

Multiple perforations and fistula formation following corticosteroid administration: A case report

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Abstract

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare systemic small- and medium-sized-vessel vasculitis. The literature contains only a few reports of gastrointestinal perforation with this condition. We report a patient with EGPA treated with high-dose steroid who underwent emergency surgery for intestinal perforations. We performed a simple repair of the 11 perforations. Intestinal fistulas developed 8 d postoperatively; they healed well after 60 d of continuous washing and negative pressure suction. The clinical data of 14 additional patients with EGPA or Churg-Strauss syndrome complicated with gastrointestinal perforation, which were reported from 1996 to 2014, were also collected and compared. The formation of multiple perforations and fistulas following high dosage steroid administration can have a good outcome with appropriate management. Meticulous attention to abdominal symptoms and appropriate interventions can result in timely management. Corticosteroid administration remains a very important perioperative procedure for EGPA.

Key words: Vasculitis; Eosinophilic granulomatosis with polyangiitis; Churg-Strauss syndrome; Gastrointestinal perforation; Surgery

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Core tip: Eosinophilic granulomatosis with polyangiitis (EGPA) complicated with intestinal perforation is very rare. It needs urgent surgical intervention but hormone administration usually covers up the situation and

delays the prognosis. We report a 43-year-old male diagnosed with EGPA by biopsy who experienced high-dose hormone administration, 11 intestinal perforations, postoperative intestinal fistula, and eventually recovered. This article aims to share the treatment course and experience.

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INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare type of necrotizing vasculitis affecting small to medium-sized vessels. It is typically characterized by asthma, lung infiltrates, necrotizing granulomas, and hypereosinophilia. It is an uncommon form of vasculitis with a prevalence that ranges from 10.7 to 13 cases/million^[1]. Gastrointestinal involvement has been reported to occur in approximately 50% of EGPA patients. Symptoms include abdominal pain, vomiting and diarrhea^[2]. Although EGPA very easily involves the digestive system, the chance of digestive tract perforation is very low and only a handful of cases have been reported. We report a case of EGPA with 11 intestinal perforations, and discuss the subsequent treatment.

CASE REPORT

A 43-year-old male with a 3-mo history of asthma was admitted to the Rheumatoid Immune Department of Shengjing Hospital in July 2013. The patient complained of a cough of one-month duration, blood-stained sputum, 14-d peripheral purpura, 3-d diarrhea, and an oral ulcer. His height was 176 cm and weight was 72 kg when admission. His temperature was 37.2 °C, his pulse was 78 per minute, and his blood pressure was 128/78 mmHg. Multiple skin purpura was found in the physical examination. Heart sounds were clear and regular with no murmur. A few moist rales were heard with lung auscultation. Abdominal examination was unremarkable. Laboratory studies revealed leukocytosis (15600/mm³) with eosinophilia (20.3%), a marked increase in inflammatory indices (ESR: 69 mm at the first hour; CRP: 176 mg/L), rheumatoid factor (656 UI/mL), and positive pANCA antibody. A pulmonary computed tomography (CT) scan revealed multiple low-density oval shadows, with the largest one measuring about 3.2 cm × 2.6 cm (Figure 1). A diagnosis of vasculitis was made. A biopsy of the nasal mucosa revealed an eosinophilic infiltration. We diagnosed EGPA according to the revised international Chapel Hill nomenclature. The patient received methylprednisolone

(120 mg intravenously daily) and ifosfamide for the treatment of the pulmonary lesions. The patient's condition exacerbated during the first three days following admission; the methylprednisolone dose was increased to 500 mg (intravenously daily × 2) and then was gradually tapered. On the 13th day after admission (160 mg methylprednisolone intravenously daily), he experienced a sudden onset of fever and abdominal pain. The physical examination revealed generalized abdominal tenderness without apparent rebound tenderness, and muscle tension. No specific treatment was given. After 11 h, the abdominal pain exacerbated and peritonitis developed. An abdominal CT scan showed an amount of free gas in the abdominal cavity (Figure 2). A laparotomy was performed immediately, which revealed scattered eleven perforations in the intestine. The proximal one was located approximately 150 cm distal from the ligament of Treitz ligament, and the distal one located approximately 50 cm from the ileocecal valve, with the largest measuring about 3 cm × 3 cm (Figure 3). Considering the high risk of short bowel syndrome, we made a simple repair of the intestinal perforations. Histopathological examination did not reveal either eosinophilic infiltration or granuloma formation of the vessels (Figure 4).

