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Histologic Findings of Severe/Therapy-Resistant Asthma from Video-Assisted Thoracoscopic Surgery Biopsies

Humberto E. Trejo Bittar, MD¹, Daniel Doberer, MD², Mitra Mehrad, MD¹, Diane C. Strollo, MD³, Joseph K. Leader, PhD³, Sally Wenzel, MD², and Samuel A. Yousem, MD¹

¹University of Pittsburgh Medical Center, Department of Pathology, Pittsburgh, PA, USA

²University of Pittsburgh Asthma Institute at University of Pittsburgh Medical Center, Pulmonary Allergy and Critical Care Medicine Division, Department of Medicine, Pittsburgh, PA, USA

³University of Pittsburgh Medical Center, Department of Cardiothoracic Surgery, Pittsburgh, PA, USA

Abstract

The histologic changes occurring in severe/therapy-resistant asthma (SA) as defined by the European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines, particularly at the level of the distal airways are unknown. This study describes the clinical, radiologic and histologic characteristics of twenty-nine SA patients who underwent video-assisted thoracoscopic surgery (VATS) lung biopsy. Pathological observations were correlated with clinical features, especially the presence of autoimmune disease (AID) (15/29, 51.7%). Ten biopsies (10/29, 34.5%) showed only small airway manifestations of asthma, while in 19 (65.5%) asthmatic granulomatosis (AG), manifested by asthmatic bronchiolitis supplemented by an alveolar septal mononuclear infiltrates with non-necrotizing granulomas, was present. SA patients without AG showed more striking small airway injury, subbasement membrane thickening and neutrophilic infiltrates. Cases with concurrent AID had a tendency to more parenchymal eosinophilic inflammation, more bronchiolocentric granulomas and a suggestion of increased responsiveness to nonsteroidal immunosuppressive therapy. Histologic examination of VATS lung biopsies in SA demonstrates diverse pathologies including cases associated with granulomatous inflammation in addition to eosinophilic infiltrates. This spectrum of histologies may link to a high incidence of autoimmune disease.

Keywords

Asthma; granulomas; inflammation; autoimmunity; airway; asthmatic granulomatosis

Introduction

Asthma is a chronic inflammatory disease manifesting as airway hyperresponsiveness and/or reversible airflow obstruction in the appropriate clinical setting (1). Severe asthma (SA), also

referred to as therapy resistant asthma, as defined by the ERS/ATS guidelines is asthma that requires high-dose inhaled/oral corticosteroids (CS) with an additional controller medication to maintain control, or that remains uncontrolled despite exhaustive therapy (2).

Classic histologic findings of asthma/SA have long been described in large airways and include mucous plugging, eosinophilic inflammation, epithelial desquamation and hyperplasia, goblet cell metaplasia, subbasement membrane thickening, subepithelial fibrosis, smooth muscle hypertrophy/hyperplasia and submucosal gland hypertrophy (3). Despite the clinical designation, asthma, and even SA, are not likely to be a single disease. Rather they represent a heterogeneous group of patients with disparate clinical, biological and therapeutic characteristics (4), in whom the underlying pathology, particularly in the distal lung, remains poorly characterized.

The histopathology of asthma and SA has been reported primarily in autopsy (5) and endobronchial/transbronchial (6–8) biopsies. For this reason, the pathologic findings of asthma in the smaller airways (those smaller than 2 mm and lacking cartilage) remain largely unknown. Recently, we described a subgroup of SA patients who underwent video-assisted thoracoscopic surgery (VATS) biopsy. Specimens obtained from these VATS biopsies allowed us to gain access to the pathology of asthma at the level of the small airways and the alveolated lung parenchyma (9). In this earlier study, we described asthmatic granulomatosis (AG), a subgroup of patients with SA whose histologic examination showed findings of asthmatic bronchiolitis with interstitial poorly formed non-necrotizing granulomas in the absence of other known causes of granulomatous lung disease. While asthma is typically not thought of as an autoimmune disease (AID), 70% of the original cohort of AG patients demonstrated either a familial or personal history of AID. Interestingly, other conditions/comorbidities associated with SA including chronic rhinosinusitis with nasal polyps (10) and aspirin-exacerbated respiratory disease (11) have been linked to autoantibody formation.

