Endobronchial Involvement in Idiopathic Hypereosinophilic Syndrome

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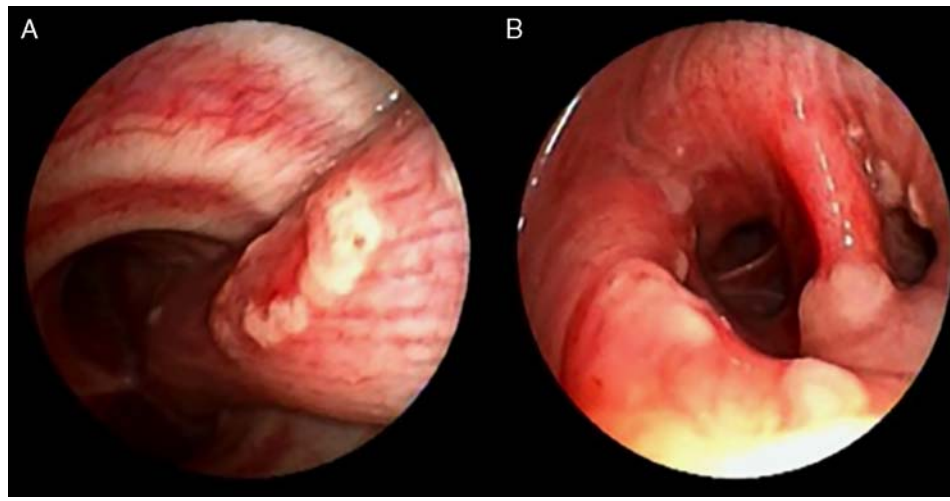

FIGURE 1. A, Flexible bronchoscopy. B, Whitish nodule-like lesions at the posterior membrane of the trachea. Similar lesions at the right lower lobe.

Parenchymal lung involvement in eosinophilic syndromes (ES) is frequent; however, it is rarely accompanied by tracheobronchial lesions. The etiologies of ES are infectious [parasites and aspergillus (allergic bronchopulmonary aspergillosis)], rheumatologic disease (antineutrophil cytoplasmic antibody–related vasculitis), drug-associated reaction, acute eosinophilic pneumonia, chronic eosinophilic pneumonia (CEP), and hypereosinophilic syndrome (HES).[1]

We present the case of a 41-year-old nonsmoking gentleman with a 3-week history of muscle weakness and pain in his right forearm. In addition, he reported a mild dry cough, no fevers, and no dyspnea. He had a past medical history of allergic rhinitis. Medications: none. Allergies: non-steroidal anti inflammatory drugs. His past family history was remarkable for his father being diagnosed with idiopathic HES several years prior. Upon physical

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examination, the patient reported pain with forearm movement and without any neurological deficit. His lungs were clear to auscultation. Blood examination showed the following: hemoglobin of 14.7 g/dL; white blood cell count of 18.800/μL; neutrophil level of 19.3%; eosinophil level 58.4% (absolute eosinophil count = 10.904); lymphocyte level of 15.7%; monocyte level of 5.9%; basophil level of 0.7%; platelet level of 256.000/μL; and IgE level of 1416 UI/mL. Aspartate amino transferase, alanine amino transferase, lactate deshydrogenase, C-reactive protein, and creatine-kinase were within normal limits. A complementary study, including parasite testing (*Trichinella*, *Strongyloides*, *Toxocara canis*, and *Ascaris lumbricoides*) and evaluation for human immunodeficiency virus, rapid plasma reagin, antinuclear antibodies, double-stranded antibody (anti-dsDNA), rheumatoid factor, complement levels, and antineutrophil cytoplasmic antibody (PR3-MPO), was negative. Chest tomography revealed mild bilateral ground-glass opacities, which were mainly in the upper lobes. A sinus computed tomography scan showed signs of sinusitis and nasal polyps. The echocardiogram was normal.

A hematological study was performed to rule out eosinophilic leukemia or other hematologic processes. Bone marrow biopsy was normal; in addition, peripheral blood samples of the jak2 and bcr-abl mutation were negative. He had a positive fip1 l1-pdrgfra fusion gene mutation.

A flexible bronchoscopy (Fuji bronchoscope) revealed whitish nodule-like lesions at the posterior membrane of the trachea and at the right and left lower lobe bronchi (Fig. 1). Bronchoalveolar lavage analysis revealed the following: total cell count of 71×10^6/100 mL; macrophage level of 41%; lymphocyte level of 1%; neutrophil level of 33%; and eosinophil level of 25%. Microbiological cultures, *Pneumocystis jirovecii*, tuberculosis, *Nocardia*, *Aspergillus*, and *Aspergillus* galactomannan were negative. Endobronchial biopsies demonstrated a bronchial ulcer with the bronchial wall containing a cellular infiltrate with neutrophils, numerous eosinophils, and abundant eosinophil granulocytes. No granulomas or vasculitis were visualized (Fig. 2).

A nasal mucosa biopsy was also performed, demonstrating ulcerative lesions with lymphocytic infiltrates and abundant eosinophil granulocytes. There was no evidence of a granuloma or vasculitis. The PAS stain for fungi was negative.