Continued intravenous therapy with intermittent ifosfamide as well as somatostatin and esomeprazole was administered postoperatively. The hormone dosage was tapered from 160 mg downward. On postoperative day 6, when the steroid was reduced to 80 mg, the patient's vasculitis exacerbated and he developed fever and new purpura on the entire body. Eight days postoperatively, an intestinal fistula developed, which was confirmed by fistulography (Figure 5). With continuous saline washing through a double-lumen cannula connected to a negative pressure suction apparatus, the drainage was about 300 mL intestinal fluid daily; the fistula slowly healed. The patient began eating on postoperative day 45. Gastric retention occurred after eating; it was treated with decompression *via* a nasogastric tube, total parenteral nutrition, and a gastric motility stimulating agent. The patient resumed eating about two months postoperatively, and the drainage was minimal. When the steroid dosage was reduced to 60 mg intravenously, the fistula healed and the patient was discharged.

Unfortunately, four months later, an intestinal fistula and vasculitis recurred. Although the amount was 5 mL daily, he was readmitted and underwent continuous washing and negative pressure suction. The fistula healed slowly during one month. When last seen in the outpatient clinic in March 2014, he was in good health without any symptoms or eosinophilia. Laboratory analysis revealed 0.1% eosinophils and negative pANCA antibodies.

DISCUSSION

EGPA, formerly named churg-strauss syndrome (CSS),



Figure 1 Pulmonary computed tomography images showing bilateral consolidation with air-bronchogram, especially in the right lung with multiple ground glass low-density shadows.

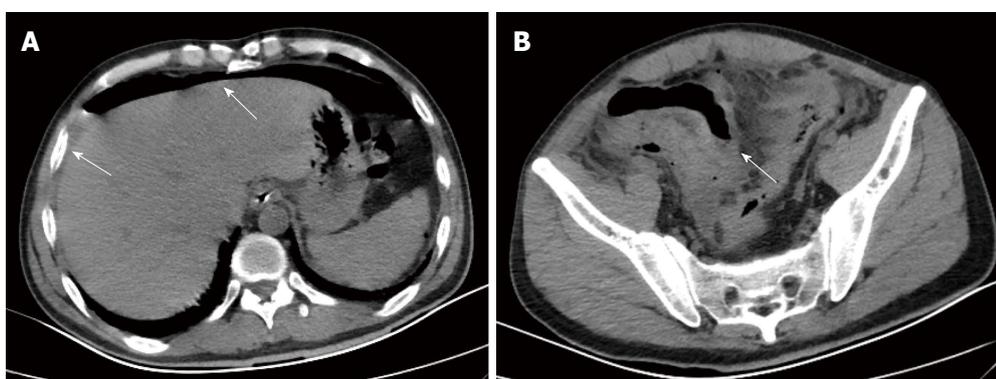


Figure 2 Abdominal transverse computed tomography images. A: Free air in the abdomen and fluid around the liver; B: Intestinal wall thickening in the right lower quadrant and seepage, scattered with free air.



Figure 3 Intraoperative findings. There were 11 perforations in the intestine. The arrow points to the bigger one measuring about 3 cm × 3 cm.

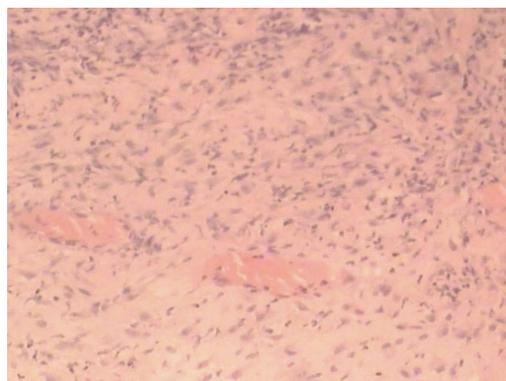


Figure 4 Histopathological examination showing a large number of infiltrated inflammatory cells (HE staining, × 100).

is characterized by the presence of severe asthma as well as blood and tissue eosinophilia. It is an uncommon form of vasculitis, with a prevalence that ranges from 10.7 to 13 cases/million. Although it is classified as vasculitis, the affected tissue usually does not show necrotizing vasculitis or granulomata, rather an apparently nondestructive infiltration of the vessel walls by eosinophils; in fact, only 40%-60% of patients with CSS have anti-neutrophil cytoplasmic antibodies (ANCA)^[3]. For this reason the diagnostic criteria remain clinical.

