Eosinophilic Esophagitis and Pharyngitis Presenting as Mass Lesion in a Patient With Inactive Rheumatoid Arthritis

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Abstract: We describe here a case of longstanding rheumatoid arthritis (RA) presenting with recurrent episodes of epigastric pain, melena, nonprogressive dysphagia, and hoarseness associated with persistent peripheral blood eosinophilia. Her RA was clinically inactive, but she had significant lymphadenopathy and hepatosplenomegaly. Computed tomographic scan of the thorax revealed circumferential wall thickening extending from the oropharynx to the gastroesophageal junction with a large polypoidal mass projecting into the lumen of the stomach. Histology revealed infiltration of the esophageal mucosa by eosinophils with a density of 40 to 80 per high-power field. The stratified squamous epithelium of the pharyngeal mucosa was also infiltrated by eosinophils with a density of more than 100 per high-power field. Eosinophilic esophagitis and pharyngitis were diagnosed, and the patient was administered corticosteroids and hydroxyurea, following which her symptoms resolved. On repeat imaging, there was significant reduction in esophageal wall thickening and luminal dilatation. There are few reports of tissue eosinophilia in association with RA, but the pathogenesis and any definite association with RA are not clear.

Key Words: rheumatoid arthritis, eosinophilia, eosinophilic esophagitis, eosinophilic pharyngitis

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Eosinophilic infiltration of the gastrointestinal (GI) tract can occur as a primary disease, or it can be secondary to parasitic infestation, drugs, and so on. Eosinophil-associated GI disorders are characterized by an infiltration of eosinophils within isolated or multiple segments of the GI tract. Primary eosinophilic esophagitis is increasingly being recognized as an immune-mediated disease that exclusively involves the esophagus.[1] We report here a case of hypereosinophilic state along with eosinophilic esophagitis and pharyngitis that occurred in a patient with longstanding inactive rheumatoid arthritis (RA), which has not been reported in the published literature. Apart from eosinophilic gastroenteritis,[2–4] tissue eosinophilia in RA has also been reported in the form of eosinophilic pneumonia,[5] eosinophilic fasciitis, eosinophilic vasculitis, and hypereosinophilic syndromes (HESs).[6] However, significance of tissue eosinophilia in RA is not clear, and it is possible that there could be more than one cause for it including an immunologic aberration.

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CASE REPORT

A 38-year-old lady from north India received a diagnosis of RA elsewhere in 1999 based on history of morning stiffness greater than 1 hr, arthritis involving proximal interphalangeal, metacarpal phalangeal, wrist, knee, elbow, ankle, and metatarsophalangeal joints; arthritis of hand joints with symmetric involvement of all the previously mentioned joints; and presence of rheumatoid nodules, positive rheumatoid factor, and characteristic radiologic changes, thereby fulfilling American College of Rheumatology criteria. She received chloroquine and low-dose methotrexate for RA only during the initial 2 years and subsequently switched over to ayurvedic medications for 6 more months. Since then, she has been off all other modalities of treatment, as she was pain-free despite the deformities. One and a half years after the diagnosis of RA, she had developed acute-onset breathlessness and stridor due to vocal cord palsy; and she has been on a tracheostomy tube since then.

She presented to us for the first time in February 2009 with multiple episodes of epigastric pain and melena since 6 years. She was also detected to have iron deficiency anemia and was given multiple blood transfusions before consulting us. She was also treated with proton pump inhibitors and a course of anti-*Helicobacter pylori* therapy. She also had nonprogressive dysphagia to solids more than liquids and hoarse voice since March 2008. There was no history of odynophagia, vomiting, early satiety, bleeding per rectum, diarrhea, jaundice, or significant weight loss.

She was documented to have peripheral blood eosinophilia at multiple instances over the last 9 years and was treated with diethyl carbamazine and antihelminthic agents. She denied any history of asthma, atopy, sinusitis, rhinitis, or food or drug allergy. She has also been on thyroxine supplementation since the year 2000 for hypothyroidism. She was not known to have hypertension or diabetes mellitus. There was no family history of atopy, malignancy, or autoimmune disorder.

On examination, rheumatoid nodules were present bilaterally over the olecranon. She had an enlarged, firm lymph node in the right axilla (central group). The liver was firm in consistency and was enlarged with a span of 16 cm. The spleen was firm and palpable 1 cm under left costal margin. She had advanced deformities and subluxations in hands and feet characteristic of RA. She had no active synovitis, and her disease activity score 28 was 2.1. She had no general systemic features, palpable purpura, or neuropathy to suggest systemic vasculitis. The rest of the physical examination was normal.

