Airway Autoimmune Inflammatory Response (AAIR) Syndrome: An Asthma-Autoimmune Overlap Disorder?

Chantal Y. Spencer, MD, Jennifer Millman, MD, Keila Veiga, MD, Alfin G. Vicencio, MD

Asthma encompasses numerous phenotypes that may require alternate approaches to diagnosis and therapy, particularly for patients whose symptoms remain poorly controlled despite escalating treatment. We describe 3 patients with apparent asthma who demonstrated unusual findings on cryobiopsy by flexible bronchoscopy and responded to therapy directed against autoimmune disease.

Among children with asthma, severe disease accounts for only 5% to 10% of cases but is responsible for an estimated 50% of health care costs.[1–3] In recent years, it has become increasingly clear that the diagnosis of asthma encompasses numerous distinct phenotypes that may require different diagnostic and therapeutic approaches.[4,5]

Flexible bronchoscopy is not routinely employed for the evaluation of asthma in children, but for adults with asthma the procedure is not uncommonly used.[6] Nevertheless, its precise diagnostic role remains somewhat vague. As such, incorporation of the procedure into asthma practice has historically been institution dependent, and its application in children with asthma has recently come under some scrutiny.[7] Here, we report 3 patients with apparent asthma whose symptoms did not respond to escalating therapy. Bronchoscopy revealed interesting visual and pathologic findings that may represent a novel disorder.

CASE REPORT

Case 1

A 9-year-old girl with previously diagnosed asthma was referred for worsening cough and difficulty breathing without any other systemic symptoms. Pulmonary function tests demonstrated reversible obstruction (forced expiratory volume in 1 second = 74% predicted, with 18% increase after albuterol). Despite treatment with inhaled corticosteroids, she required albuterol daily for cough and wheeze, and she required multiple courses of oral corticosteroids. Her symptoms worsened, and therapy was eventually upgraded to 230 μg/21 μg of fluticasone-salmeterol (2 puffs twice daily). Because of continued progression and ongoing requirement for oral steroids, and before considering monoclonal antibody therapy, the patient underwent flexible bronchoscopy, which demonstrated extensive nodular lesions in the trachea and main bronchi (Fig 1A). The results of bronchoalveolar lavage cultures (including bacteria, fungi, and *Mycobacterium*) were negative, but an endobronchial cryobiopsy of the lesions revealed nonnecrotizing granulomas, which is suspicious for an autoimmune process (Fig 1B). A rheumatology consultation was obtained, but serologic studies were negative. Given the findings on biopsy coupled with failure of aggressive asthma therapy, a joint decision was made to start 800 mg/160 mg of

abstract

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Dr Spencer provided clinical care for all patients, interpreted data, and contributed to writing and revising the initial draft; Drs Millman and Veiga were involved in clinical management for select patients, acquired and interpreted data, and contributed to writing the initial draft; Dr Vicencio provided clinical care for all patients, conceptualized the manuscript, interpreted all data, and critically revised the final version; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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trimethoprim-sulfamethoxazole twice daily as maintenance therapy for a possible autoimmune disease with airway involvement. Thereafter, the patient's cough resolved, her requirement for asthma therapy diminished, and her bronchoscopy normalized (Fig 1C). She remained on trimethoprim-sulfamethoxazole therapy during the subsequent year, requiring low-dose inhaled corticosteroid therapy only during the winter season and sporadic albuterol with upper respiratory infections.