Gastrointestinal involvement is present in 32.6% of CSS patients. In 29.11% of the cases, the large bowel is involved, in 53.5%, the small bowel is involved, in 16.6%, the gastroduodenal region is involved, and in 6.3%, pancreatitis and cholecystitis occur. The mortality rate is 11.9%^[4-6]. Although gastrointestinal symptoms are common, perforated ulcers are relatively uncommon and only a small number of cases have been documented in the literature^[7]. Because multiple organs are involved and peritonitis symptoms are not typical, complicated clinical manifestations occur, which delays

Table 1 Summary of cases of Churg-Strauss syndrome/eosinophilic granulomatosis with polyangiitis with digestive perforation in the English literature

Ref.	year	Age/sex	Initial symptoms	WBC (/mm ³)	Eosino (%)	Hormone	Perforation	treatment	Histology	Second perforation	Prognosis
Ikoma <i>et al</i> ^[10]	2014	19/ female	Asthma	24700	39	Yes	Ileum	Anastomosis	Transmural infiltration of numerous eosinophils with thrombosis and extensive involvement of small arteries	No	Alive
Kaul <i>et al</i> ^[11]	2014	58/ male	Low-grade fever	94000	42	Yes	Ileo-caecal junction	Ileostomy	Transmural inflammation of sub-mucosal and serosal vessels with perivascular infiltrate comprising of lymphomononuclear cells and eosinophils	No	Alive
Assmann <i>et al</i> ^[12]	2014	32/ male	Dyspnea, fatigue, fever and chest pain	-	5500/1	Yes + cyclophosphamide	Middle part of jejunum	Anastomosis	-	No	Alive
Assmann <i>et al</i> ^[12]	2014	36/ male	Dyspnea, fatigue, fever and chest pain	-	4900/1	Yes + cyclophosphamide	Colon transversum	Anastomosis	Eosinophilic infiltration and thrombotic vessel occlusion	No	Alive
Çiledağ <i>et al</i> ^[8]	2012	35/ male	Anorexia	-	35	Yes	Small intestine	Repair	-	No	Died
Venditti <i>et al</i> ^[13]	2011	69/ male	Abdominal pain	-	-	Yes	Right and transverse colon	Ileostomy	Multiple ulcers, extravasal granulomas and mucosal pseudopolyps	No	Alive
Zanaboni <i>et al</i> ^[14]	2008	43/ male	Asthma	32000	65	Yes	Small intestine	Anastomosis	Necrotizing ischemic vasculitis with inflammatory granulomatous infiltrates of lymphocytes, polymorphonuclear cells and eosinophils	Yes	Alive
Rolla <i>et al</i> ^[15]	2007	55/ male	Asthma	15500	21	Yes	Ileum	Anastomosis	Granulomatous vasculitis with eosinophilic infiltration	No	Alive
Murakami <i>et al</i> ^[5]	2004	51/ female	Asthma	27650	62	Yes	Ileum	Anastomosis	Angiitis of small vessels surrounded by eosinophilic infiltration and granuloma of the vessels	No	Died
Nagashima <i>et al</i> ^[16]	2002	67/ male	Asthma	18500	65	Yes	Intestine	Anastomosis	Vasculitis in the small arteries and arterioles characterized by thrombotic occlusion with fibrinoid necrosis of the vascular wall and prominent inflammatory cell infiltration in the perivascular region	No	Alive
Nakamura <i>et al</i> ^[17]	2002	31/ male	Epigastralgia	19700	40	Yes	Jejunum and ileum	Anastomosis	Multiple ulcerative lesions with remarkable eosinophilic infiltration and thrombosis obstruction of small vessels	No	Alive
Alvarez <i>et al</i> ^[18]	2002	64/ female	Urticaria, recurrent rhinitis, and asthma	10000	34	Yes	Intestine	Anastomosis	Wall ulcerations, vascular thrombosis with fibrinoid necrosis, and eosinophilic infiltrates	Yes	Died
Kim <i>et al</i> ^[4]	2000	72/ female	Asthma	6600	14	Yes	Sigmoid colon	Anastomosis	Ulceration with heavy infiltrations of eosinophils, neutrophils and lymphoplasm cells	-	-

Sharma <i>et al</i> ^[19]	1996	16/ male	Low-grade, continuous fever and wheezing sounds in the chest	12600	70	Yes	Jejunum	Anastomosis	Necrotizing vasculitis with marked eosinophilic infiltration of medium-to- small blood vessels and extravascular granulomas	No	Died
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Figure 5 Fistulography showing that after injection of contrast agents, the intestine of the right lower quadrant abdomen developed a fistula.

treatment and results in a poor prognosis.