Investigations revealed hemoglobin of 10.4 g/dL; mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration were 82.8 fl, 27.6 pg, and 33.3 g/dL, respectively. The total white blood cell count was 10,000/μL with 34% eosinophils. Platelet count was 258,000/μL. Serum alanine aminotransferase and creatinine were normal. Stool examination revealed no parasites. Rheumatoid factor was positive with a titer of greater than 624 IU/mL. Serum immunoglobulin E was 652 IU/mL. Antineutrophil cytoplasmic antibodies

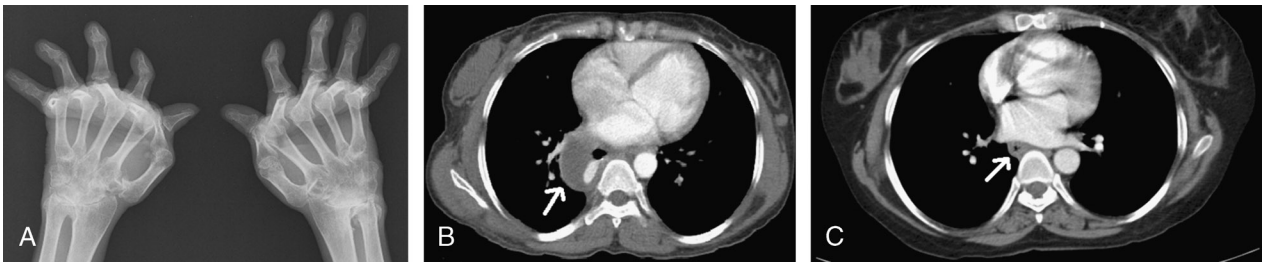

FIGURE 1. A, X-ray of the hands showing characteristic radiologic features of RA. B, Computed tomographic images of the thorax demonstrating asymmetric circumferential wall thickening of the esophagus (white arrow), proximal esophageal dilatation, and periesophageal extension. C, Repeat CT images of the thorax 15 months after initiation of therapy showing significant reduction in the degree of the wall thickening and proximal luminal dilatation (white arrow).

were negative. Characteristic radiologic features of RA were noted on x-ray hands (Fig. 1A).

Contrast-enhanced computed tomography (CT) scan of the thorax and abdomen revealed asymmetric circumferential wall thickening of the mid and lower thoracic esophagus (Fig. 1B), encasing the azygos vein and aorta. Similar wall thickening was noted in the cervical esophagus, oropharynx, larynx, and cricopharynx. The gastroesophageal junction had a large polypoidal component projecting into the lumen of the stomach. There were proximal esophageal dilatation and diverticula. Multiple cervical, mediastinal, axillary, and intra-abdominal nodes measuring 10, 8, 17, and 14 mm were noted.

Upper GI endoscopy revealed a cystic mass from the posterior part of pharynx abutting the epiglottis. A pharyngeal diverticulum was present. An ulceroproliferative "growth" of 3 × 4 cm was seen in the fundus. Biopsy from the "growth" revealed gastroesophageal mucosa with ulceration and polypoid inflammatory granulation tissue. The adjacent esophageal lamina propria was densely infiltrated by eosinophils with a density of 40 to 80/high-power field (Fig. 2A).

Indirect laryngoscopy revealed a mass with a smooth outline arising from the posterior pharyngeal wall just below epiglottis covering the pharyngeal inlet and was assumed to be the cause of the stridor. The vocal cords could not be visualized. Biopsy revealed polypoid pharyngeal mucosa with the lining stratified squamous epithelium densely infiltrated by eosinophils with a density of greater than 100 per high-power field (Fig. 2B).

Bone marrow biopsy showed normocellular marrow with erythroid hyperplasia and eosinophilia. Axillary lymph node biopsy revealed reactive hyperplasia. As a part of the workup for HES, echocardiography was done, which did not show abnormalities.

In view of the suspicion of an underlying neoplastic process, laparoscopy and open biopsy of the body of the stomach along with mesenteric, para-aortic, and fundic lymph nodes were performed. None of the tissues on which biopsy was performed showed any evidence of malignancy, vasculitis, or eosinophilic infiltrates. The gastric wall, in particular, showed no evidence of eosinophilia.

A diagnosis of hypereosinophilia with eosinophilic esophagitis and pharyngitis was made in accordance with consensus guidelines of the American Gastroenterological Association Institute and North American Society of Pediatric Gastroenterology, Hepatology and Nutrition.[1] She was treated with corticosteroids (deflazacort, a prednisolone derivative) and hydroxyurea along with proton pump inhibitors. Dramatic improvement was noted as early as 3 months after the start of therapy, which was sustained until the last visit in June 2010. All the GI symptoms including dysphagia and melena resolved completely. Eosinophil counts normalized (Table 1). Indirect laryngoscopy 6 months later showed decreased size of the mass; the right vocal cord had minimal movement, and the left cord was fixed. One and a half years after the first visit, the left vocal cord palsy persisted, but the right vocal cord was mobile. These improvements suggest that the vocal cord palsy was caused by the pharyngeal mass.

