Eosinophilic ascites with marked peripheral eosinophilia: a diagnostic challenge

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Eosinophilic disease of the gastrointestinal tract is rare and is characterized by the presence of gastrointestinal symptoms in association with eosinophilic infiltration of any part of the gastrointestinal tract. Clinical presentation of eosinophilic gastroenteritis (EGE) varies not only by the part of the gastrointestinal tract involved but also with the depth of eosinophilic infiltration of the gut wall. We describe the case of a 41-year-old woman with a history of atopy who presented with severe abdominal pain and diarrhoea. Investigations showed large-volume eosinophil-rich ascites and a markedly elevated peripheral blood eosinophil count and immunoglobulin E level. Bone marrow aspirate, trephine biopsy and T-cell studies showed no evidence of underlying haematological malignancy. Vasculitic disease and parasitic infection were systematically excluded. Colonic and upper gastrointestinal biopsies confirmed a diagnosis of EGE with eosinophilic ascites. The patient

was treated with systemic corticosteroids and dietary allergen elimination with dramatic therapeutic response. The diagnostic and therapeutic challenges associated with EGE in its various forms are discussed. *Eur J Gastroenterol Hepatol* 00:000–000 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Eosinophilic disease of the gastrointestinal (GI) tract is characterized by the presence of gastrointestinal symptoms in association with eosinophilic infiltration of any part of the GI tract, which cannot be attributed to another cause. Clinical presentation of eosinophilic gastroenteritis (EGE) varies according to the site affected and the depth of eosinophilic infiltration of the gut wall [1,2]. We describe a case of EGE manifesting as ascites and severe abdominal pain in a young woman with a history of gallbladder disease and atopy.

Case report

A 41-year-old woman presented to the emergency department with a 3-week history of worsening severe abdominal pain associated with bloating, nausea, vomiting and diarrhoea. She had undergone a laparoscopic cholecystectomy for acute cholecystitis 4 months previously and a right salpingectomy for salpingitis 3 years previously. In addition, she had a history of gastritis treated with a proton pump inhibitor and a bleeding disorder of undefined aetiology. The patient reported multiple drug allergies with a clinical history of both urticarial skin rashes and positive skin-prick and intradermal testing in response to penicillins and macrolides. Her family history was positive for Von

Willebrand's disease, ovarian and breast cancer. There was no history of recent travel. Despite severe abdominal pain, the patient was systemically well. Clinical examination showed diffuse abdominal tenderness and moderate distension.

Initial investigations indicated a leukocytosis of $18.3 \times 10^9/l$ with an eosinophilic predominance of $10.2 \times 10^9/l$, 56% (normal range $0.0\text{--}0.4 \times 10^9/l$, 1–3%). The full blood count was otherwise unremarkable. C-reactive protein was mildly elevated, but erythrocyte sedimentation rate, liver function tests and amylase were all normal. Given the history of recent cholecystectomy, an urgent abdominal ultrasound was performed. Ultrasound identified a large volume of intra-abdominal free fluid.

The diagnosis at this point was unclear. Differential diagnoses of bile leak with incidental eosinophilia, EGE, variants of the hyper-eosinophilic syndrome (HES), paraneoplastic eosinophilia (possibly related to ovarian cancer), Churg–Strauss syndrome and parasitic infection were all considered.

The blood film showed mature eosinophils. Although bone marrow aspirate and trephine biopsy showed an increased myeloid-to-erythroid ratio with an increase in the

eosinophilic component, there was no evidence of dysplasia. Further investigation to exclude the HES showed no *JAK-2* mutation and no evidence of 4q12 interstitial chromosomal deletion causing the *FIP1L1-PDGFR α* fusion gene, effectively excluding a primary myeloproliferative disorder. T-cell subsets were also analysed to exclude the lymphocytic variant HES and showed no evidence of clonal expansion or phenotypic aberrancy.

Antineutrophil cytoplasmic antibodies were negative, whereas plain chest radiograph and urinalysis showed no abnormality. Although immunoglobulin E (IgE) was moderately elevated, multiple stool samples for ova and parasites were negative. Tissue transglutaminase antibody was negative.

Cancer antigen-125 (CA-125) was mildly elevated. Computed tomography of the abdomen and pelvis (Fig. 1) showed moderate-volume ascites but no solid organ tumour or omental deposits. Diagnostic ascitic tap under ultrasound guidance was performed and a small volume of turbid brown fluid was sent for routine analysis. Cytology showed mixed inflammatory cells with prominent eosinophils, but no malignant cells.

