Asthmatic granulomatosis as a rare variant of uncontrolled severe asthma

Rakin H. Choudhury, MD^a , Helen Hashemi, MD^a, Tuan Tran, MD^b , Haiying Zhang, MD^b, and Mark W. Millard, MD^c

^aDepartment of Internal Medicine, Baylor University Medical Center, Dallas, Texas; ^bDepartment of Pathology, Baylor University Medical Center, Dallas, Texas; ^cDivision of Pulmonary and Critical Care Medicine, Baylor University Medical Center, Dallas, Texas

ABSTRACT

Asthmatic granulomatosis (AG) is a variant of severe asthma, first described in 2012, that consists of small airway changes compatible with asthma as well as interstitial nonnecrotizing granulomas. Treatment of AG requires immunosuppression as opposed to the traditional asthma therapy of inhaled steroids. We describe a 5-year course of a patient with AG that has shown no improvement with immunosuppression or other standards of therapy.

KEYWORDS Asthmatic granulomatosis; immunosuppressive therapy; severe asthma; video-assisted thoracoscopic surgery

The prevalence of severe asthma ranges from 5% to 10% of all asthmatics.¹ Growing evidence suggests that severe refractory asthma may represent a multitude of pathologically unique disorders.²

Asthmatic granulomatosis (AG) is one such asthma variant that was first described in 2012.³ Since AG clinically mimics severe asthma, diagnosis is often delayed. Lung biopsies are the only way to diagnose and distinguish this entity. This report presents a case in which diagnosis was ultimately made by pathologic findings. However, the clinical course has caused confounding results.

CASE DESCRIPTION

A 40-year-old man with a history of childhood asthma, a 2-pack-year smoking history, prolonged exposure to pet dander, and moderate atopy with formal testing (serum immunoglobulin E [IgE] levels of 101.6 IU/mL) presented with a severe asthma exacerbation at age 35 after being symptom-free for 27 years. On admission he had pronounced end-expiratory wheezes, a forced expiratory volume in 1 second of 40%, peripheral blood eosinophilia of 8%, and a fractional exhaled nitric oxide of 101 parts per billion. After treatment of his acute exacerbation, his asthma therapy was escalated to include a long-acting beta-agonist, long-

acting muscarinic antagonist, leukotriene receptor antagonist, inhaled corticosteroids, and systemic corticosteroids. Attempts to wean prednisone <20 mg caused relapse. Diagnostic evaluation for his severe asthma, including multiple bronchoscopies, a hypersensitivity pneumonitis panel, antineutrophil cytoplasmic antibodies, rheumatoid factor, antinuclear antibodies, aldolase, C-reactive protein, erythrocyte sedimentation rate, and gastrointestinal assessment, was negative. Further testing included imaging without features of interstitial lung disease or air trapping, a sleep study finding consistent with obstructive sleep apnea that was treated with continuous positive airway pressure, and a right heart catheterization without evidence of pulmonary hypertension. Video-assisted thoracoscopic surgery was performed, and biopsy revealed airway remodeling consisting of bronchioles with prominent smooth muscle hyperplasia and patchy subepithelial fibrosis. In addition to the above findings, a scattered small focus of ill-defined nonnecrotizing interstitial granulomatous inflammation suggestive of AG was seen (*Figure 1*). Results of cultures obtained during video-assisted thoracoscopic surgery were negative, and postoperative complications included acute bronchospasm that required observation.

Corresponding author: Rakin H. Choudhury, MD, Department of Internal Medicine, Baylor University Medical Center, 3500 Gaston Avenue, Dallas, TX 75246 (e-mail: Rakin.choudhury@bswhealth.org)

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Figure 1. Photomicrographs of hematoxylin and eosin–stained tissue sections from the right lung wedge biopsy. **(a)** Prominent smooth muscle hyperplasia of the small airway (100× magnification). **(b)** A focus of subepithelial fibrosis of the small airway (100× magnification). **(c, d)** Rare small foci of ill-defined interstitial nonnecrotizing granulomatous inflammation (200× magnification).

