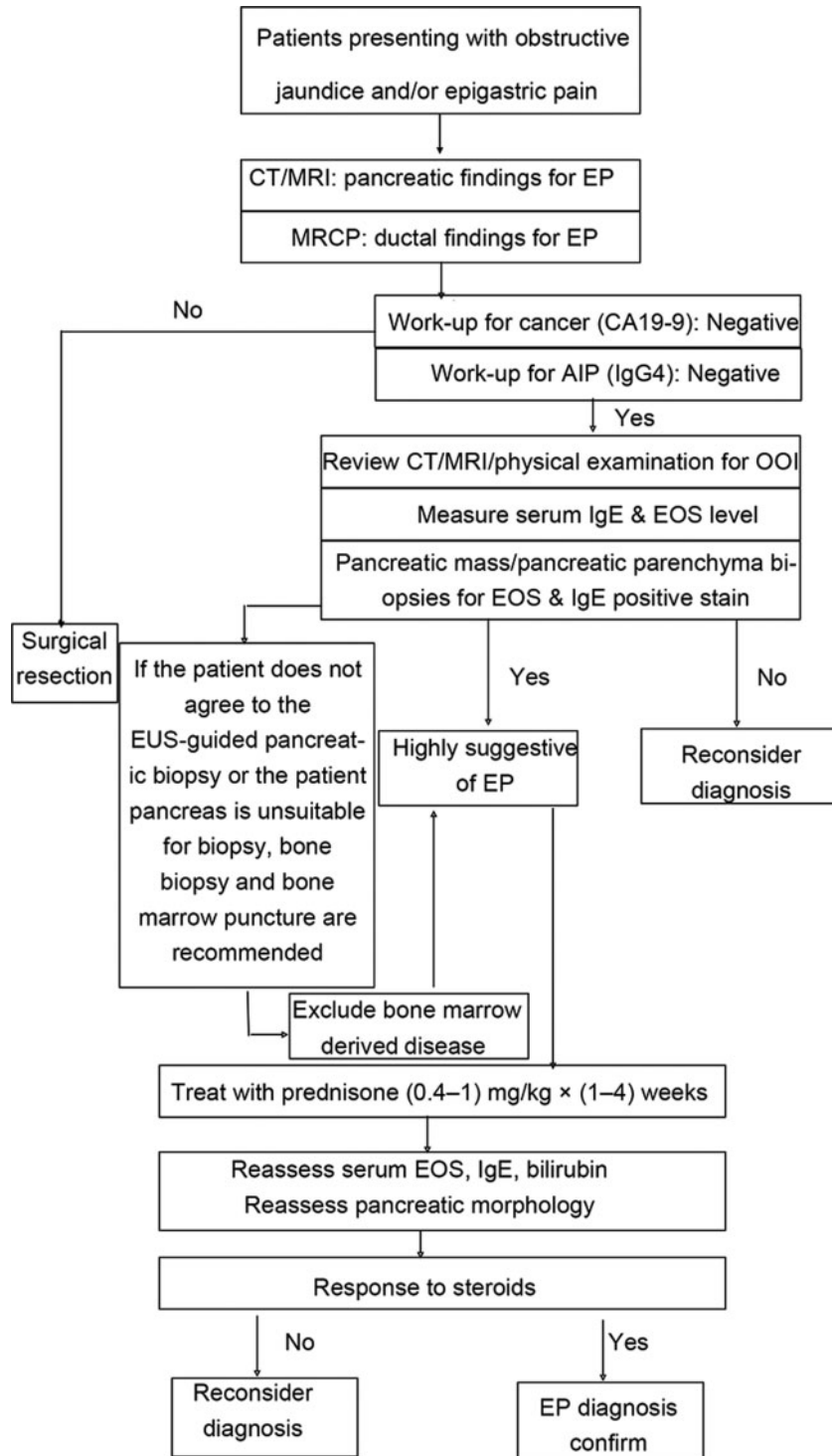


Figure 4. This schematic drawing shows a flow to diagnose. CT, computed tomography; MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography; EP, eosinophilic pancreatitis; CA19-9, cancer antigen 19-9; IgE, immunoglobulin E; IgG4, immunoglobulin G4; OOI, other organ involvement; EOS, eosinophils; EUS, endoscopic ultrasound.

outcomes among the remaining patients were not clearly indicated. Patients with EP have a relatively better prognosis than those with tumors.

Food allergy is defined as an adverse immune response to food [48]. Food allergy is mostly associated with an increase in Th2 cytokines, IgE, and eosinophils in response to allergens [49]. The first elimination diet for treatment of EP was published in

1995 and involved exclusive feeding of an amino-acid-based formula for ≥ 6 weeks [50]. The elimination diets consisted of eliminating the six food groups most commonly associated with food allergy in a pediatric population in Chicago (cow's milk protein, wheat, eggs, soy, peanut/tree nuts, and fish and seafood) for 6 weeks [51]. Today, elimination diets are effective treatments for eosinophilic gastrointestinal disorders and

irritable bowel syndrome [52–54]. Food elimination may be a potentially effective treatment for EP. Topical/systemic corticosteroids and food elimination have led to significant reductions in tissue eosinophil counts [55].

