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CASE REPORT

Abdominal ascites in children as the presentation of eosinophilic gastroenteritis: A surgeon's perspective

Lan-Jie Cheng, Shu-Cheng Zhang*

Department of Pediatric Surgery, Shengjing Hospital of China Medical University, 36, Sanhao Street, Heping district, Shenyang 110004, PR China

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KEYWORDS
Abdominal ascites;
Eosinophilic gastroenteritis;
Peripheral eosinophilia;
Methylprednisolone

Summary
Background: Abdominal ascites is a common problem in general surgery. The causes include parasitic diseases, tuberculosis, malignancies, hypoalbuminemia, abdominal inflammatory diseases, and peritonitis. Eosinophilic gastroenteritis (EG) has also been reported to be an infrequent cause. To our knowledge, most instances of abdominal ascites from EG have occurred in adults and been reported by physicians or gastroenterologists. Herein, we report a small series of children who presented with eosinophilic ascites from a surgeon's perspective.
Methods: Five children with EG (male: 3; female: 2) were selected for review of medical data and diagnostic reports.
Results: The patients typically presented with intermittent abdominal pain ($n = 5$), diarrhea and nausea ($n = 2$), abdominal distension ($n = 2$), fever ($n = 2$), and histories of allergic disease ($n = 3$). Peripheral eosinophilia was regularly noted, three children showing elevated IgE levels. Abdominal ultrasound and CT performed in each instance demonstrated abdominal ascites. Surgical intervention was elected in two patients. Dietary control and a methylprednisolone regimen were then instituted in all children, followed by full clinical remissions. After a regular follow-up, all patients are doing well.
Conclusions: Surgeons should be aware of EG as a rare cause of ascites, even in a pediatric population and especially in children with strong histories of allergic diseases, peripheral blood eosinophilia, and/or family histories of EG. It is important to avoid unnecessary surgical intervention, because dietary control and methylprednisolone treatment are effective remedies.

Introduction

Abdominal ascites is a common problem in general surgery. The causes include malignancies, hypoalbuminemia, abdom-

* Corresponding author.
E-mail address: zhangshucheng76@126.com (S.-C. Zhang).

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inal inflammatory diseases, peritonitis, parasitic diseases, tuberculosis, and lacteal duct abnormalities. In the pediatric population, eosinophilic gastroenteritis (EG) is an uncommon cause of pediatric abdominal ascites [1]. By accepted definition, EG is an inflammatory disease of unknown etiology that is characterized by gastrointestinal signs and symptoms such as pain or distention of the abdomen, nausea, vomiting, diarrhea, and loss of weight. This occurs in conjunction with peripheral eosinophilia, leading to eosinophilic infiltration within layers of the gastrointestinal wall [2—5].Clinical manifestations are related to histologic levels of eosinophilic wall infiltration and the particular segment or segments involved. Involvement of the tunica serosa, observed in 10% of cases, typically results in eosinophilic ascites [2,5].

Most instances of abdominal ascites from EG have occurred in adults and been reported by physicians or gastroenterologists. Herein, we report a small series of children who presented with eosinophilic ascites in order to improve awareness and management of abdominal ascites in childhood.

Methods

The ethics committee of Shengjing Hospital at China Medical University granted access to medical records for a retrospective review of clinical data. A total of 5 consecutive children, who presented with ascites (male: 3; female: 2), aged 8 to 12 years were diagnosed with EG between January 2005 and December 2015. The diagnosis was based on clinical presentation, peripheral eosinophilia, serum IgE level, and response to empirical therapy. The following parameters were investigated: gender, age, initial presentation, physical findings, laboratory and imaging findings, cytology and pathology findings, and bone marrow biopsy findings. Treatments (e.g. surgical intervention, dietary control, and steroid therapy) were also reviewed. Children were regularly followed for a median of 5 years after discharge. A summary of patient characteristics is shown in Table 1.