The patient was diagnosed with a pdfgra-related myeloproliferative HES, and treatment with corticosteroids and imatinib was started. The patient had significant improvement in his symptoms, and blood examinations were within the normal range. At the 2-month follow-up visit, he had normal blood and chest computed tomography findings. No follow-up bronchoscopy was performed.

DISCUSSION

HES is a heterogeneous disease characterized by severe eosinophilia, persistent peripheral blood eosinophilia, organ damage related to eosinophilia,

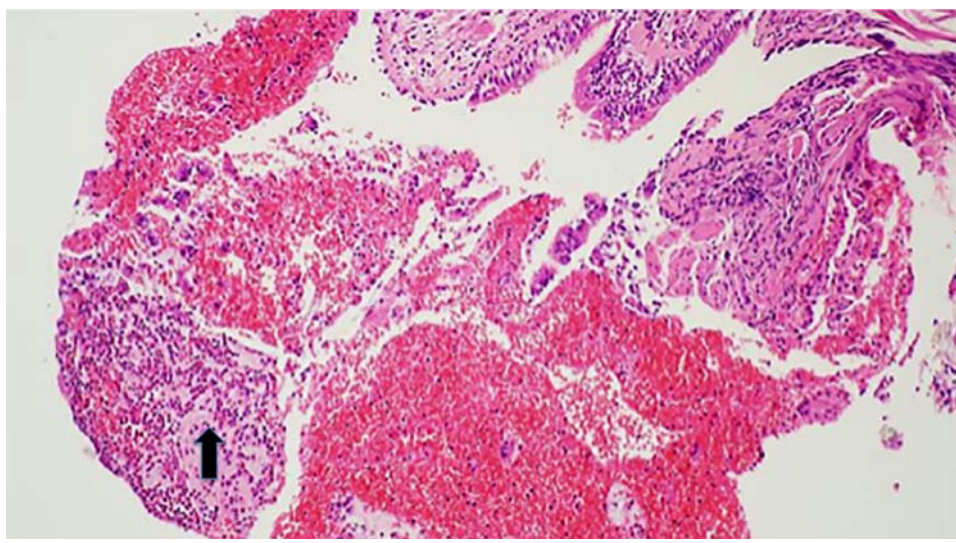

FIGURE 2. Hematoxylin-eosin staining showed bronchial mucosa ulcer with epithelial cell denudation and necrosis; and the arrow indicates fibrinoleukocytic infiltrates and abundant eosinophil granulocytes.

and the exclusion of all other potential causes of hypereosinophilia.[2] The diagnostic criteria proposed since 2012 include the following: (1) hypereosinophilia (absolute eosinophil count of >1500 cells/μL for 1 mo checked on >2 occasions); (2) evidence of eosinophil-mediated target organ damage with the exclusion of all other potential causes of hypereosinophilia (alternatively, tissue hypereosinophilia can be identified in addition to an elevated absolute eosinophil count with tissue hypereosinophilia, which is defined as eosinophils accounting for >20% of nucleated cells in bone marrow); and (3) extensive tissue infiltration of the target organ by histologic analysis and histologic evidence of eosinophil degranulation in a target tissue in the absence of eosinophils in that target tissue.[2] Pulmonary symptoms include cough, dyspnea, sputum, and fever. IgE can be elevated but is not universally seen or necessary for the diagnosis. There is no characteristic radiologic pattern. Dulohery et al[1] reported 12 patients with HES who had different radiologic manifestations; the most frequent findings were ground-glass opacities, nodules, consolidation, interlobular septal thickening, and pleural effusion. There was no endobronchial involvement.

Endobronchial lesions associated with eosinophilic pneumonia are extremely rare. Most have been reported with CEP or eosinophilic granulomatous with polyiangiitis (EGPA) (Churg Strauss syndrome). The presence of whitish nodular-like lesions in the airway is similar to the findings seen in other eosinophilic-associated diseases.[1,3] Matsuda and colleagues reported on 36 patients with eosinophilic pneumonia and bronchoscopy examination, describing only 2 cases of endobronchial involvement (both in association with CEP). Three cases of EGPA with tracheobronchial involvement have also been reported; the most common finding is the presence of whitish bronchial mucosa lesions. In these cases, pathology examination revealed a bronchial mucosa ulcer, including eosinophil dense infiltrates in association with local necrosis.[4,5] The prognosis of tracheobronchial lesion in association with parenchymal infiltrate is unknown. However, in a retrospective study, 5.6% of eosinophilic pneumonia with parenchymal involvement revealed tracheal nodules; characteristically, blood examination revealed severe eosinophilia, and patients had high fever. Especially in the case of CEP, the clinical response to treatment is good in several cases, and bronchial lesions disappear after corticosteroid treatment.[3]

The treatment of these disorders typically involves corticosteroids or a combination with a steroid-sparing agent. For pdfgra-related myeloproliferative HES, imatinib is the first choice, and it has a clinical response ratio of 90%. Hydroxyurea would be more appropriate to use as the myeloproliferative-variant HES in the event that imatinib fails; biologics like interleukin-5 (mepolizumab) are promising, but they remain under investigation.[2]

CONCLUSIONS

To the best of our knowledge, this is the first report of a patient with idiopathic HES and endobronchial involvement. These airway lesions are similar to the published endobronchial manifestations associated with CEP and EGPA, and improvement after corticosteroids confirms the diagnosis.

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