Diseases commonly coexisting with hypereosinophilic disease

Food allergies manifest in a variety of clinical conditions within the gastrointestinal tract, skin, and lungs [56]. Manohar et al. [48] showed that acute pancreatitis has been provoked after the consumption of mustard, milk, eggs, bananas, fish, and kiwi fruits. Food allergies can cause the recruitment of eosinophils and increased serum IgE [56].

Eosinophilic high type 2 airway inflammation is present in ~50% of adults with asthma [57]. Eosinophilic esophagitis and asthma are frequently found as comorbid conditions in children/adults, and these two conditions have similar Th2 response-driven pathophysiology [58].

Eosinophils contribute to chronic intestinal inflammation in inflammatory bowel disease (IBD) patients [59]. In general, eosinophils are increased in IBD. Filippone et al. [60] suggested that eosinophils play an important role in IBD pathogenesis, with clear indications of changes in cytokine, chemokine, and receptor mediator profiling. Seasonal relapses of IBD may increase eosinophil activity because of exposure to allergens [61].

Primary sclerosing cholangitis (PSC) is a rare, chronic cholestatic liver disease characterized by intrahepatic or extrahepatic stricture or both with bile-duct fibrosis [62]. Eosinophilia and an increase in serum IgE have been reported to be associated with PSC [63–65]. The pathogenesis of PSC may be associated with hypereosinophilic syndrome or allergic reactions [63]. Horiuchi et al. [66] suggested that eosinophils and products released by eosinophils such as major basic protein may lead to inflammation and fibrotic changes in the bile ducts.

Conclusions

At this stage, there are no clear diagnostic criteria and each patient's clinical manifestations are different. We seek to determine the diagnosis through biochemical tests and imaging studies to reduce unnecessary surgery. A diagnosis of EP is made based on the histopathological examination of pancreatic sections. The results of histopathological examinations often show that the pancreas is purely or predominantly infiltrated by eosinophils with no sign of any tumor cells. Pancreatic-imaging studies may support the diagnosis. Increased serum IgE levels, systemic hypereosinophilia, and eosinophilic infiltrates in other organs of the gastrointestinal tract may also lead to a diagnosis. If diagnostic uncertainty occurs, glucocorticoid diagnostic treatment may be beneficial. Since a preoperative diagnosis of EP is difficult to establish, most patients undergo laparotomy, since malignancy cannot be excluded. However, it must be stressed that invasive diagnosis and treatment can impact the prognosis of the patient. It can thus be suggested that prompt gastrointestinal and pancreatic biopsies should be performed in an effort to avoid unnecessary surgical intervention [8]. Due to their similar clinical and imaging features, a fair number of EP patients are misdiagnosed with pancreatic tumor. As treatment options and the extent of a particular therapy may vary considerably, it is essential to differentiate EP from a pancreatic tumor [1, 2, 5–10] and from other disorders, such as AIP [42, 67–70], leukemia [71], inflammatory myofibroblastic tumors

[72], chronic pancreatitis [73], and histiocytosis X [74]. There is no international diagnostic standard or flow chart for EP at this stage. A retrospective analysis of the clinical manifestations, histology, serology, imaging, other organ involvement, and responses to steroid therapy was conducted for 19 patients with EP (Table 1). The purpose of this review was to evaluate and validate the clinical criteria (Table 2) and algorithm (Figure 4) for EP. Secondary EP should also be considered on the differential diagnosis.

Corticosteroids are the therapeutic gold standard for EP treatment. The initial dose is 80 mg/day of prednisolone and the imaging results are reviewed after 2–4 weeks of treatment. Steroids can induce apoptosis of eosinophils, suppress the synthesis and effects of eosinophil-survival factors, and stimulate phagocytic cells to engulf eosinophils [31, 75]. The rate of apoptosis in eosinophils is increased when the glucocorticoid receptor combines with dexamethasone [75]. Glucocorticoids can alleviate the suffering of patients and the economic costs to patients compared to surgical treatment. In addition, long-term hormone therapy is more beneficial to the prognosis of patients and reduces the recurrence rate.

Supplementary Data

Supplementary data is available at *Gastroenterology Report* online.

Authors' contributions

Y.S., L.X.S., and B.C. conceived of the study and participated in its design and coordination. Y.S., K.K., and D.P. performed the literature research, analysed the data, and wrote the manuscript. B.C., M.J.S., and Y.L.L. corrected the manuscript. All authors read and approved the final manuscript.

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Conflicts of interest

None declared.

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