CASE REPORT

Recurrent Acute Pancreatitis Due to Eosinophilic Gastroenteritis. Case Report and Literature Review

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ABSTRACT

Context Eosinophilic gastroenteritis is characterized by eosinophilic infiltration of any gastrointestinal segment from the esophagus to the rectum, most commonly, the stomach and the duodenum. Clinical manifestations range from non-specific gastrointestinal complaints to more specific symptoms such as protein-losing enteropathy, malabsorption, luminal obstruction and eosinophilic ascites.

Case report We report the case of a 35-year-old woman with recurrent gastric outlet obstruction due to eosinophilic infiltration of the stomach and the duodenum. There was a history of two episodes of acute pancreatitis as well as eosinophilia of bone marrow and ascites.

Conclusions Although unusual, eosinophilic gastroenteritis may be complicated by symptomatic acute pancreatitis. Seven previous cases have been reported in the literature, and a comparison was made. The pancreatitis is probably due to duct obstruction, but some cases of eosinophilic gastroenteritis have pancreatic tissue eosinophilia. Most cases respond to medical treatment, and surgery is usually unnecessary.

INTRODUCTION

Eosinophilic gastroenteritis (EGE) was initially described by Kaijser in 1937 [1], and several hundred cases have since been reported. Eosinophilic cells can accumulate in any part of the gastrointestinal tract from the esophagus to the rectum; the most commonly affected are the stomach and the duodenum [2, 3, 4]. According to the classification by Klein, three different disease patterns of EGE can be discerned: mucosal, submucosal and serosal, although more than one layer may be involved [2, 5]. The clinical manifestations depend on which wall layer and which bowel segments are predominantly involved. Thus, mucosal disease may result in anemia, protein-losing enteropathy, and malabsorption, whereas muscle layer infiltration typically causes luminal obstruction [2, 4, 5]. The rarest form is serosal disease with eosinophilic ascites [2, 4]. However, many of the clinical manifestations are non-specific, such as nausea, vomiting, crampy abdominal pain, and diarrhea, thus making a diagnosis may be difficult [2, 4].

This paper reports a case of EGE causing recurrent acute pancreatitis which is an extremely unusual complication. A survey of the literature reveals only seven reported cases [6, 7, 8, 9, 10, 11, 12]. The association

of EGE and pancreatic disease will be discussed.

CASE REPORT

A 35-year-old woman was referred with symptoms of gastric outlet obstruction.
The patient smoked, but had no history of alcohol or drug abuse. She was allergic to horses and cats. There was no family history of pancreatic or gastrointestinal disease.
She had had repeated episodes of self-limiting crampy abdominal pain and alimentary vomiting lasting a few weeks since she was 20 year old. Repeated gastroscopies were normal.
At the age of 27, the patient was admitted to hospital with acute, epigastric pain, vomiting and an elevated serum amylase level of 1,605 U/L (reference range: 0-300 U/L). Blood eosinophils were elevated (13.8 $x10^9$/L; reference range: 0-0.45 $x10^9$/L). A blood marrow aspirate contained massive eosinophilic infiltration. Fecal parasites were negative. Abdominal ultrasound showed ascites. Abdominal CT scan showed dilated small bowel loops and ascites. On follow-up, there was no intestinal obstruction, but the intestinal wall was considered edematous. ERCP showed edema and compression of the descending duodenum and a juxtapapillary diverticulum, but no pathology in the biliary or the pancreatic ducts.
Three years later, she was readmitted with epigastric pain, vomiting and increased serum amylase, 1,101 U/L. Blood eosinophils were 3.0 $x10^9$/L. Transient elevations of bilirubin (maximum value 39 µmol/L; reference range: 0-17 µmol/L), transaminases and alkaline phosphatase were seen. On gastroscopy, a duodenal stenosis made intubation difficult, and macroscopically "erosive duodenitis" was present. Biopsies showed a mixed infiltrate of lymphocytes, plasma cells, macrophages and eosinophils. Examination of the duodenal juice for parasites was negative. A plain abdominal film showed dilated small bowel loops. A barium study of the stomach and duodenum showed a stenosis of the bulb. Ultrasound showed no gallstones, but the