Thoracoscopic biopsies for the diagnosis and treatment of other inflammatory lung diseases, like interstitial lung disease, are well established. However, performing thoracoscopic biopsy is not a common practice in the management of SA. We therefore aimed to characterize the spectrum of histologic findings in VATS lung biopsies of patients with SA, with a focus on determining if there was a morphologic distinction between patients with and without AID.

Materials and Methods

Study group

Thirty-three surgical lung biopsies were obtained on patients with a clinical diagnosis of SA referred to the University of Pittsburgh Asthma Institute at the University of Pittsburgh Medical Center between 2007 and 2015. All patients met criteria for SA by the ERS/ATS definition (2), and biopsy was indicated clinically due to the severity of their asthma, the lack of response to conventional asthma medication and to rule out asthma mimickers or other comorbidities. Relevant clinical and radiologic features were obtained from the medical records, including AID history. Care was taken to collect information to exclude other possible lung diseases including infection, hypersensitivity pneumonitis, sarcoidosis,

immunodeficiency, and aspiration pneumonia. AID included diseases with a clinical diagnosis documented by rheumatologist or other clinician, in the setting of positive autoimmune serologies associated with functional defects. For the purpose of this study, AID also included diseases with known autoimmune physiopathology (e.g. type-1 diabetes mellitus) and diseases with unbalanced immunity pathways leading to altered self-immunity with or without autoantibodies (e.g. Crohns disease/psoriasis) (12). Some of the histologic and clinical findings of selected patients included in this study were reported elsewhere (9). This research was approved by the University of Pittsburgh Institutional Review Board. All patients gave informed consent for additional use of their tissue and medical records for research purposes.

Pathologic and radiologic analysis

Wedge biopsies of lung parenchyma from at least two lung lobes were available for histologic examination in each patient. Each biopsy was formalin fixed and paraffin embedded and included 4 to 12 hematoxylin-eosin stains sections. Ziehl Neelsen and Gomori methenamine silver stains were performed on all cases. Microbiological cultures for aerobic and anaerobic bacteria (including mycobacteria) and fungal organisms were negative in all cases. All patients had a multidetector chest CT performed within 3 months of lung biopsy. CTs were reviewed by consensus by a chest radiologist (D.C.S.) and a pulmonologist (D.D.). CTs were evaluated for the presence or absence of hyperlucency, air trapping, ground glass opacities, bronchial wall thickening and bronchiectasis.

Of the original 33 cases, 4 cases (12.1%) were excluded as the biopsies demonstrated other lung pathologies (1 case of hypersensitivity pneumonitis and 3 cases of aspiration pneumonia). The remaining 29 cases were reviewed blindly to clinical data. Histologic findings of asthma were recorded as either present or absent, focusing on their presence in the smaller airways and alveolated parenchyma. Histopathologic features assessed included mucous plugging, bronchiolectasis, subbasement membrane thickening, goblet cell metaplasia, smooth muscle hypertrophy, airspace organization, lymphoid aggregates and presence/absence of granulomas with detailed description of their morphologic characteristics and location. Presence and location of airway and parenchyma inflammation was also recorded.

As part of the clinicopathologic analysis, cases were first segregated into those cases of SA with and without changes of asthmatic granulomatosis. The cases were then further assessed for the presence or absence of clinical AID. Asthmatic granulomatosis was defined in a previous publication (9), as a patient with SA with small airway histologic changes of asthma associated with alveolar septal mononuclear infiltrates and interstitial non-necrotizing granulomas, in the absence of a clinical history of hypersensitivity pneumonitis, sarcoidosis, aspiration pneumonia or other cause for granulomatous disease. Given the small numbers of cases included in this study, formal statistics were not performed and the results are presented as descriptive analyses only.