Given the family history of breast and ovarian cancer, elevated CA-125 and the uncertain diagnosis, a decision was made to perform a diagnostic laparoscopy. At laparoscopy, 2.5 l of brown ascitic fluid was drained and sent for further analysis. The stomach, small bowel, colon and adnexa appeared macroscopically normal. Fallopian remnant biopsies and ovarian cyst fluid cytology showed no evidence of malignancy. However, ascitic fluid cytology showed abundant eosinophils (Fig. 2).

Upper GI endoscopy and colonoscopy were performed. This showed mild diffuse erythematous oesophagitis, gastritis and duodenitis, and a mildly inflamed colonic

mucosa (Fig. 3). Serial biopsies were sent for histopathological examination. Diffuse increased eosinophilic infiltrate in the muscularis mucosa, but not the mucosa, was noted in oesophageal, gastric, duodenal and colonic biopsies. Intense eosinophilic infiltrates were observed in a single colonic biopsy (Fig. 4). These findings were consistent with a diagnosis of serosal or muscular EGE with eosinophilic ascites. Of note, retrospective re-examination of the patient's cholecystectomy specimen indicated chronic cholecystitis with mixed eosinophilic and lymphocytic infiltrates, in addition to cholelithiasis.

Although the patient had a history of atopy and drug hypersensitivity, food-specific IgE levels were not

Fig. 2

Ascitic fluid cytology (high power): abundant eosinophils are present in the fluid specimen. No malignant cells are seen.

Fig. 1

Computed tomography of the abdomen and pelvis, axial sections (a) and coronal view (b) showed moderate-volume ascites without identifiable cause.

Fig. 3

Endoscopic image on upper gastrointestinal endoscopy demonstrated gastritis on retroflexed view.

significantly elevated. Treatment was initiated with oral prednisolone 60 mg once daily with a slow weaning course. Therapeutic response was monitored clinically and with daily full blood count, weight and abdominal girth. Serial IgE and C-reactive protein levels were also assessed. Response to corticosteroid treatment was dramatic, with a reduction in eosinophil count from $10.4 \times 10^9/l$ after a single dose (Fig. 5), with a more gradual reduction in symptoms.

During subsequent outpatient follow-up, the patient developed symptoms of dysphagia. Swallowed fluticasone and oral nonenteric-coated budesonide were commenced, with significant improvement. The eosinophil count remained within normal limits with corticosteroid wean to 15 mg once daily but unfortunately, the patient's symptoms relapsed and the eosinophil count increased with further dose reductions. Despite the negative food-specific IgE testing, it was decided to undertake a trial oligoantigenic diet as a steroid-sparing strategy before consideration of systemic leukotriene antagonism or biologic agents. After just 3 days of an oligoantigenic diet comprising poultry, rice, pulses and root vegetables, the patient was symptom free, with an eosinophil count of $0.9 \times 10^9/l$. Despite gradual tailored reintroduction of foodstuffs, dietary modification has allowed tapering of prednisolone to 5 mg once daily and discontinuation of budesonide without recurrence of symptoms or profound eosinophilia. The patient continues to be monitored closely by the Immunology, Gastroenterology, Haematology and Clinical Nutrition services at our Institution.

Discussion

EGE is a rare condition characterized by symptomatic eosinophilic infiltration of any part or layer of the

Fig. 4

Colonic biopsy (low power): There is intense eosinophil infiltration, consistent with the diagnosis of eosinophilic gastroenteritis.

gastrointestinal tract. EGE can occur in adult and paediatric populations [3–10] and although the condition is generally more common in men [11], the serosal form with ascites more commonly affects women [12].

The pathophysiology of EGE remains unclear, but there is a strong association with atopy, with 80% of patients reporting a personal history of asthma, eczema, allergic rhinitis or allergy [13]. The association with atopy suggests a genetic component and, unsurprisingly, approximately 16% of patients with EGE have a family member with a similar condition [13]. It is hypothesized that in individuals with familial predisposition towards IgE-mediated reactions, exposure to certain environmental precipitants or indeed autoantigens results in eosinophil proliferation and activation, as would physiologically occur in response to parasitic infection [14]. Activated eosinophils release an array of cytotoxins by degranulation, including major basic protein, eosinophil cationic protein and others, producing tissue damage both directly and by downstream production of cytokines and leukotrienes. Eosinophil degranulation also triggers the release of histamine from mast cells, further perpetuating inflammation and cell damage [13]. This hypothesis is supported by several studies identifying major basic protein and eosinophil cationic protein deposits in areas of tissue damage in a manner similar to that described in other atopic conditions [15–18].