diameter of the common bile duct was 15 mm. An abdominal CT scan showed ascites, and a dilation of the common bile duct to 20 mm. ERCP was carried out again without a specific pathology, but duodenal intubation was difficult. The patient was discharged in good health after 4 weeks and at a 2 month follow-up, she was free of symptoms with normal liver function tests and a repeat abdominal CT scan was normal.
Further hospital admissions occurred 2 and 4 years later, because of abdominal pain and vomiting. Blood eosinophils were 2.9 and 5.3 $x10^9$/L, respectively. Liver function tests and amylase were normal on these occasions. Fecal parasites were negative. Gastroscopy showed "duodenitis", and biopsies revealed a predominantly eosinophilic infiltrate in the *lamina propria*. Abdominal ultrasound showed dilation of the common bile duct to 11 mm. An MRCP was normal; the common bile duct was considered normal. Barium studies showed a 2 cm duodenal diverticulum whereas the large intestine was normal.
At age 35, the patient was admitted to hospital after several weeks of epigastric fullness and pain, anorexia and nausea. Liver function tests and amylase were normal. Plain abdominal films revealed isolated small bowel loops. Gastroscopy showed gastric retention and duodenal obstruction. CT scanning revealed ascites and increased wall thickness in the duodenum and the small bowel. Ascite cytology contained eosinophilic cells. An exploratory laparotomy was done because of persisting gastric retention and a suspicion of malignancy.
A 7 cm obstructing lesion was found in the pylorus at laparotomy together with gross thickening of the stomach and the duodenum. The outer and inner surfaces were normal, but the wall of the pylorus and duodenum was rigid and measured up to 22 mm. The small and the large intestine also appeared to be thickened and there was capillary dilatation on the intestinal surface. The intestines appeared hypercontractile; the slightest touch elicited a series of spastic, propagating contractions. The pancreas was macroscopically normal as seen at the
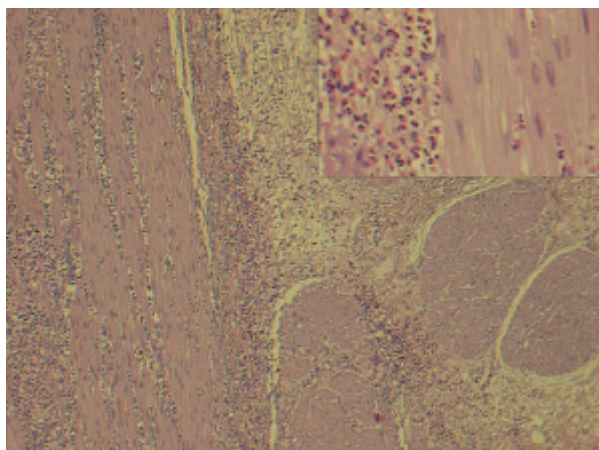
Figure 1. Photomicrograph of the gastric-duodenal wall showing submucosal and muscular layers infiltrated with eosinophilic granulocytes. (Close view on top; hematoxylin-eosin staining)

posterior surface of the lesser sack, and parietal peritoneum, liver, gallbladder and spleen also appeared without pathology. A distal gastric resection *ad modum* Billroth II with gastrojejunostomy and enteroanastomosis was done. The thickened duodenal bulb was carefully sutured with two layers of absorbable monofilament. On the 3rd day, the patient was reoperated on for drainage of a duodenal stump leakage. The patient was discharged 21 days postoperatively in good clinical condition. On light microscopy of the resected specimen (Figure 1), the submucosa and the muscular layers of the stomach and the duodenum were densely infiltrated with eosinophilic granulocytes. In the lamina serosa, scattered eosinophils were seen.

A postoperative, abdominal MR-scan including MRCP showed a 1 cm juxtapapillary diverticulum, but was otherwise normal (Figure 2a,b). At a 30 month postoperative follow-up, the patient had mild dumping syndrome, but was otherwise free of symptoms.

DISCUSSION

EGE is a rare disease and its diagnosis may be difficult. Eosinophilia can be a clue to the diagnosis, but may be absent in as many as 20% of cases [2]. Further examinations should include endoscopy with mucosal biopsies. Patchy involvement of the bowel as well as the difficulty of obtaining diagnostic