Results

Clinical data

The clinical features of the 29 cases are summarized in Table 1. Cases were segregated according to the morphologic presence of AG and then subsequently according to the presence of AID, into four groups: SA only (SA, n=5), SA with AID (SA-AID, n=5), SA with morphologic features of AG without AID (SA-AG, n=9) and with AID (SA-AG-AID, n=10). Thus, AG with or without AID was diagnosed in 19 out 29 cases (65.5%), and of these cases, 10 out of 19 (52.6%), had a diagnosis of AID. The remaining cases (10/29, 34.5%) demonstrated only morphologic findings of asthma without granulomas, and of these cases, 50% had a diagnosis of AID.

For all groups, the majority of patients were female and of comparable age. SA patients had the earliest age of onset of symptoms. Most of the patients had no history of smoking. All 29 cases had physiologic evidence of airflow obstruction with reduced ratio of forced expiratory volume in 1 second and forced vital capacity (FEV/FVC) and forced expiratory flow, midexpiratory phase (FEF_{25-75%}) (Table 1). Extensive clinical evaluation including precipitating antibodies for hypersensitivity pneumonitis was negative.

Of the 5 cases in the SA-AID group, one had rheumatoid arthritis (RA), one had antiphospholipid syndrome, one had thyroid AID, one had Crohns disease and one had type-1 diabetes mellitus. Of the 10 cases in the SA-AG-AID group, 2 had RA, 1 had systemic lupus erythematosus, 2 had an undifferentiated connective tissue disorder, 2 had antiphospholipid syndrome, 2 had thyroid AID and one had psoriasis.

Chest CT scans findings are summarized in Table 1. Air trapping was seen in all cases. Interestingly, bronchial wall thickening, a finding commonly associated with the diagnosis of asthma (13), was seen in all patients of the SA and SA-AID groups, in 7 out of 9 of patients with SA-AG, but only in 3 out of 6 of the SA-AG-AID patients. No bronchiectasis was seen in the SA-AG-AID group. Of note, no masses or consolidation were seen in any of the study patients.

After the biopsy, all patients received treatment with alternative nonsteroidal immunosuppressive or cytotoxic medications, including azathioprine, methotrexate, or anti-tumor necrosis factor- α . A positive patient response was considered as a reduction in steroid therapy, while maintaining or improving lung function (Forced Expiratory Volume in 1 second (FEV1)) with fewer CS-requiring exacerbations during follow up. Patients with SA-AID and SA-AG-AID appeared to have a better treatment response when compared to the other two groups (Table 1).

Pathologic findings

The histopathology findings in the small airways and parenchyma for each group are summarized in Table 2. Histologic findings of asthmatic bronchiolitis with smooth muscle hypertrophy were seen in all cases (Figure 1). Other morphologic changes of asthma affecting the distal smaller airways were also seen, although less frequently in the AG groups. Subbasement membrane thickening was seen in all SA and SA-AID cases, but was

present in fewer cases of SA-AG and SA-AG-AID (5 out of 9 and 2 out of 10 cases, respectively). Similarly, goblet cell metaplasia and mucus plugging were observed less often in SA-AG-AID (5 out of 10 cases) while it was seen in 4 out of 5 of the SA and SA-AID cases, and in 7 out of 9 of the SA-AG cases.

Ill-defined, non-necrotizing granulomas composed of epithelioid histiocytes aggregates with or without giant cells and without a concentric rim of fibrosis, as seen in sarcoidosis, were observed in all AG cases (Table 2 and Figure 3). The non-necrotizing granulomas were mostly located in the interstitium. Airway-centered granulomas were generally more frequent in the SA-AG-AID group when compared to the SA-AG group (6 out of 10 vs 2 out of 9).

Submucosal eosinophils and lymphocytes were seen in similar percentages of cases for all groups, with a tendency toward higher numbers in the SA group. In contrast, neutrophils were seen in 4 out of 5 of SA cases, but only in 1 out of 9 of SA-AG cases, in 2 out of 5 of SA-AID and in 4 out of 10 SA-AID-AG cases. (Table 2 and Figure 2). Similar distributions of inflammatory cells were identified in the adventitia of the small airways, again with neutrophils being less frequent in the SA-AG and SA-AG-AID groups (Table 2).