Results

Signs, symptoms, and presentation

Presenting signs and symptoms included intermittent abdominal pain ($n = 5$), diarrhea and nausea ($n = 2$), abdominal distension ($n = 2$), fever ($n = 2$), and history of allergic disease ($n = 3$). On physical examination, mild abdominal tenderness and shifting dullness were noted (Table 1).

Peripheral eosinophilia and IgE level

The peripheral blood cell counts showed an increased in eosinophils (range, $2.8—6.0 \times 10^9$ cells/L) with 30.1—41.3% of WBCs. Blood films confirmed prominent eosinophilia with no immature cells or blasts. Total IgE values were clearly elevated in 3 children, and IgE to specific allergens (pollens, fungi, milk, eggs, fish, beans, shrimp, and rice) was documented in 3 children (Table 1).

Imaging and cytologic examinations

Ultrasound and abdominal CT performed in all 5 children demonstrated overt abdominal ascites, as well as slight edema and thickening of the bowel wall or mesentery in patients 1 and 2 (Fig. 1A—C). Esophagogastroduodenoscopy (EGD) was undertaken in the initial two children only, revealing features of a nonspecific superficial gastritis: erythema, ulcerations, and focal gastric and duodenal erosions (Fig. 1D). Gastric mucosal biopsies obtained from these two children displayed mucosal eosinophilic infiltration (12—15/mm^2 in patient 1 and 18—21/mm^2 in patient 2, Fig. 1E). Given the superficial nature of such biopsies, high-power examinations were restricted to lamina propria of mucosa (muscularis and serosa not included). In all children, diagnostic paracentesis produced clear, colorless fluid containing WBCs (5800/mL) with > 90% eosinophils and no tumor cells. The bone marrow biopsies of 2 children disclosed hypercellular marrow with hyperplasia of the eosinophilic myeloid series (Fig. 1F).

Differential diagnosis

All potential known causes of ascites were systematically excluded (Table 2). In particular, urine and stool cultures were negative; and tests assessing liver and renal function, coagulation, serum albumin, and inflammatory markers were all within normal ranges. Screening for hepatitis B and C viruses, HIV, Epstein—Barr virus, and cytomegalovirus were also negative, and amylase levels of urine/serum were normal. Likewise, urinary metanephrines and hydroxyindoleacetic acid levels were normal. Parasitic infestations were ruled out through routine stool examinations (no parasitic cysts or ova) and enzyme-linked immunosorbent assays. In addition, chest x-ray films, purified protein derivative tests (PPD tests), and polymerase chain reaction (PCR)-based assay served to rule out tuberculosis. Diagnostic paracentesis and composition analysis were performed to exclude lacteal rupture.

Patient management

Initial interventions

Two patients were hospitalized locally before referral to our unit. One underwent emergency appendectomy for acute appendicitis. The surgical specimen was not available for histologic examination. The other patient with presumed primary peritonitis underwent periodic drainage of ascitic fluid and antibiotic therapy. Both patients were subsequently referred to our unit for refractory ascites of unknown origin. Given the results of EGD, diagnosis of EG was established.

Dietary control

Because there was a high suspicion for EG, we empirically instituted dietary restrictions in all 5 children. Documented food allergies included milk ($n = 3$), eggs ($n = 3$), fish ($n = 2$), beans ($n = 2$), shrimp ($n = 1$), and rice ($n = 1$). All identified food allergens were excluded from the children's diets for at least 6 months, and then gradually re-introduced.

Table 1 Presentation, diagnosis, and treatment of consecutive patients with eosinophilic gastroenteritis ($n = 5$).