Symptoms of EGE vary depending on the affected part of the GI tract and depth of infiltration, with mucosal forms typically associated with nausea, vomiting, diarrhoea, malabsorption and protein-losing enteropathy. In contrast, transmural involvement presents with subacute obstruction due to mural thickening or acute obstruction due to intussusception or volvulus. The rare serosal form

presents with symptoms of bloating and eosinophil-rich ascites [12]. The stomach and duodenum are the most commonly affected sites in EGE, with colonic involvement being less common [12]. However, it is unclear whether this represents bias related to accessibility to endoscopic biopsy [13].

Eosinophilic infiltration of the biliary tree can occur in isolation [19–25] or in the context of parasitic infection [26], eosinophilic vasculitis [27–29], HES [22,30] or EGE [31–34]. Documented hepatobiliary involvement in EGE is very rare, with only four cases identified within the English literature [31–34]. In patients with EGE, biliary involvement can result in cholecystitis, cholangitis or a combination of both [31–34]. Although primary eosinophilic cholecystitis has been reported in patients with concomitant cholelithiasis, intense eosinophilic infiltration is more commonly a feature of acalculous cholecystitis [35]. In addition, eosinophilic infiltration of the gallbladder wall can occur in patients with symptomatic gallstone disease in the absence of any eosinophilic disorder [36]. It is therefore uncertain whether our patient's initial presentation with acute cholecystitis may have represented an early manifestation of EGE or simply symptomatic cholelithiasis.

In a patient with peripheral and GI eosinophilia, a broad spectrum of differential diagnoses must be considered. The presence of hepatosplenomegaly, cardiac symptoms, blood film abnormalities or evidence of marrow suppression should arouse suspicion of HES. In contrast, coexistent asthma, sinusitis, mononucleitis multiplex or an evolving nephritic-type picture is indicative of Churg–Strauss syndrome. A history of recent travel to the tropics should raise suspicion of parasitic infection such as toxocariasis, ascariasis, *Strongyloides stercoralis*, *Trichuris trichiura* and *Enterobius vermicularis*. In any case, it is essential that parasitic infection is completely ruled out before treatment of EGE as initiation of corticosteroid therapy in the presence of occult parasitic infection may result in catastrophic disseminated disease.

HES comprises a group of idiopathic, myeloproliferative and lymphoproliferative conditions characterized by persistent peripheral and tissue hyper eosinophilia associated with end organ damage, without another underlying cause (such as allergy or infection) [37,38]. HES may be classified into clonal and reactive hyper eosinophilia. Whereas clonal eosinophilia is associated with myeloproliferative disorders, for example, chronic myeloid leukaemia or chronic eosinophilic leukaemia, reactive polyclonal hyper eosinophilia may result from overproduction of IL-5 by a population of clonal or immunophenotypically aberrant T lymphocytes. As such, in patients with marked or persistent peripheral eosinophilia, it is important to exclude an underlying clonal process, and bone marrow aspirate and trephine biopsy are recommended [9]. Further investigation to exclude HES may be indicated in certain cases, and should assess for each of the pathogenetically distinct

variants of HES. For example, cytogenetic clonality of eosinophils implies a diagnosis of chronic eosinophilic leukaemia. A subset of these patients has the so-called *FIP1L1-PDGFR α* (*F/P*)-associated HES, in which a sporadic haematopoietic stem cell chromosomal rearrangement occurs, producing the *F/P* fusion gene on 4q12. The *F/P* fusion gene can be detected using reverse transcription polymerase chain reaction or fluorescent in-situ hybridization for surrogate markers of the chromosomal abnormality. In patients with a reactive polyclonal eosinophilia, analysis of T-cell subsets may detect a phenotypically aberrant T-cell population, whereas assessment of T-cell receptor gene rearrangement patterns can be used to determine clonality in patients with an underlying lymphoproliferative disorder [39]. These investigations are essential in the work-up of a patient with possible HES as certain variants, in particular *F/P*-associated HES, show dramatic therapeutic response to the tyrosine kinase inhibitor imatinib [39].

