Case Report

Unforeseen Gastrointestinal Events Following Antituberculous Therapy

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Abstract

Eosinophilic enteritis is a rare entity affecting human gastrointestinal tract. The exact etiology is unknown, and some drugs are implicated in causing this condition. We report a case of drug-induced eosinophilic enteritis, caused by antituberculous therapy (ATT). The cessation of ATT-induced clinical remission and symptoms were reproduced on drug re-challenge, which corroborated our diagnosis.

Keywords: Antituberculous therapy, ascites, eosinophilic gastroenteritis

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Introduction

Eosinophilic enteritis is a rare and benign inflammatory disorder, affecting small intestine, characterized by tissue infiltration of the intestinal wall with eosinophils, with or without peripheral eosinophilia.[1]

Several causes have been attributed to eosinophilia-induced gastrointestinal (GI) tract involvement including diseases such as inflammatory bowel disease, connective tissue disorder, parasitosis, malignancy, and drugs. Last but not the least, certain drugs have been implicated in causing eosinophilia. Here, we report an interesting case of drug-induced eosinophilic enteritis, offending agent being antituberculous therapy (ATT).

Case Report

A 55-year-old female presented to our emergency department with a history of diffuse abdominal pain and occasional nonbilious vomiting associated with loss of weight and appetite of 20 days duration. She had been recently diagnosed as having tuberculosis-related cervical lymphadenopathy and was started on standard quadruple ATT directly observed treatment regimen (rifampin 600 mg/isoniazid [INH] 300 mg/day, pyrazinamide 1 g/day, and ethambutol 800 mg/day). Two weeks after commencement, her symptoms started and gradually progressed. She consulted her family physician who advised her to stop ATT 5 days back and was referred to our department.

On examination, she was emaciated (body mass index = 18.4), there was no generalized/local lymphadenopathy, and systemic examination including respiratory and abdominal examination was within normal limits.

Her baseline blood, urine, and stool examination was normal, except for the fact that she had significant eosinophilia in hemogram and peripheral smear (eosinophils - 40%, absolute eosinophil count - 6000) [Figure 2]. Chest X-ray was normal, and abdominal ultrasonogram showed moderate ascites without any organomegaly. Peripheral smear did not show any parasites or abnormal cells. Kidney, liver, and thyroid function tests were normal, and cardiac evaluation was unremarkable.

Ascitic fluid analysis was suggestive of low serum ascites albumin gradient (3.6 mg/dl − 3.2 mg/dl = 0.4) and high protein (4.6 mg/dl) ascites. Ascitic fluid eosinophil count was 30%, and malignant cytology was negative. Hence, in view

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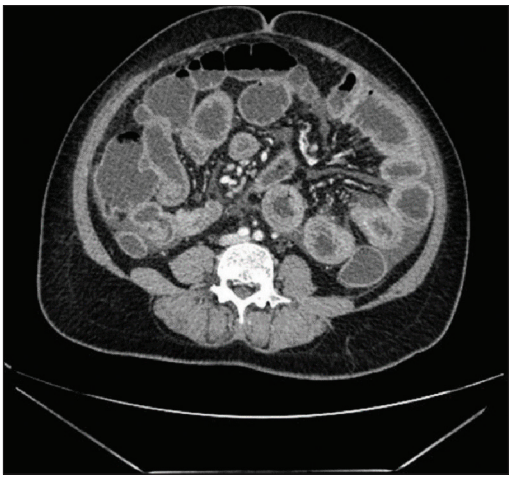

Figure 1: Contrast-enhanced computed tomography abdomen showing jejunal and ileal wall thickening with small mesenteric nodes and ascites