	Gender	Age	Presentation	Examinations			Initial diagnosis	Treatments	Follow-up interval
				Ultrasound and CT	Peripheral eosinophil count and IgE level	Other imaging and cytologic examinations			
1	M	12y	Abdominal pain, diarrhea and nausea, and fixed tenderness of right lower abdomen	Overt abdominal ascites demonstrated by CT in all five patients, as well as edema and thickening of the bowel wall or mesentery (patients 1 and 2 only)	IgE: 732.03 IU/mL[a] WBC: 11.3×10^9/L[b] Eo: 3.8×10^9/L[c] Eo%: 33.6%[d]	EGD: superficial gastritis; Biopsy: eosinophils ($12-15/mm^2$) infiltrating mucosa; Bone marrow: active proliferation Ascitic fluid cytology: WBC 5800/mL, Eo% 90.6%	Acute appendicitis	Appendectomy; Methylprednisolone IV: 2 mg/kg.d, 7 days[#] OR: 48 mg/d (max)[##] Dietary control	9 years
2	F	12y	Intermittent abdominal pain, fever, upper respiratory tract infection, and history of allergic disease		IgE: 889.12 IU/mL WBC: 14.9×10^9/L Eo: 6.0×10^9/L Eo%: 40.3%	EGD: superficial gastritis; Biopsy: eosinophils ($18-21/mm^2$) infiltrating mucosa; Bone marrow: active proliferation Ascitic fluid cytology: WBC 6670/mL, Eo% 91.2%	Primary peritonitis	Abdominal drainage; Methylprednisolone IV: 2 mg/kg.d, 10 days OR: 48 mg/d (max) Dietary control	8 years
3	F	8y	Abdominal pain, fever, diarrhea and nausea, and history of allergic disease		IgE: 145.33 IU/mL WBC: 9.3×10^9/L Eo: 2.8×10^9/L Eo%: 30.1%	EGD and bone marrow: biopsies not taken; Ascitic fluid cytology: clear and colorless with no tumor cells, WBC 4900/mL, Eo% 98.1%	Acute gastroenteritis	Methylprednisolone IV: 2 mg/kg.d, 7 days OR: 48 mg/d (max) Dietary control	4 years
4	F	10y	Intermittent abdominal pain, abdominal distension, and history of allergic disease		IgE: 157.69 IU/mL WBC: 10.9×10^9/L Eo: 4.5×10^9/L Eo%: 41.3%	Ascitic fluid cytology: no tumor cells, WBC 6490/mL, Eo% 98.4%	Abdominal ascites	Methylprednisolone IV: 2 mg/kg.d, 7 days OR: 48 mg/d (max) Dietary control	3 years
5	M	12y	Intermittent abdominal pain, and abdominal distension		IgE: 959.64 IU/mL WBC: 9.9×10^9/L Eo: 3.7×10^9/L Eo%: 37.4%	Ascitic fluid cytology: no tumor cells, WBC 5300/mL, Eo% 95.9%	Abdominal ascites	Methylprednisolone IV: 2 mg/kg.d, 10 days OR: 48 mg/d (max) Dietary control	8 months

WBC: white blood cell count; Eo: peripheral eosinophil count; Eo%: proportion of eosinophils in peripheral blood; IV: intravenous; OR: oral.

[a] Normal reference range for total IgE, 1.3—165.3 IU/mL.

[b] Normal reference range for WBC, $3.5-9.9 \times 10^9$ cells/L.

[c] Normal reference range for Eo, $0.04-0.49 \times 10^9$ cells/L.

[d] Normal reference range for Eo%, 0.7—7.8%.