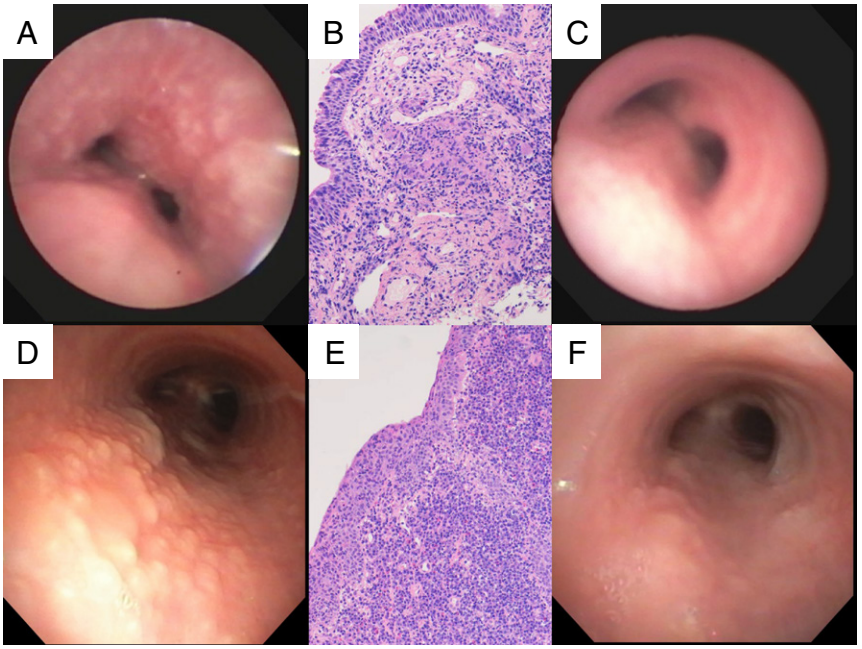

FIGURE 1
A and D: Pretreatment bronchoscopy demonstrating mucosal nodules. B and E: Pathology demonstrating granulomas (B) and dense lymphoplasmacytic infiltrates (E). C and F: Posttreatment bronchoscopy demonstrating visual improvement after treatment with trimethoprim-sulfamethoxazole.

Case 2

A previously well 15-year-old girl presented with a 2-year history of daily cough associated with intermittent chest pain and shortness of breath without any other systemic symptoms. An extensive evaluation, including allergy and immunology testing, sweat test (because she has a brother with cystic fibrosis), laryngoscopy, flexible bronchoscopy, and CT scan of the chest and sinuses, had been completed before referral to our institution but was unrevealing. Similarly, antibiotics, antihistamines, antireflux therapy, β agonists, and oral corticosteroids did not improve symptoms. Additional evaluations performed in our institution included a methacholine challenge, which was consistent with a diagnosis of asthma (provocation concentration 20, the dose of methacholine at which FEV1 falls by 20% of baseline, = 0.949 mg/mL, indicating significant airway reactivity), but treatment with 230 μg/21 μg fluticasone-salmeterol (2 puffs twice daily) failed to improve symptoms. A flexible bronchoscopy was repeated in our institution which demonstrated nodules along the posterior tracheal wall (Fig 1D). Endobronchial cryobiopsies revealed dense lymphoplasmacytic infiltrates but no obvious granulomas (Fig 1E). The results of bronchoalveolar lavage cultures (including bacteria, fungi, and *Mycobacterium*) were negative. Given the bronchoscopy findings, an autoimmune workup was initiated, which revealed a positive antinuclear antibody (1:160), positive antineutrophil cytoplasmic antibody (1:640), and positive myeloperoxidase antibody (132 AU/mL). Although the rheumatology consultation failed to assign a specific vasculitic diagnosis, the patient was started on 800/160 mg trimethoprim-sulfamethoxazole twice daily for treatment of a suspected autoimmune disease with airway involvement. A repeat flexible bronchoscopy demonstrated an improvement, but not a complete resolution, of tracheal nodules (Fig 1F) accompanied by a resolution of the cough. The dose of trimethoprim-sulfamethoxazole was decreased to 3 times weekly after 8 months of therapy, which was accompanied by a relapse in symptoms, increased serologic markers, and recurrence of tracheal nodules on bronchoscopy. Azathioprine was added to her chronic therapy with subsequent improvement.

Case 3

A 3-year-old boy was being managed for recurrent wheeze and cough. He was seen in the emergency department on several occasions and treated successfully with β agonists and oral steroids (~10 courses in the previous year). Despite an initiation of 0.25 mg of budesonide twice daily, he continued to require monthly oral steroid courses. After referral to pediatric pulmonology, he was noted to have a frequent left-sided wheeze and as such underwent flexible bronchoscopy, which demonstrated left bronchomalacia and nodular changes in the tracheal mucosa similar to that seen in the previously described patients. The results of bronchoalveolar lavage cultures were negative (including bacteria, fungi, and *Mycobacterium*). Endobronchial cryobiopsy demonstrated a nonnecrotizing granuloma. Subsequent blood work

