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Unforeseen Gastrointestinal Events Following Antituberculous Therapy

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Eosinophilic enteritis is a rare disorder, affecting human gastrointestinal tract (GIT). 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 antituberculosis therapy (ATT). The cessation of ATT induced clinical remission and symptoms were reproduced on drug re-challenge, which corroborated our diagnosis.

Keywords: Eosinophilic gastroenteritis; anti tuberculous therapy (ATT); DRESS syndrome.

1. INTRODUCTION

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

Several causes have been attributed to eosinophilia induced gastrointestinal (GI) tract involvement including diseases like inflammatory bowel disease, connective tissue disorder, parasitosis, malignancy, drugs etc. Last but not the least, certain drugs have been implicated in causing eosinophilia. Here we report a case of

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drug induced eosinophilic enteritis, offending agent being antituberculosis therapy (ATT).

2. CASE REPORT

A 55 year old female presented to our emergency department with history of diffuse abdominal pain and occasional non bilious vomiting associated with loss of weight and appetite of twenty days duration . She had been recently diagnosed as having tuberculosis related cervical lymphadenopathy and was started on standard quadruple antituberculosis therapy Directly observed Treatment Regimen (DOTS) (Rifampin 600 mg / Isoniazid 300 mg/day, Pyrazinamide1g/day, and Ethambutol 800 mg/day). Two weeks after commencement, her symptoms gradually progressed. She consulted her family physician, who in turn stopped ATT and 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 significant eosinophilia in hemogram and peripheral smear (Eosinophils-40%, Absolute Eosinophil count-6000). Chest x ray was normal, and abdominal ultrasonogram (USG) showed moderate ascites without any organomegaly. Peripheral smear did not show any parasites or abnormal cells. Kidney, liver, thyroid function test were normal and cardiac evaluation was unremarkable.

Ascitic fluid analysis was suggestive of low Serum Ascites Albumin Gradient (SAAG) (3.6mg/dl-3.2mg/dl=.4), high protein (4.6mgdl) ascites. Ascitic fluid eosinophil count was 30 percent and malignant cytology was negative. Hence in view of the exudative ascites, to localize the lesion, we proceeded with Contrast CT of abdomen which showed proximal jejunal and ileal wall thickening with multiple small mesenteric nodes and mild ascites. We performed upper and lower GI endoscopy and took segmental biopsies which were within normal limits. To evaluate small bowel we proceeded with enteroscopy, and took multiple jejunal biopsies. Even though endoscopy appeared normal, histology revealed eosinophilic infiltration of jejunum (25-30/hpf) and there was no evidence of granuloma, parasite or malignancy.

To rule out hematopoietic cause, hematologist opinion was obtained and as per their advice, bone marrow examination and biopsy was done which 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, connective tissue disorders/ malignancies/vasculitis. We suspected drug induced cause and, reviewed the existing literature about drugs causing eosinophilic gastroenteritis.

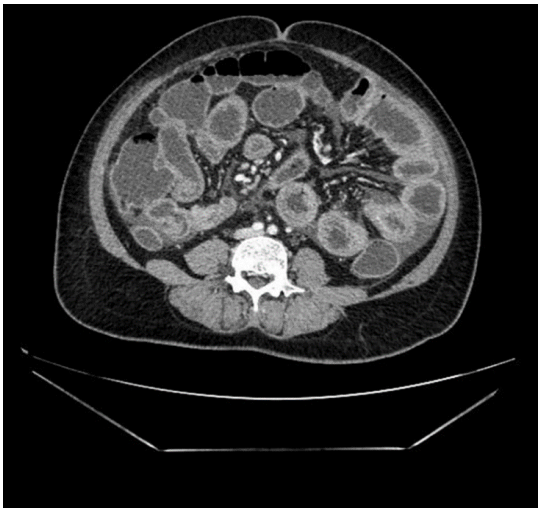


Fig. 1. CECT abdomen showing jejunal and ileal wall thickening with small mesenteric nodes and ascites