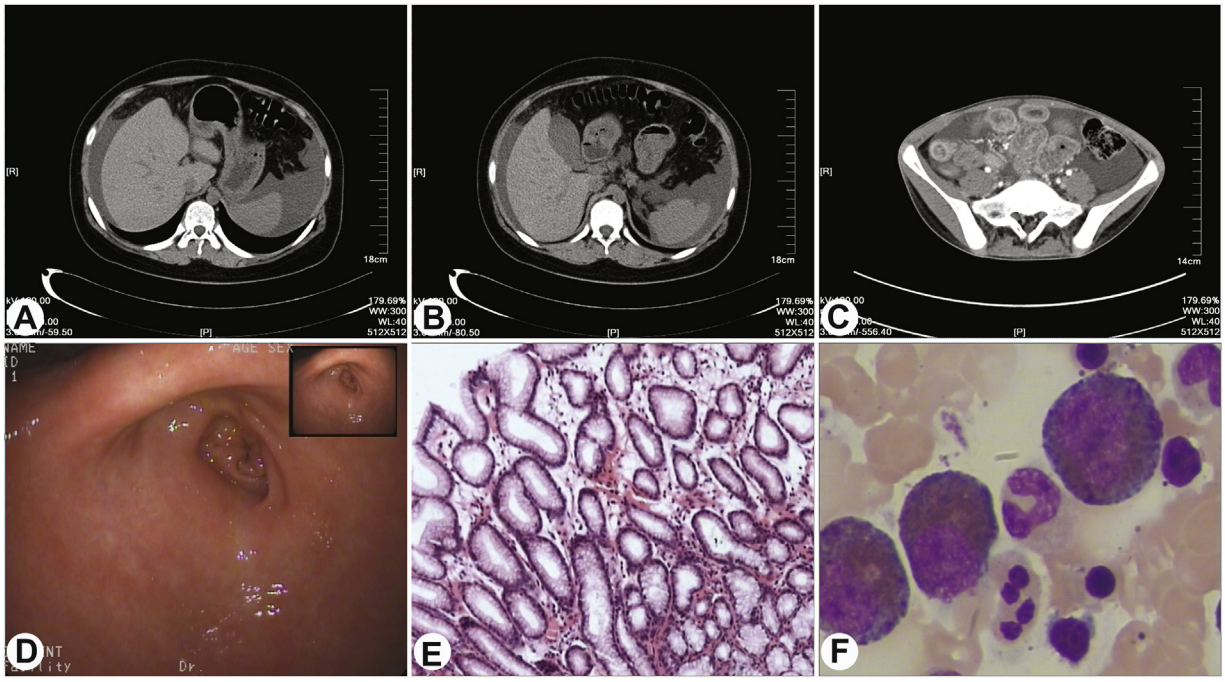

Figure 1 Imaging and cytologic examinations of patients with EG. A—C. Abdominal CT of 12 year-old boy with eosinophilic gastroenteritis demonstrating overt ascites of the hepatorenal space, splenorenal space, and abdominal cavity with numerous mesenteric lymph nodes and slight edema/thickening of bowel wall or mesentery. D. View at esophagogastroduodenoscopy, showing nonspecific superficial gastritis with slight erythema, ulcerations, or focal erosions. E. Gastric mucosal biopsies with eosinophilic infiltrates of mucosa (12—15/mm^2). F. Bone marrow examination displaying proliferative activity: 59.6% granulocytes, 21.2% erythrocytes, and 21.2% eosinophils (a relative abundance).

Table 2 Differential diagnosis of abdominal ascites.

Diagnosis	Differential points	
	Presentations	Examinations
Intraluminal inflammatory disease (appendicitis)	History of infection and fixed tenderness of right lower abdomen demonstrated on physical examination	Peripheral blood neutrophils and CRP elevated; imaging examination (ultrasound and CT) give valuable diagnostic clues
Primary peritonitis	History of infection	Peripheral blood neutrophils and CRP elevated; blood cultures positive for pathogen
Parasitoses	History of polluted food and/or direct contact with diseased fluid or feces	Stool and body fluid examinations at least 3 times in search of pathogen or parasitic ovum
Tuberculosis	History of direct contact with diseased fluid or patients	Sputum examination, chest x-ray film, PPD test and PCR-TB
Acute gastroenteritis	History of poisonous food simulating viral or bacterial infection	Stool leukocyte and CRP elevated; stool cultures positive for pathogenic microbes
Hypoalbuminemia	History of hepatic or renal disease or changes in nutritional status (fasting or malnutrition)	Serum albumin and total protein for diagnosis
Gastrointestinal malignancy	Abdominal distension, abdominal pain, fatigue, anorexia, circulatory disorder, multi-organ failure, and other systemic complications	Imaging examinations (ultrasound, CT, and MR) showing primary tumor; paracentesis cytology in search of tumor cells
Chylous ascites	Abdominal distension, abdominal pain	Milky ascitic fluid verified by composition analysis
Portal hypertension	History of chronic liver disease, splenomegaly and abdominal collaterals	Laboratory testing and/or serum albumin determinations and imaging of the liver helpful for diagnosis
Eosinophilic Gastroenteritis	Strong history of allergic disease, and/or a family history of EG	IgE level and peripheral blood eosinophils