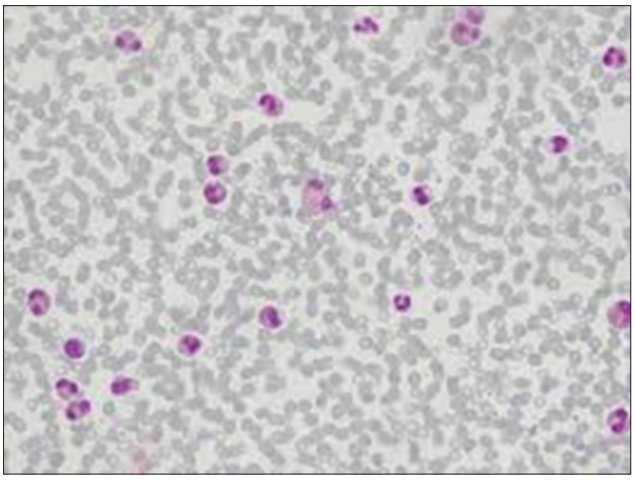

Figure 2: Peripheral smear showing eosinophilia

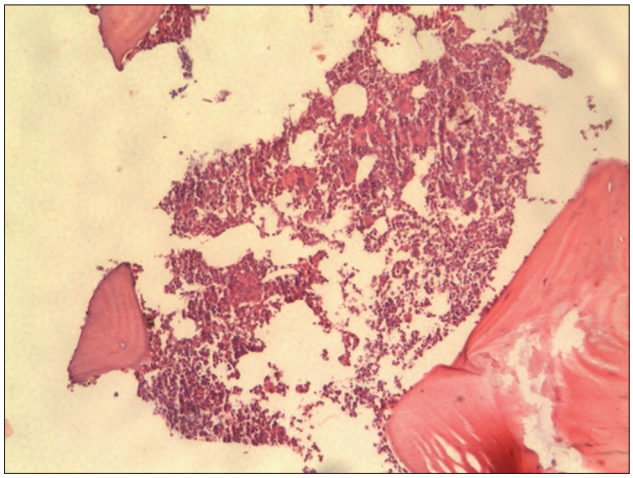

Figure 3: Bone marrow examination showing eosinophillic precursors without any malignant cells

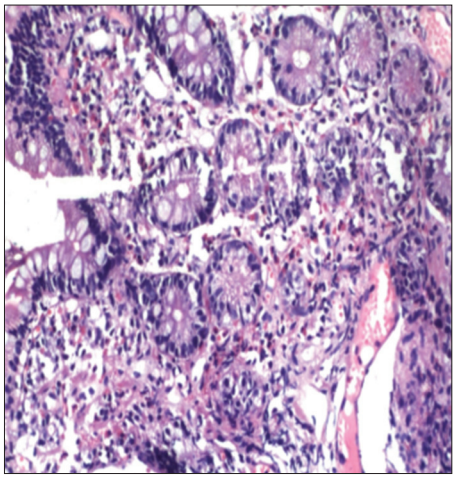

Figure 4: Low- and high-power views of jeunal and ileal biopsy specimen showing marked tissue eosinophilia

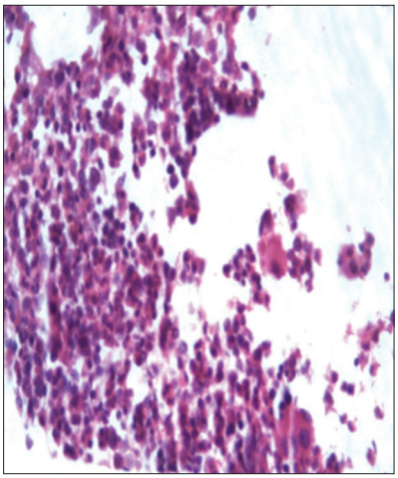

Figure 5: Low- and high-power views of jeunal and ileal biopsy specimen showing marked tissue eosinophilia

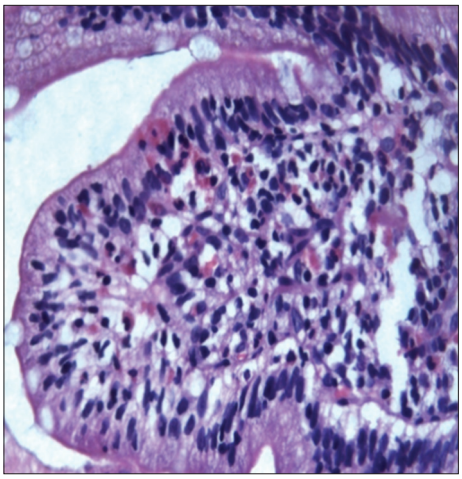

Figure 6: Low- and High-power views of jeunal and ileal biopsy specimen showing marked tissue eosinophilia

of exudative ascites, to localize the lesion, we proceeded with contrast-enhanced computed tomography of the abdomen which showed proximal jejunal and ileal wall thickening with multiple small mesenteric nodes and mild ascites [Figure 1]. We did panendoscopy (upper and lower GI scopy) and took