Inflammatory infiltrates were seen in the alveolated lung parenchyma, manifesting as patchy interstitial/perivenular mononuclear cells infiltrates. Eosinophils were not found in the alveolated parenchyma of SA cases, were seen in 1 out of 9 of SA-AG cases, in 1 out of 5 SA-AID cases and in 3 out of 10 SA-AG-AID case (Figure 2). In contrast, neutrophils were not found in the alveolated parenchyma of SA-AID and SA-AG-AID groups, while they were present in 1 out of 5 and in 2 out of 9 of the SA and SA-AG cases, respectively. Lastly, lymphocytes were seen in the alveolated parenchyma in all groups, but were slightly more frequently found in the AG groups (with or with AID, Figure 2). Small and scattered lymphoid aggregates were detected in the parenchyma in all groups, with less frequency on the SA-AG group. A minor component of airspace organization was also seen in all groups (Table 2).

There was no evidence of mycobacterial or fungal microorganisms by Ziehl Neelsen and Gomori methenamine silver stains, respectively. Vasculitis, necrosis, aspirated/foreign material, honeycombing and fibroblastic foci were not identified in any of the study cases. Similarly, other findings commonly associated with involvement of the lung by a systemic AID (e.g. RA, systemic lupus erythematosus, etc), including pleuritis, follicular bronchiolitis/ bronchitis and constrictive bronchiolitis were not seen in any of the cases.

Discussion

Asthma has long been considered a large airway disease with the small airways referred to as the “silent zone” (14, 15). Although physiologic approaches to identifying asthma in the small airways suggest disease, pathologic study of this region from the lung of living asthmatics is extremely rare. Consequently, the histopathologic findings of asthma at the level of the distal airways and alveolated lung parenchyma are largely unknown, with pathologic studies based primarily on cartilaginous airway observations on transbronchial/

endobronchial biopsies and autopsy studies, often from many decades ago (16). Here we describe the morphologic findings of the largest cohort of SA patients studied via VATS lung biopsy. We found AG in 65.5% (19/29) of SA patients, a diagnosis based on the presence of non-necrotizing granulomas in association with traditional morphologic findings of asthma, validating the importance of this newly described disease (9).

Morphologic examination of these 29 patients with SA showed a degree of asthmatic bronchiolitis in all cases, confirming the involvement of the small airways in this group of difficult to treat asthmatics. Perhaps not surprisingly, smooth muscle hypertrophy was observed in all samples from all patients, suggesting that this morphologic finding is a sensitive pathologic feature of small airways disease in the clinical setting of asthma. However, smooth muscle hypertrophy can also be seen in other airway diseases, including chronic bronchitis, such that it cannot be considered a finding specific to asthma (17).

This increase in smooth muscle could well explain why the critical-physiologic characteristic of asthma, bronchodilator reversibility/airway hyperresponsiveness was observed in all the patients. In contrast, although we found other morphologic findings of asthma in all groups, these findings were less prominent in the SA-AG groups particularly in those with AID, suggesting that together with granulomas, lack of traditional asthmatic findings might suggest the diagnosis of AG. Evaluation of tissue from more patients will be needed to determine whether this lack of remodeling features differentiates SA-AG groups from SA without AG groups. Clinically, this lack of remodeling also suggests that appropriate therapies could return lung function to normal or near normal in AG patients.

Our data supports the hypothesis that SA might represent a hybrid of asthma and involvement of the lung by AID. Asthma is typically not considered an autoimmune disease. However, the fact that most of our patients are middle age females, many with coexistent clinical diagnoses of AID, suggest a novel airway-centered role of autoimmunity in a subtype of SA patients. Others have also suggested an association between autoimmunity and asthma pathophysiology, including a proposed role for anti-platelet antibodies (18). Similarly, autoantigens have been proposed to play a role in atopic dermatitis, urticarial and asthma, perhaps under Type-1-mediated interferon- γ regulated mechanisms (19). Recent bronchoalveolar lavage studies of SA strongly link Type-1 immunity with a subset of SA patients with high levels of interferon- γ (20, 21).