Table 1. The patient's pulmonary function tests and immunosuppressive medications

Date	FEV1 (L) (%)	FeNO (ppb)	Steroid dose (mg/d)	Immune-modulating drug (mg/d) ^a
10/19/2015	2.30 (60%)	40	Prednisone (40)	Omalizumab-CellCept (2000)
1/29/2016	2.56 (67%)	41	Prednisone (40)	—
4/19/2016	3.01 (80%)	58	Prednisone (20)	Mepolizumab
5/19/2016	1.76 (46%)	68	Prednisone (15)	Mepolizumab
6/23/2016	2.31 (61%)	81	Prednisone (60)	Mepolizumab-CellCept (2000)
8/10/2016	2.28 (60%)	30	Prednisone (60)	Mepolizumab-CellCept (2000)
9/20/2016	2.05 (54%)	17	Prednisone (60)	Mepolizumab-azathioprine (100)
1/4/2017	2.55 (68%)	18	Prednisone (60)	Reslizumab
3/28/2017	1.22 (32%)	21	Methylprednisolone (32)	Reslizumab
6/14/2017	2.27 (60%)	30	Methylprednisolone (32)	Reslizumab
7/11/2017	2.21 (59%)	24	Methylprednisolone (32)	Reslizumab
8/16/2017	2.31 (62%)	40	Methylprednisolone (32)	Reslizumab
11/21/2017	2.36 (63%)	44	Methylprednisolone (32)	Reslizumab
1/15/2018	1.27 (34%)	16	Methylprednisolone (32)	Tofacitinib, reslizumab
4/23/2018	2.55 (68%)	16	Methylprednisolone (24)	Tofacitinib

^aThe patient was also taking a maximum dose of long-acting muscarinic antagonist, long-acting beta-agonist, inhaled corticosteroid, zileuton, and as-needed short-acting beta-agonist inhaler.

FeNO indicates fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 second.

Multiple therapies were unsuccessful including bronchial thermoplasty, mycophenolic acid, mepolizumab, reslizumab, omalizumab, azathioprine, intravenous immunoglobulin, and tofacitinib. The patient is currently being evaluated for treatment with infliximab. *Table 1* summarizes progression of the patient's pulmonary function.

DISCUSSION

Asthma is characterized by recurrent symptoms of coughing, wheezing, and shortness of breath that is due to bronchial hypersensitivity, inflammation, and airflow obstruction that is reversible with bronchodilator therapy. Severe asthma fails to respond to therapy and patients are steroid-dependent.² Recent literature suggests that patients with severe asthma may experience different entities of respiratory disease such as AG.² These entities mimic asthma symptoms but do not necessarily share the same pathology or treatment. For this reason, these processes are likely separate diseases that mimic asthma symptoms. While biopsy is not necessary to diagnose asthma, it has a role in severe refractory asthma. Pathologically, asthma displays thickening of the subepithelial basement membrane, inflammatory cell infiltration with eosinophils, goblet cell hyperplasia, and smooth muscle hyperplasia.⁴ AG not only has characteristics of asthma but also displays interstitial nonnecrotizing granulomas. These pathologic findings presented a new target of therapy for researchers in Pittsburgh. Azathioprine, infliximab, methotrexate, and mycophenolic acid were all used in patients with the diagnosis of AG. With immunosuppressive therapy, improvement was seen in all patients, including a decreased oral corticosteroid requirement, improved symptoms, and improved forced

expiratory volume.³ These findings reinforce the idea of pursuing biopsies in patients with severe refractory asthma. This allows for differentiation between asthma and variants of asthma that may respond to different therapies. While our patient meets the criteria for diagnosis of AG, he has not responded in the same clinical manner as previous patients. He is the only patient with AG that has shown no improvement with inhaled steroids, interleukin-5 antagonists, IgE inhibition, and immunosuppression. He still requires >20 mg of prednisone. He is now receiving tofacitinib, a Janus kinase pathway inhibitor. Janus kinase inhibitors have experimentally been described in the treatment of asthma by inhibiting the pathway that differentiates T helper 2 cells, which produce asthma symptoms.⁵ To our knowledge, this treatment has never been validated before and is one of his last options.

ORCID

Rakin H. Choudhury <http://orcid.org/0000-0002-0343-8388>
Tuan Tran <http://orcid.org/0000-0002-3243-0764>

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