Medical therapy

Because steroids have proven to be an effective strategy for the treatment of EG, intravenous methylprednisolone was initiated at a daily dose of 2 mg/kg for 7—10 days in all patients. Once the ascites had resolved and the peripheral eosinophilia and IgE levels had normalized, steroids were given orally at a maximal dosage of 48 mg/d, which was gradually tapered by lowering the dose by 4 mg every 3 days.

Follow-up

Through dietary control and a methylprednisolone treatment regimen, all five children became symptom-free and achieved full clinical remission. After discharge, all were followed regularly (median: 5 years; range: 8 months to 9 years). At present, they are doing well, no relapses having occurred.

Discussion

EG is a heterogeneous disorder of both children and adults with a peak incidence in the third to fifth decade. Besides the serosal form, in which 75% of affected patients are women, EG is predominantly a male disorder (3:2 ratio) [4,6,7]. Eosinophilic involvement of the gastrointestinal tract occurs in multiple locations. Eosinophils are equally likely to be found in the stomach or duodenum, or in both. In addition, one-third of patients have concurrent involvement of the esophagus or colon [8,9].

Given its wide array of nonspecific symptoms and relatively low prevalence, the diagnosis of EG requires a high index of suspicion. Laboratory data have relatively little utility in characterizing the patient population. Although the levels of markers associated with nonspecific inflammation and allergy are consistently elevated, the levels vary greatly. However, there are a few revealing findings. First, peripheral blood eosinophilia is increased in 50% to 100% of patients with EG, with the magnitude of eosinophilia often paralleling the severity of symptoms. Another important index is an elevated total serum IgE, with radioallergosorbent test (RAST) positivity for food allergens found in 60% of patients [5,9]. In this case series, both peripheral eosinophilia and increased total serum IgE levels were present. Along with the patient history and physical findings, there was little doubt about the diagnosis. On the other hand, radiographic and endoscopic manifestations of EG are often variable and nonspecific, contributing little to the diagnosis [4]. In our patients, overt ascites and slight abdominal inflammatory changes were the sole demonstrable features in radiographic and endoscopic examinations.

The symptoms and presentations of EG are diverse, because eosinophilic infiltration varies in different layers of the gastrointestinal tract. EG has been classified accordingly into three subtypes affecting mucosa, muscularis, and subserosa [2,5]. Especially in the pediatric population, patients with mucosal inflammation usually present with protein-losing enteropathy and malabsorption. In EG involving the muscularis, obstruction is a frequent presentation, and most often involves the distal stomach. Obstruction of the distal stomach requires careful differentiation from congenital pyloric stenosis or other sources of gastric outlet obstruction. Eosinophilic ascites is generally associated with the serosal form of EG and responds well to steroid treatment, [4] as described in the children reported here.

Eosinophilic ascites is extremely rare in children. Herein, we report a small series of children who presented with ascites. The unexplained peripheral eosinophilia raised the possibility of EG. The diagnosis was confirmed by analysis of ascitic fluid and supported by evidence of eosinophilic infiltration of the upper gut in 2 children. Although EGD was not performed, the diagnosis of EG was still likely for the other 3 children after other causes of ascites were excluded. Eosinophilic abscesses and aggregates of eosinophils within muscularis or serosa are deemed pathognomonic signs, and a positive correlation between eosinophil levels and disease severity has been verified. In serosal EG, however, analysis of peritoneal fluid offers the most decisive clue, showing a sterile exudative effusion containing up to 95% eosinophils [1,10].