The prevalence of granulomatous inflammation in non-severe asthma or in otherwise normal lungs has not been well studied. We found no granulomas in seventeen adult autopsy cases with a known diagnosis of well-controlled asthma and morphologic evidence of asthmatic bronchitis who died of non-pulmonary causes (9). Hung et al. studied the presence of non-neoplastic pathology in 347 lung resections for mass lesions and found granulomatous inflammation away from the lesion in only 7.8% of the cases (22). These data indicate that the high prevalence of non-necrotizing granulomas in our cohort of SA cases is a distinctive histologic finding of SA.

Our study has some limitations. First, our study group is small which affects the strength of our conclusions and limits our ability to perform statistical analysis. Second, our

morphologic assessment was subjective, without defined criteria for each of the histologic findings. Also, our findings might be altered by the fact that our cohort of patients had been treated with high doses of both inhaled and systemic CSs, which might affect the distribution of the inflammatory infiltrates, especially eosinophils. Lastly, in our cases of AG, we considered the possibility that the non-necrotizing granulomas were an expression of other disease, for example hypersensitivity pneumonitis, aspiration pneumonia, infections, or even the underlying AID such as RA or Crohns disease. Although some of these etiologies were excluded clinically by imaging and other laboratory studies, the possibility of “non-traditional” lung involvement by the underlying AID cannot be entirely excluded.

In summary, surgical lung biopsies in patients with clinical SA can be of clinical utility to rule out mimickers of asthma. AG is the most common finding in this cohort of SA. Thus pathologists should be aware of this newly described disease with some of the morphologic changes of asthma but with additional ill-defined, predominantly interstitial granulomas. As of yet, there are no morphologic findings that identify coexistent AID in patients with SA. The specificity of parenchymal eosinophils and bronchiolocentric granulomas requires further investigation in larger numbers of biopsies to confirm statistical differences. Similar to interstitial lung disease, we propose that SA should have a clinical–radiological–pathological approach to management, as some pathologic subgroups (with coexistent AID) appear to have better response to immunosuppressive therapy (SA-AID and SA-AG-AID).

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Figure 1. Morphologic findings in the small airways of severe/therapy-resistant asthma (SA). (A) SA case showing mucus plug, goblet cell metaplasia and mixed submucosal predominantly eosinophilic infiltrate. (B) SA with concurrent autoimmune disease (SA-AID) case. (C) Small airways of asthmatic granulomatosis (SA-AG). (D) SA-AG with concurrent autoimmune disease (SA-AG-AID). Small airway demonstrates mucus plug and smooth muscle hypertrophy (hematoxylin and eosin, $\times 200$).

Figure 2.
(A) Small airway in severe/therapy-resistant asthma (SA) showing subbasement membrane thickening and neutrophilic inflammation (asterisks). (B) Asthmatic granulomatosis with concurrent autoimmune disease (SA-AG-AID) case showing a patchy interstitial mononuclear infiltrate with eosinophils and lymphocytes (hematoxylin and eosin, $\times 400$).

Figure 3. Severe/therapy-resistant asthma manifesting as asthmatic granulomatosis (SA-AG) showing patchy mononuclear cell infiltrates associated with an ill-defined, poorly formed non-necrotizing granulomas, containing lymphocytes, histiocytes and giant cells, located in the interstitium (A and B) and with bronchiolocentricity in SA-AG with concurrent autoimmune disease (SA-AG-AID) (C and D) (hematoxylin and eosin, $\times 200$).

Table 1

CLINICAL PROFILE OF SEVERE/THERAPY RESISTANT ASTHMA (SA), SA WITH CONCURRENT AUTOIMMUNE DISEASE (SA-AID), SA MANIFESTING AS ASTHMATIC GRANULOMATOSIS (SA-AG) AND SA-AG WITH CONCURRENT AUTOIMMUNE DISEASE (SA-AG-AID) PATIENTS.