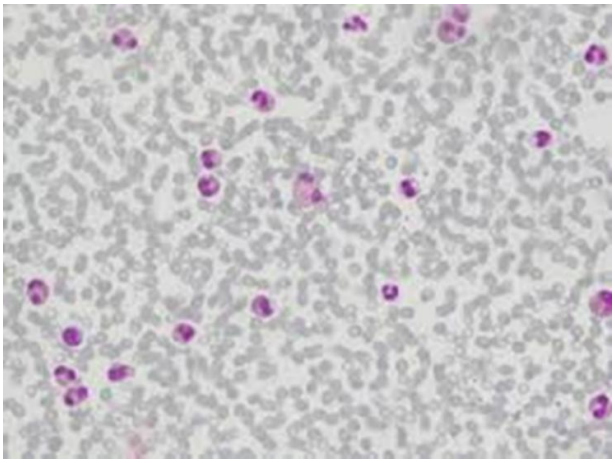


Fig. 2. Peripheral smear showing eosinophilia

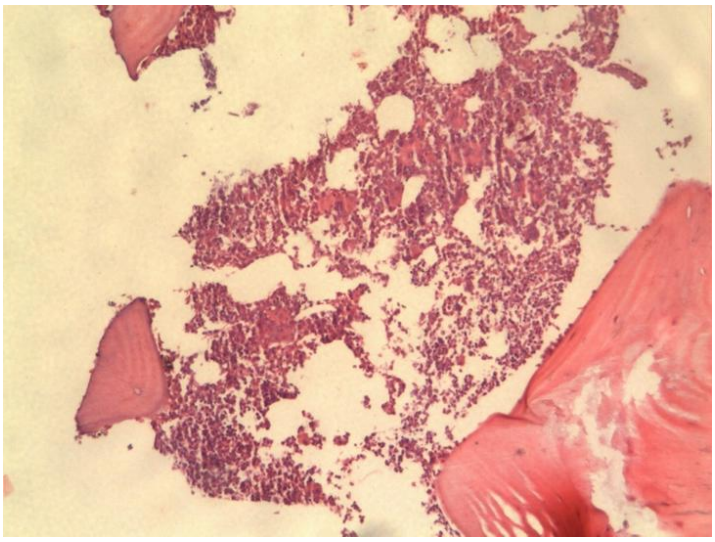
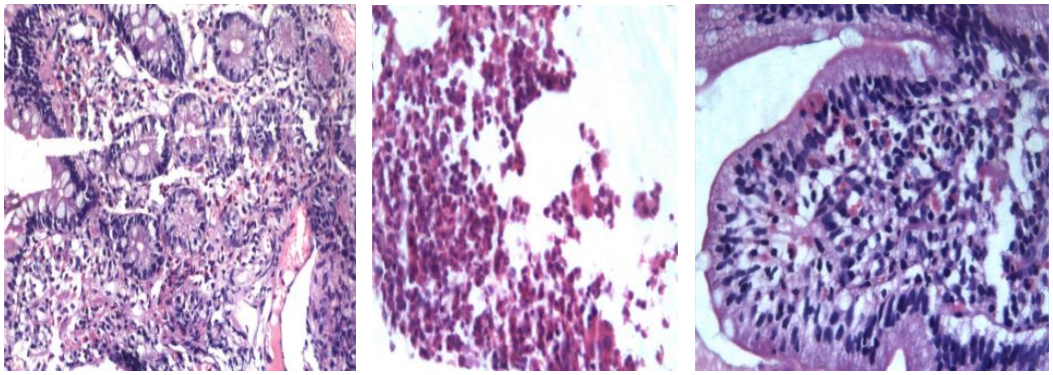


Fig. 3. Bone marrow examination showing eosinophillic precursors without any malignant cells



Figs. 4, 5 & 6. Low and High power views of jeunal and ileal biopsy specimen showing marked tissue eosinophilia