EG presenting as overt ascites requires differentiation from other potential causes (Table 2) [1,10—12]. Secondary ascites due to the intraluminal inflammation of the gut (as in appendicitis) is the commonest form of abdominal ascites. A careful physical examination is essential to check for fixed tenderness of right lower abdomen, and imaging studies may reveal valuable clues.

Primary peritonitis, which is rarely diagnosed preoperatively, is an uncommon disease that accounts for pediatric abdominal emergencies. It is often associated with urinary or hepatic pathology or systemic infection. Increased levels of peripheral blood neutrophils and C - reactive protein (CRP) along with clear signs of infection and blood cultures positive for pathogenic bacteria aid in the diagnosis [11].

Parasitic infestations are one of the most common causes of ascites in most of Asia and Africa, and can be ruled out by routine stool examinations (no parasitic cysts or ova) and enzyme-linked immunosorbent assays [1]. Ascites caused by hypoalbuminemia is usually associated with hepatic or renal diseases or even extreme nutritional deficiencies (fasting or malnutrition). A variety of abdominal malignancies may also result in ascites, for which paracentesis with cytologic examination might be informative.

Abdominal tuberculosis, one of the most common causes of ascites, constitutes up to 12% of extrapulmonary tuberculosis in China, with the abdomen being the sixth most frequent site of extrapulmonary involvement. Abdominal tuberculosis presents a diagnostic dilemma because of its varied and nonspecific clinical presentation and the lack of a single very specific and sensitive diagnostic test. A common clinical feature, an adequate imaging study, endoscopy, laparotomy, biopsy with histopathology, mycobacterial isolation, PPD testing, the QuantiFERON-TB Gold test, the GeneXpert Assay, MULTIPLEX PCR, and clinical response to antituberculosis therapy have been used for early diagnosis [12].

Ascites is a serious complication of cirrhosis and portal hypertension, arising most frequently in children with advanced liver disease. Chylous ascites is the extravasation of milky chyle, which is rich in triglycerides, into the peritoneal cavity. It can occur as a result of trauma or obstruction of the lymphatic system, the most common causes of which are malignancy (hepatoma, small bowel lymphoma, small bowel angiosarcoma, and retroperitoneal lymphoma), cirrhosis, and trauma after abdominal surgery.

In children, the most common causes of chylous ascites are congenital abnormalities such as lymphangiectasia, mesenteric cyst, and idiopathic ''leaky lymphatics''. The diagnosis of chylous ascites is made by peritoneocentesis with analysis of the ascitic fluid. An ascitic triglyceride concentration greater than 200 mg/dL is consistent with chylous ascites [13].

Acute gastroenteritis, which can be caused by viral or bacterial infections, most commonly manifests as the sudden onset of vomiting, diarrhea, fever, and stomach cramps. However, abdominal ascites is also a rare sign of gastroenteritis. A complete blood count and a fecal test or even a fecal culture should easily provide the diagnosis. Ultimately, we must consider EG in any patient with voluminous ascites, and obtain IgE levels and peripheral blood samples to check for eosinophilia, so that EG is not overlooked.

The therapeutic mainstays in patients with EG are corticosteroids and avoidance of food antigens [3,4,14]. Fortunately, all of the patients in our series responded to corticosteroid treatment and controlled diets. Other medical therapies of EG include antihistamines, sodium cromoglycate, and ketotifen. Ketotifen, both an antihistamine and mast cell stabilizer, has been used successfully as the sole therapeutic intervention to treat eosinophilic ascites [15]. Casella et al have recommended ketotifen as first-line therapy for eosinophilic ascites, because it is a relatively inexpensive and safe drug [15]. However, for our patients, neither ketotifen nor other antihistamines were used, because the ascites was severe in all the children; and their parents wanted highly effective therapies that led to rapid resolution of the signs and symptoms. Therefore, methylprednisolone administered at a dose of 2 mg/kg/d led to complete remission in all 5 children and normalization of the eosinophil counts within 7 to 10 days of therapy. The overall prognosis of EG is good because of the excellent response to steroids as the first-line therapy. EG carries a good and long-term prognosis, although the clinical course may entail periodic remissions and relapses. Continued low-dose therapy may thus be required for sustained remissions.