	SA	SA-AID	SA-AG	SA-AG-AID
Age, mean (range)	47 (41 – 51)	55 (49 – 61)	53 (35 – 63)	49 (33 – 62)
Gender				
Female	5/5	4/5	7/9	9/10
Male	0	1/5	2/9	1/10
Age of onset	22 (5 – 45)	34 (5 – 46)	34 (3 – 62)	26 (5 – 48)
Smoking history				
Never	4/5	5/5	6/9	7/10
Active	1/5	0	1/9	1/10
Former	0	0	2/9	2/10
FEV1%	70 +/- 15.5	56.8 +/- 9.6	69.9 +/- 9.9	66.7 +/- 5.9
FEV/FVC	64 +/- 8.4	64 +/- 8.2	61.1 +/- 4.6	62.1 +/- 4
FEF _{25-75%}	47.8 +/- 15.4	33.4 +/- 10.7	35.1 +/- 6.9	36.3 +/- 5.4
Autoimmune disease				
Connective tissue disorder	0	1/5	0	3/10
Undifferentiated connective tissue disorder	0	0	0	2/10
Antiphospholipid syndrome	0	1/5	0	2/10
Thyroid AID	0	1/5	0	2/10
Other	0	2/5	0	1/10
Radiologic (CT) findings:				
Hyperlucency	3/4	3/4	7/9	2/6
Air trapping	4/4	4/4	9/9	6/6
Ground glass	1/4	0	1/9	0
Bronchial wall thickening	4/4	4/4	7/9	3/6
Bronchiectasis	4/4	2/4	6/9	0
Response to immunomodulators:				
Positive response	3/5	4/5	6/9	8/10
No response	2/5	1/5	3/9	1/10
Not tolerated	0	0	0	1/10

Abbreviations: FEV1%: forced expiratory volume in one second percentage; FEV/FVC: ratio of force expiratory volume in 1 second and force vital capacity; FEF_{25-75%}: forced expiratory flow, midexpiratory phase; AID: autoimmune disease; CT: computed tomography.

Table 2

HISTOPATHOLOGIC FEATURES OF SEVERE/THERAPY RESISTANT ASTHMA (SA), SA WITH CONCURRENT AUTOIMMUNE DISEASE (SA-AID), SA MANIFESTING AS ASTHMATIC GRANULOMATOSIS (SA-AG) AND SA-AG WITH CONCURRENT AUTOIMMUNE DISEASE (SA-AG-AID) PATIENTS.

	SA	SA-AID	SA-AG	SA-AG-AID
Small Airways				
Mucus plugging	4/5	4/5	7/9	5/10
Bronchiolectasis	4/5	2/5	4/9	7/10
Goblet cell metaplasia	4/5	4/5	7/9	5/10
Subbasement membrane thickening	5/5	5/5	5/9	2/10
Submucosal fibrosis	5/5	5/5	8/9	8/10
Smooth muscle hypertrophy	5/5	5/5	9/9	10/10
Submucosal inflammation				
Eosinophils	4/5	3/5	5/9	6/10
Neutrophils	4/5	2/5	1/9	4/10
Lymphocytes	3/5	3/5	7/9	7/10
Peribronchiolar/adventitial				
Eosinophils	3/5	2/5	5/9	5/10
Neutrophils	3/5	2/5	1/9	1/10
Lymphocytes	5/5	5/5	6/9	9/10
Granulomas	0	0	9/9	10/10
Morphology				
Poorly-formed	NA	NA	9/9	10/10
Non-necrotizing	NA	NA	9/9	10/10
Location				
Interstitial	NA	NA	7/9	8/10
Airspace	NA	NA	1/9	0
Airway-centered	NA	NA	2/9	6/10
Angio-centered	NA	NA	0	1/10
Random	NA	NA	0	1/10
Parenchyma				
Inflammation				
Eosinophils	0	1/5	1/9	3/10
Neutrophils	1/5	0	2/9	0

	SA	SA-AID	SA-AG	SA-AG-AID
Lymphocytes	1/5	1/5	5/9	4/10
Airspace organization	1/5	1/5	3/9	1/10
Lymphoid aggregates	3/5	3/5	3/9	5/10

Abbreviations: NA: non-applicable.