biopsies in muscular or serosal disease may result in false negative specimens [2]. Laparoscopic full-thickness biopsies may be indicated [3]. Establishing the diagnosis also requires exclusion of other causes of eosinophilic gut infiltration, such as food allergy, drug idiosyncrasy, parasitic/ helminthic infestation, connective tissue disease, vasculitis, malignancy, Crohn's disease, and non-tropical sprue, etc. [3, 4]. Another important differential diagnosis is the hypereosinophilic syndrome which is characterized by: 1) persistent eosinophilia
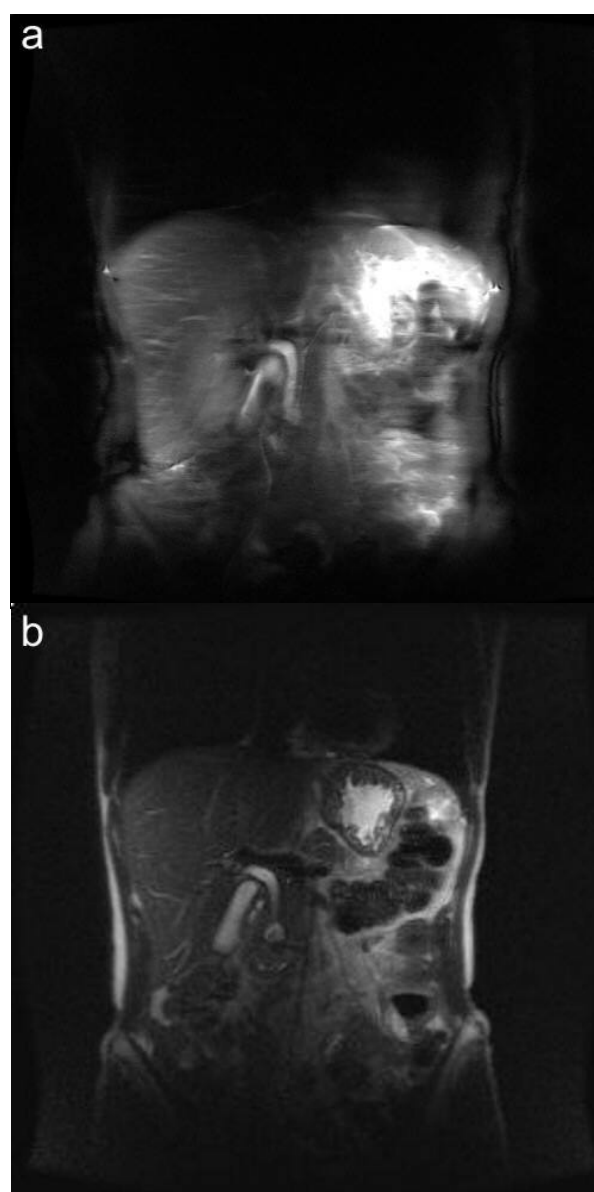

Figure 2. Abdominal MR-scanning showed a 1 cm juxtapapillary diverticulum. The intra- and extra-hepatic bile ducts and the pancreatic duct are normal, and without calculi or other pathology.

lasting more than 6 months, 2) exclusion of other causes of eosinophilia and 3) extraintestinal organ involvement (skin, lymph nodes, heart, lungs, liver, spleen, CNS, etc.). Some authors speculate that the hypereosinophilic syndrome and EGE may represent overlapping entities [8, 13, 14, 15]. The difficulties in establishing a diagnosis of EGE are illustrated by the present case which was unclear before surgery. The resected gastroduodenal specimen contained a massive eosinophilic infiltration (Figure 1), especially of the muscle layer, and the resulting gastric outlet obstruction explains most of the symptomatology. This pattern of disease seems to have already been present from the beginning. Data indicate the gastroduodenal segment as a chief target of the disease which, however, commonly involves multiple segments of the gastrointestinal tract [2, 3, 4]. Our patient also had subserosal eosinophilic infiltration and eosinophilic ascites, which is a well-known variant of EGE [2, 3, 4].

The most interesting feature in our case involved the episodes of acute pancreatitis, occurring seven and ten years after the onset of disease. A pattern of epigastric pain and elevation of serum amylase 4-5 times the normal value was seen. The patient had no history of gallstones or overconsumption of alcohol. A juxtapapillary diverticulum without contents was found on barium studies, MRCP and ERCP; the bile ducts and the pancreatic duct were otherwise without specific pathology (Figure 2a,b). Although acute pancreatitis is more common in patients

Table 1. Characteristics of patients found in the literature with eosinophilic gastroenteritis and acute pancreatitis.