A systematic review of the literature was performed using the keywords "Churg-Strauss syndrome/eosinophilic granulomatosis with polyangiitis" and "gastrointestinal perforation" in PubMed to search articles from 1951 to December 2014. In China, CSS/EGPA with gastrointestinal perforation is very rare, and there is no relevant report. The articles were restricted to English language only. Duplicate reports and papers with important data missing were excluded. We included the papers on digestive tract perforation with CSS/EGPA, and compared the characteristics (Table 1). The average patient age was 46.3 years (range: 16-72 years; males: 10; females: 4). A half of the patients were complicated with the symptom of asthma, and all of them had received corticosteroid treatment. Their prognosis was poor, with 4/13 (30.77%; case 13 was unknown) dying during hospitalization, although the causes of death were very different. A second perforation of the digestive system occurred in 2 (15.38%) of 13 patients (case 13 was unknown).

Ulceration, perforation, and stenosis of the gastrointestinal tract are assumed to be the results of ischemia caused by vasculitis. The small intestine is the most commonly affected site^[8]. Immunosuppressive therapy, especially large-dosage corticosteroids, may play an important role in the development of an intestinal perforation. However, sometimes, it is difficult to distinguish clinically whether the intestinal perforation is due to vasculitis itself or immunosuppression^[9].

Treatment of a gastrointestinal perforation in patients with active vasculitis can be challenging. A delayed diagnosis may lead to a delayed cure, as in our patient. First, we did not pay adequate attention to the digestive symptoms: Sour regurgitation, heartburn,

and abdominal pain. Second, the symptoms of peritonitis are often atypical in patients receiving long-term administration of glucocorticoids. Third, when the digestive tract perforation occurred, the patient was in the rheumatic ward. As a result of consultation, diagnosis, and department transference, treatment delay can occur. Fourth, the gastrointestinal perforation may occur during a clinical remission. The perforation of this case occurred during the process of steroid tapering. Pathologic examination of the perforated bowel revealed no significant eosinophil infiltration.

In conclusion, improved awareness of gastrointestinal symptoms may allow for timely management of a perforation. Multiple perforations and fistulas caused by high dosage steroids can have a good outcome with appropriate management. Prompt surgical treatment is necessary. The choice of the appropriate surgical approach should be based on the time the perforations occurred, their size, numbers, and sites. Adequate steroid administration and intensive care play an important role during perioperative treatment.

COMMENTS

Case characteristics

A 43-year-old male with a 3-mo history of asthma, a cough of one-month duration, blood-stained sputum, 14 d of peripheral purpura, 3 d of diarrhea, and an oral ulcer. On the 13th day after admission, the patient experienced a sudden onset of fever and abdominal pain. And the abdominal pain exacerbated and peritonitis developed rapidly.

Clinical diagnosis

History of asthma, peripheral purpura, and peritonitis.

Differential diagnosis

Granulomatosis with polyangiitis, microscopic polyangiitis, and polyarteritis nodosa.

Laboratory diagnosis

Laboratory studies revealed leukocytosis (15600/mm³) with eosinophilia (20.3%), a marked increase in inflammatory indices (ESR: 69 mm at the first hour; CRP: 176 mg/L), rheumatoid factor (656 UI/mL), and positive pANCA antibody.

Imaging diagnosis

A pulmonary computed tomography (CT) scan revealed multiple low-density oval shadows, with the largest one measuring about 3.2 cm × 2.6 cm. An abdominal CT scan showed free air in the abdomen.

Pathological diagnosis

A biopsy of the nasal mucosa revealed an eosinophilic infiltration.

Treatment

Continued intravenous hormone therapy with intermittent ifosfamide

perioperatively, and intestinal perforation repair.

Related reports

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare type of necrotizing vasculitis affecting small to medium-sized vessels; it is typically characterized by asthma, lung infiltrates, necrotizing granulomas, and hypereosinophilia. Gastrointestinal involvement even perforation is more unusual and results in a poor prognosis.

Term explanation

EGPA with multiple intestinal perforations is very rare. Prompt surgical treatment is necessary. Adequate steroid administration and intensive care play an important role during perioperative treatment.

Experiences and lessons

Reasonable amount of hormone administration is the key point during the treatment. Excess hormone may induce intestinal perforation while insufficient amount could induce disease relapse and intestinal fistula postoperatively.

Peer-review

This is an interesting case report and the paper is well written.

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