Repeat CT thorax and abdomen (Fig. 1C), 15 months after start of therapy, showed significant reduction in the degree of the wall thickening, proximal luminal dilatation, and periesophageal extension when compared with the previous study. Significant

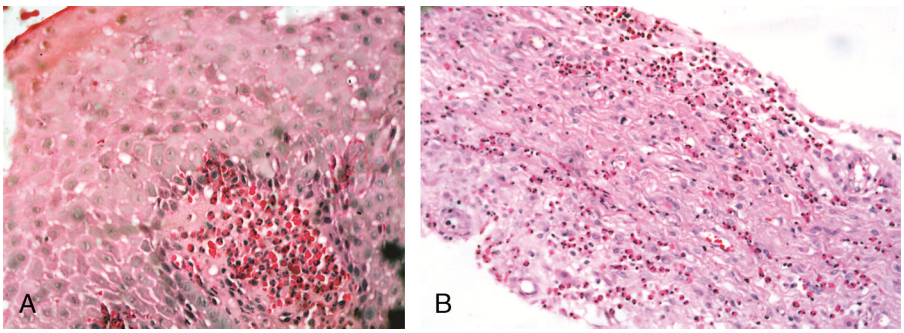

FIGURE 2. A, High-power view of esophageal mucosa with dense infiltration by eosinophils of the lamina propria (hematoxylin-eosin stain, original magnification ×400). B, Medium-power view of pharyngeal epithelium showing dense infiltration by eosinophils (hematoxylin-eosin stain, original magnification ×200).

TABLE 1. Showing Serial Laboratory Parameters at Baseline and After Therapy

Laboratory Parameter	Baseline	5 mo After Treatment	15 mo After Treatment
Hemoglobin, g/dL	10.4	14.6	13.4
Total white cell count, cells/μL	10,000	19,600	12,100
Eosinophils, %	34%	1%	2%
C-reactive protein	0.618	0.589	1.24
Erythrocyte sedimentation rate, mm/hr	Not done	17	28

reduction in the size of the previously enlarged nodes (axillary, cervical, abdominal nodes) was noted.

DISCUSSION

Our patient had characteristic features of eosinophilic esophagitis in the form of dysphagia, food impaction, and nonresponsiveness to proton pump inhibitors. There was no evidence of other organ involvement in this lady with longstanding hypereosinophilia. Presence of hepatosplenomegaly and lymphadenopathy in this patient could be due to immune hyperplasia as evidenced in the lymph node biopsy. This patient fulfills the criteria for overlap HES, which is the term applied to disorders with blood eosinophilia of 1500/μL or greater in the setting of single-organ involvement.[7]

Eosinophilia in RA may be due to allergy or drugs or due to coexistent parasitic infestation.[8] It may be due to disease activity or rheumatoid vasculitis. Eosinophilia has been reported as an adverse effect of drugs such as gold, penicillamine, sulfasalazine, and even methotrexate. Now, with lesser use of gold and penicillamine, the confounding effect of drugs seems to be less likely. Our patient too was off drugs for more than 7 years and did not have any known predisposing factors for eosinophilia.

Apart from peripheral eosinophilia, case reports of tissue eosinophilia involving isolated organs in the setting of hypereosinophilic state in RA exist in the literature. To the best of our knowledge, there are only 3 reports of eosinophilic digestive disease associated with RA in the literature.[2–4] Ng et al.[4] reported a case of eosinophilic enteritis in a lady with RA of 10 years' duration. Their patient did not have any tender or swollen joints, suggesting inactive disease. In another case report of idiopathic hypereosinophilia in a lady with RA of 10 years' duration, Chaudhuri et al.[6] mentioned that the joint disease was clinically inactive. Their patient, however, was on gold for 5 years before detection of HES; hence, a drug-induced process in that case could not be ruled out, unlike that in our patient.

Eosinophilic esophagitis usually presents in adults as dysphagia more to solids and food impaction. It is increasingly being recognized as an immune-mediated disease because of allergic response to an airborne or dietary allergen in the majority of cases. It is a T_H2 pathway–driven process like other hypereosinophilic states, mediated mainly by cytokines IL-5 and IL-13 as evidenced in animal studies.[9] As opposed to this, RA is predominantly a T_H1/T_H17-driven disease. It is known that T_H2 cytokines can have an ameliorating effect on the course of RA. It is noteworthy that our patient as well as those mentioned previously had mild or inactive RA at the time of diagnosis of eosinophilia. We can only speculate on the reasons that halted the progression of an erosive arthritis in this patient especially when she was off any form of treatment. Perhaps this can be explained by a switch from T_H1/T_H17 pathway to T_H2 pathway causing the arthritis to remit and paving the way for hypereosinophilic disorders. Rheumatoid vasculitis is also known to occur when the arthritis is quiescent. Interestingly, both hypereosinophilic state and vasculitis have predominantly T_H2-mediated pathology.[10]

In conclusion, we would like to highlight the importance of considering this rare but interesting entity as an important differential in deformed, longstanding, and inactive RA presenting with GI symptoms. Eosinophilic esophagitis in RA is easy to diagnose, if there is a high index of suspicion, and treatment is rewarding as in our case.

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