In summary, this case series serves to remind pediatric surgeons that a diagnosis of EG must be entertained in every patient presenting with ascites (with or without peripheral eosinophilia), especially children having strong histories of allergic diseases, peripheral blood eosinophilia, or familial EG.

Disclosure of interest

The authors have not supplied their declaration of competing interest.

References

[1] Agrawal S, Vohra S, Rawat S, Kashyap V. Eosinophilic ascites: a diagnostic and therapeutic challenge. World J Gastrointest Surg 2016;8(9):656—9.
[2] Talley NJ, Shorter RG, Phillips SF, Zinsmeister AR. Eosinophilic gastroenteritis: a clinicopathological study of patients with disease of the mucosa, muscle layer, and subserosal tissues. Gut 1990;31(1):54—8.
[3] Ko HM, Morotti RA, Yershov O, Chehade M. Eosinophilic gastritis in children: Clinicopathological correlation, disease course, and response to therapy. Am J Gastroenterol 2014;109(8):1277—85.
[4] Reed C, Woosley JT, Dellon ES. Clinical characteristics, treatment outcomes, and resource utilization in children and adults with eosinophilic gastroenteritis. Dig Liver Dis 2015;47(3):197—201.
[5] Egan M, Furuta GT. Eosinophilic gastrointestinal diseases (EGIDs) beyond eosinophilic esophagitis (EoE). Ann Allergy Asthma Immunol 2018.
[6] Mansoor E, Saleh MA, Cooper GS. Prevalence of eosinophilic gastroenteritis and colitis in a population-based study, from 2012 to 2017. Clin Gastroenterol Hepatol 2017;15(11):1733—41.
[7] Jensen ET, Martin CF, Kappelman MD, Dellon ES. Prevalence of eosinophilic gastritis, gastroenteritis, and colitis: estimates from a national administrative database. J Pediatr Gastroenterol Nutr 2016;62(1):36—42.
[8] Walker MM, Potter M, Talley NJ. Eosinophilic gastroenteritis and other eosinophilic gut diseases distal to the oesophagus. Lancet Gastroenterol Hepatol 2018;3(4):271—80.
[9] Cianferoni A, Spergel JM, Muir A. Recent advances in the pathological understanding of eosinophilic esophagitis. Expert Rev Gastroenterol Hepatol 2015;9(12):1501—10.
[10] Elliott JA, McCormack O, Tchrakian N, Conlon N, Ryan CE, Lim KT, et al. Eosinophilic ascites with marked peripheral eosinophilia: a diagnostic challenge. Eur J Gastroenterol Hepatol 2014;26(4):478—84.
[11] Hadley GP. Intra-abdominal sepsis — epidemiology, aetiology and management. Semin Pediatr Surg 2014;23(6):357—62.
[12] Delisle M, Seguin J, Zeilinski D, Moore DL. Paediatric abdominal tuberculosis in developed countries: case series and literature review. Arch Dis Child 2016;101(3):253—8.
[13] Lizaola B, Bonder A, Trivedi HD, Tapper EB, Cardenas A. Review article: the diagnostic approach and current management of chylous ascites. Aliment Pharmacol Ther 2017;46(9):816—24.
[14] Zhang M, Li Y. Eosinophilic gastroenteritis: a state-of-the-art review. J Gastroenterol Hepatol 2017;32(1):64—72.
[15] Casella G, Villanacci V, Bassotti G. Eosinophilic ascites resolution with Ketotifen. Mayo Clin Proc 2011;86(10):1027.