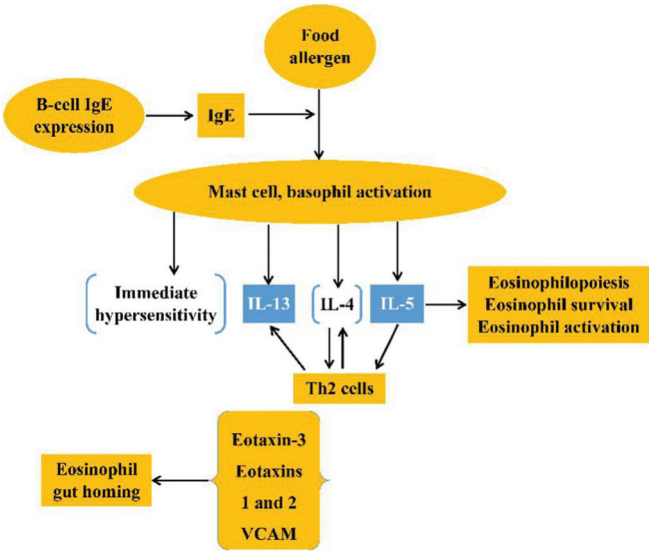

Figure 7: Flowchart showing mediators and mechanisms of eosinophil activation

segmental biopsies which were within normal limits. Hence, to evaluate small bowel, we proceeded with push enteroscopy, in the absence of double bowel enteroscopy, and took multiple jejunal biopsies. Even though endoscopy appeared normal, histology revealed eosinophilic infiltration of the jejunum (25–30/hpf) and there was no evidence of granuloma, parasite, or malignancy [Figures 4-6]. Emerging agents include mepolizumab–anti-IL-5 agent, omalizumab (anti-IgE antibody), and antieotaxin antibodies.[10] [Figure 7].

To rule out hematopoietic cause, hematologist opinion was obtained, and as per their advice, bone marrow examination and biopsy done showed eosinophilic precursors without any malignant shift.

With a final diagnosis of eosinophilic enteritis associated with peripheral and marrow eosinophilia, we strived to find the etiological cause. There was no history of atopy, food allergy, family history, respiratory tract infections, parasitosis, and connective tissue disorders/malignancies/vasculitis. We suspected drug-induced cause and hence reviewed the existing literature about drugs causing eosinophilic gastroenteritis [Table 1].

A recent hemogram taken before commencing ATT and repeated outside was normal (2% eosinophil count and a normal peripheral smear). With this history and no other drug/past history available, we reasonably concluded ATT as the offending agent.

All four front-line drugs have been implicated in causing eosinophil-associated disorders. Lange *et al*. described case of rifampicin-associated eosinophilic colitis.[2] Rifampicin-induced drug reaction with severe eosinophilia and systemic symptoms (DRESS). Rifampicin-induced lichenoid eruptions have also been described.[3,4] INH has been implicated in DRESS syndrome by Ditto *et al*.[5,6] DRESS syndrome and GI eosinophilia have been described with pyrazinamide and ethambutol.[7,8] Hence, we completely withheld ATT and started steroids (1 mg/kg) for 2 weeks followed by a 6-week taper, along with antihistaminics (levocetirizine 5 mg) and antihelminthic agents (diethylcarbamazine - 2 mg/kg).[1]

Table 1: Drugs causing eosinophilic gastroenteritis

Antimalarials
Antibiotics (cephalosporin, penicillin, nitourantoin)
ACE inhibitors
Anticonvulsants
NSAIDs
Azathioprine
5-ASA
Proton pump inhibitor
ATT

ATT: Antituberculous therapy, NSAIDs: Nonsteroidal anti-inflammatory drugs, 5-ASA: Five-aminosalicylic acid, ACE: Angiotensin-converting enzyme

Six weeks into follow-up, we reassessed her, her hemogram was normal, symptoms resolved, and repeat enteroscopy and histology were normal. Hence, after few days, we reintroduced INH and ethambutol. Initially, she was asymptomatic for 10 days; however, she soon developed abdominal pain again. Baseline investigations revealed eosinophilia on hemogram (10%), repeat ultrasonogram showed free fluid, and she was advised further workup; however, she was not willing and was subsequently lost to follow-up.

Discussion

First described by Kaisger *et al*. in 1937, eosinophilic enteritis is a rare disease (more in middle-aged people). The pathogenesis is incompletely understood but thought to a combination of genetic predisposition, family history, atopy, etc.[9]

Three types have been described: mucosal (60%), presenting as failure to thrive and malabsorbtion; muscular (30%), presenting with vomiting and obstructive symptoms; and serous (5%–10%), presenting with exudative ascites as in our patient.[1,10]

Drug-induced eosinophilic enteritis is still a rarer phenomenon. As all the four drugs have been implicated in causing eosinophilia, in this scenario, we cannot pinpoint one exact drug that caused the presentation. Anyway, it is safe and reasonable to attribute this to the starting of ATT since its inception leads to the clinical picture, which was promptly reversed on withdrawing ATT, along with the reappearance of symptoms postre-challenge. Unfortunately, since the patient was lost to follow-up, we could not fully document the clinical course. Because of rarity of disease, no guidelines exist for the treatment of drug-induced eosinophilic GI enteritis, let alone eosinophilic gastroenteritis. Stopping offending agents and starting antihelminthic and antihistaminics are the common remedial measures taken. Steroids can also be given in severe cases, as we have done in our case and can be tapered over a period of 1 month. Emerging agents include mepolizumab–anti-IL-5 agent, omalizumab (anti-IgE antibody), and antieotaxin antibodies.[10]

To sum it up, considering all these facts and background into equation, this is a rare case of ATT-induced eosinophilic enteritis.

Acknowledgment

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Conflicts of interest

There are no conflicts of interest.

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