Peripheral eosinophilia was marked in our patient, with 56% eosinophilic predominance (normal range 1–3%); however, there was no evidence of a clonal population of eosinophils or T cells, and profound peripheral eosinophilia in EGE is associated with the serosal form. However, it should be noted that the eosinophil count can be normal at presentation in up to 23% of EGE in general, which may further obscure the diagnosis [9]. Elevated IgE levels may be present and both eosinophil count and IgE may be useful in monitoring response to treatment, which is typically dramatic in cases of serosal EGE with eosinophilic ascites [9], as shown in Fig. 5.

Although the endoscopic changes of eosinophilic oesophagitis are characteristic and well described, eosinophilic infiltration of the rest of the GI tract produces much less marked macroscopic changes and as such histopathological diagnosis is essential. However, because of the patchy nature of the disease, endoscopic biopsy may be negative in up to 13% of individuals with confirmed EGE [10]. This is particularly true of the serosal form, where mucosal infiltration may be minimal [12]. In such cases, ascitic sampling or laparoscopic serosal biopsy may be required to confirm the diagnosis.

The prognosis for patients with EGE is relatively good, and a proportion of cases of EGE may be so mild that no treatment is indicated or spontaneous remission is achieved [9]. In patients who are persistently symptomatic, the current standard treatment is high-dose oral corticosteroids with a slow weaning course, and the response is typically very good [40]. For localized disease or where systemic corticosteroid treatment is not well tolerated, topical corticosteroid therapy in the form of swallowed fluticasone or nonenteric coated budesonide may be of benefit [41]. It is unclear whether topical corticosteroid treatment is as efficacious in serosal EGE as in the mucosal variant.

Fig. 5

Graphs showing the response to treatment of peripheral blood eosinophil count ($\times 10^9/l$), percentage eosinophils (%), immunoglobulin E (IgE) levels (kU/l) and C-reactive protein levels (mg/l). Red arrows indicate the initiation of corticosteroid treatment. Note that the values trend upwards as corticosteroid therapy is weaned.

The typical course of the disease following treatment is not well described. Although some patients may achieve remission off corticosteroids, others seem to follow a

relapsing and remitting course [40] and, for this reason, there has been recent interest in the development of steroid-sparing strategies [13]. In patients with mucosal

disease, there is anecdotal evidence for the use of sodium cromoglycate for its mast cell-stabilizing properties, especially in individuals with a strong history of atopy or elevated serum IgE, and mucosal predominant disease [42]. However, leukotriene receptor antagonists such as montelukast have been used successfully to treat the serosal form of EGE [43,44]. Monoclonal antibodies directed against IgE and IL-5 (Omalizumab and Mepolizumab, respectively) as targeted treatments for EGE and other eosinophilic conditions show some promise in early clinical studies [45]. In addition to the above pharmacological approaches, it may be possible to significantly reduce steroid dependence in patients with food allergy through elimination, oligoantigenic or elemental diets [13,46,47]. Although patients with EGE may have significantly elevated total IgE, the utility of food-specific IgE levels for the prediction of response to dietary elimination in eosinophilic gastrointestinal disorders is controversial [48,49]. Therefore, food challenge studies are essential in this group of patients.

Conclusion

We describe the case of a 41-year-old woman with a history of atopy and gallbladder disease who presented with severe abdominal pain, diarrhoea and vomiting. Investigations indicated large-volume eosinophil-rich ascites and a markedly elevated peripheral blood eosinophil count and IgE level. Colonic and upper gastrointestinal biopsies confirmed a diagnosis of EGE with eosinophilic ascites. The patient was treated with systemic corticosteroids, with dramatic therapeutic response. Eosinophilic ascites is a rare presentation of EGE and is typically associated with serosal disease, which behaves in a manner distinct from the more common mucosal EGE. The diagnosis of EGE should be considered in patients with a strong history of atopy presenting with GI symptoms. In the presence of extra-intestinal symptoms or markedly elevated eosinophil counts, it is important to consider other more serious causes of systemic eosinophilia. Histopathological diagnosis is essential and is complicated by the patchy nature of mucosal disease and the paucity of mucosal infiltration in the serosal predominant form. Fortunately, prognosis is usually very good and in patients with relapsing disease, corticosteroid and diet therapy can be highly effective. In addition, topical agents and novel targeted pharmacologic therapies provide promise for steroid-free remission for patients with EGE.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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