Case, author	Sex, age at onset (years)	Allergies	Epigastric pain	Blood eosinophils (x10^9/L)	Serum amylase [a] (U/L)
1. Vazquez Rodriguez [6]	F 40	No	Yes	?	1,600 (N/a)
2. Smith [7]	F 9	No	Yes	1.4-14[*]	4,800 (N/a)
3. Bastid [8]	M 21	No	Yes	0.4-0.7	600 (0-300)
4. Maeshima [9]	M 27	No	Yes	13.0[*]	2,340 (0-420)
5. Barthet [10]	M 18	Yes	Yes	0.6	135 (0-110)
6. Polyak [11]	F 59	No	Yes	3.1	392 (0-115)
7. Christopher [12]	M 47	No	Yes	2.3[*]	256 (0-90)
8. Present case	F 27	Yes	Yes	13.8 3.0	1,605 (0-300) 1,101 (0-300)

Table 1. (continued)

Case, author	Number of confirmed pancreatitis episodes	Pancreatic resection or biopsy	Eosinophilic infiltration of pancreas	Other organs involved
1. Vazquez Rodriguez [6]	1	Yes	Yes	Stomach, duodenum, small intestine
2. Smith [7]	4	Yes	Yes	Duodenum, small intestine
3. Bastid [8]	1	Yes	Yes	Stomach, duodenum
4. Maeshima [9]	1	N/a	?	Stomach, duodenum
5. Barthet [10]	1	Yes	Yes	Duodenum, liver
6. Polyak [11]	1	N/a	?	Stomach, duodenum
7. Christopher [12]	1	Yes	No	Duodenum
8. Present case	2	N/a	?	Stomach, duodenum, intestines, ascites, bone marrow

[a] Reference range is reported in parentheses
[*] value calculated from total leukocyte and differential counts
N/a: not available

with a juxtapapillary diverticulum [16, 17, 18], there is controversy about the pathogenesis. It is generally believed that the association is secondary to the increased incidence of biliary stones seen in patients with a juxtapapillary diverticulum [16, 19, 20]. In a recent multivariate analysis of 350 patients, no correlation between acute pancreatitis and juxtapapillary diverticulum was found when the confounding effect of gallstones was accounted for [20].

The most conspicuous finding in our patient was the massive eosinophilic infiltration of the gastroduodenal wall which may have led to the obstruction of the biliary and pancreatic ducts as described in some previous reports [21, 22, 23]. A MEDLINE search of acute pancreatitis in association with EGE revealed seven previous cases of this unusual complication (Table 1) [6, 7, 8, 9, 10, 11, 12]. All patients in Table 1 had eosinophilic infiltration of the duodenum and, in our view, occlusion of the pancreatic duct is therefore the most probable cause of the pancreatitis. The exact risk of acute pancreatitis is difficult to assess as both under- and over-reporting may occur, but the life-time risk for the individual patient could well be as high as 1-2%.

As also seen in Table 1, an eosinophilic infiltrate of the pancreas was present in 4 out of 5 patients where pancreatic biopsy was available. EGE associated with eosinophilic infiltration of the pancreas, usually termed "eosinophilic pancreatitis", but without acute pancreatitis, has been described by several authors [14, 23, 24, 25, 26]. Furthermore, isolated eosinophilic pancreatitis without extrapancreatic disease has also been reported [27, 28]. A pancreatic tumor with or without pancreaticobiliary obstruction, and hence pancreatic resection due to a suspected malignancy, was the usual mode of presentation in these cases. As eosinophils contain several cytotoxic/antihelminthic factors and proinflammatory mediators, the possibility that eosinophils may elicit pancreatitis due to a direct toxic effect has been considered [3, 4, 29]. Other examples where pancreatic damage by invading eosinophils has been discussed include the hypereosinophilic syndrome [13, 14, 30] and also pancreatic pseudocysts with eosinophilic infiltration [26, 31, 32]. However, whether invading eosinophils may really damage pancreatic tissue or if they can cause pancreatitis in the context of EGE is unknown. It should also be noted that pancreatic tissue eosinophilia occurred in several other pancreatic disorders in a recent, comprehensive pathological study [26].

Clinically, EGE may thus be associated with both symptomatic acute pancreatitis as well as with "eosinophilic pancreatitis" or even a pancreatic mass. Before embarking upon pancreatic surgery, eosinophil counts and, in relevant cases, further diagnostic work-up such as endoscopy with biopsy are important since resection is unnecessary in these cases [3, 10]. In the 3 cases in Table 1 where pancreatic resection was avoided (patients 4, 6, and 8), the acute pancreatitis was self-limiting and without complications. Although several surgical complications of EGE exist, they are rare, and surgery should rarely be necessary [33, 34]. It should also be noted that the thickened bowel wall may make surgical resection difficult and prone to anastomotic dehiscence, as was the case in our patient and a previously reported case [6]. Regarding medical treatment, dietary manipulation and treatment with prednisone or prednisolone, 40-60 mg daily have been widely used [3, 4, 34]. More recently, non-steroid alternatives such as cromolyn, montelukast (Singulair), hydroxyurea, azathioprine and ketotifen have been tried with some effect [3, 4].

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