Table 1. List of drugs causing eosinophilic gastroenteritis

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

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] and Rifampicin induced DRESS (dug reaction with severe eosinophilia and systemic symptoms). Rifampicin induced lichenoid eruptions have also been described [3,4]. Isoniazid(INH) has been implicated in DRESS syndrome by AM Ditto et al. [5,6]. DRESS syndrome and GI eosinophilia has also been described with pyrazinamide and ethambutol [7,8]. Hence we completely withheld ATT, and started her on steroids (1 mg/kg) for two weeks followed by a six weeks tapering dose, along with antihistaminics (levocetrizine 5mg) and antihelminthic agents (Diethylcarbamezepine-2mgkg) [1].

After six weeks of follow-up, we reassessed the patient. Her hemogram was normal, symptoms resolved, enteroscopy and histology were normal. After few days, we reintroduced Isoniazid and ethambutol. Initally, she was asymptomatic for ten days, however she soon developed abdominal pain again. Baseline investigations revealed eosinophilia on hemogram (10%) and ultrasonogram showed free fluid, she was advised further workup, however she was not willing and was subsequently lost of follow-up.

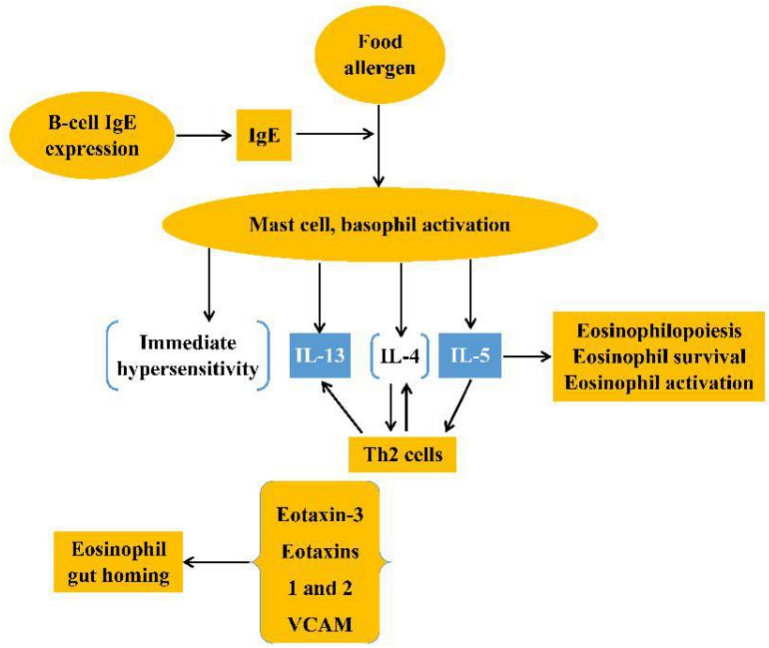


Fig. 7. Flow chart showing mediators and mechanisms of eosinophil activation

3. DISCUSSION AND CONCLUSION

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 has been implicated in causing eosinophilia, and in this scenario, we cannot pinpoint one exact drug that caused the presentation. Anyway it's safe and reasonable to attribute this to the starting of ATT since its inception lead to the clinical picture, which was promptly reversed on withdrawing ATT, along with the reappearance of symptoms post rechallenge. Unfortunately since the patient was lost of the follow-up, we could not fully document the clinical course .Because of rarity of disease, no guidelines exist for treatment of drug induced eosinophilic GI enteritis, let alone eosinophilic gastroenteritis. Stopping offending agents, starting antihelminthic drugs, and anthistaminics are the common remedial measures. Steroids can also be given in severe cases, as we have done in our patient and they ma be tapered over a period of one month. Emerging agents include mepoluzimumab-Anti IL-5 agent, Omalizumab (Anti IgE antibody), anti-eotaxin antibodies etc [10].

To sum it up, considering all these facts and background into equation, this is a rare case of antituberculous therapy (ATT) inducing eosinophilic enteritis.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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