TABLE 1 Patient Demographic and Clinical Data

	Patient 1	Patient 2	Patient 3
Patient demographics and history			
Age at diagnosis, y	9	15	3
Sex	Female	Female	Male
Ethnicity	Hispanic	Caucasian	Hispanic
BMI	23.75	23.28	20.89
Family history of asthma	Yes	No	Yes
Family history of autoimmune disease	Yes	Yes	No
Clinical data			
Age at onset of asthma or respiratory symptoms	2 y	13 y	Infancy
Reversible obstruction	Yes, pre- and postbronchodilator spirometry	Yes, methacholine challenge	Yes, clinical observation
Pulmonary function before treatment with trimethoprim-sulfamethoxazole[a]	FEV_1 = 81% predicted; FEV_1/FVC = 77; FEF 25%–75% = 55% predicted	FEV_1 = 95% predicted; FEV_1/FVC = 79; FEF 25%–75% = 76% predicted	N/A
Pulmonary function after treatment with trimethoprim-sulfamethoxazole[a]	FEV_1 = 90% predicted; FEV_1/FVC = 80; FEF 25%–75% = 65% predicted	FEV_1 = 96% predicted; FEV_1/FVC = 90; FEF 25%–75% = 95% predicted	N/A
Blood eosinophils, μL^{-1}	217	183	324
Serum immunoglobulin E, IU/mL	177	26	498
Immunocap results	Positive for cat, dog, ragweed, grass	Negative	Positive for cockroach, cat, dog, ragweed

Asthma control test (ACT) data were not included for the following reasons: (1) Patient 2 was managed at an outside institution for 2 y before her referral, and a diagnosis of airway autoimmune inflammatory response syndrome was established soon after referral; as such, no pretreatment ACT values are available. (2) There is no standardized and validated ACT for patient 3 because of his age. FEF, forced expiratory flow; FEV, forced expiratory volume; N/A, not available.

[a] Average value, 6-mo period (minimum of 2 measurements).

demonstrated a positive rheumatoid factor (45 IU/mL), positive C-reactive protein (14.1 mg/L), and positive erythrocyte sedimentation rate (88 mm/hour). His condition improved slightly with an increased dose of 0.5 mg of budesonide twice daily and the addition of montelukast. The family decided against a trial of trimethoprim-sulfamethoxazole, opting instead for close follow-up (including periodic autoimmune blood work) and repeat bronchoscopy in a year, depending in part on the frequency of symptoms.

DISCUSSION

We present 3 patients with apparent asthma and pathologic features of autoimmune inflammation in the airway. Although all patients had evidence of reversible airway obstruction, a cardinal feature of asthma, only 2 had evidence of allergic sensitization (see Table 1 for patient data). Because of a poor response to asthma therapy, we must consider the possibility that our patients' respiratory symptoms were not solely due to asthma but rather were the earliest manifestation of an autoimmune process that has not yet fully emerged or one that has not yet been recognized. To date, none of our patients have displayed additional signs of systemic disease characteristic of other rheumatologic diagnoses.

All patients eventually underwent flexible bronchoscopy (propofol sedation and laryngeal mask airway), which was critical in directing management. Key diagnostic features included (1) airway nodules and (2) pathology suggestive of an autoimmune response. Often referred to as "follicular tracheitis," airway nodularity is frequently encountered among physicians who perform bronchoscopy and is often attributed to gastroesophageal reflux or chronic inflammation.[8] However, because these lesions are rarely biopsied, their precise etiology remains unknown. Importantly, for 2 of the described patients, granulomas were noted only on biopsy specimens obtained by using the flexible cryoprobe; biopsies obtained during the same procedure by conventional forceps showed only generalized inflammation. Although we have used the flexible cryoprobe for select patients in recent years,[9] this technology has not been widely adopted in pediatric pulmonology practices. However, previous reports in adults suggest that the cryoprobe may be superior to forceps for endobronchial biopsy by obtaining larger, well-preserved specimens that are free of crush artifact.[10] To our knowledge, there are no reports demonstrating the use of the flexible cryoprobe for endobronchial biopsy in children, but a recent report demonstrated its utility for removing foreign bodies in children.[11] For our patients, we used the 1.9-mm flexible contact cryoprobe (Erbe USA, Inc, Marietta, GA) through the 2.0-mm channel of

the pediatric bronchoscope (MP160; Olympus, Center Valley, PA). The tip of the probe was placed directly on a nodule, and the freezing mechanism was activated for 2 to 3 seconds to achieve adhesion. With continued activation of the freezing mechanism while applying steady traction, the bronchoscope and probe were removed en bloc until the biopsy released (we previously performed several procedures with adult colleagues).

Although large airway involvement (ie, stenosis) has been described in select rheumatologic diseases in children, most notably granulomatosis with polyangiitis (GPA),[12] none of our patients met the criteria for a specific entity. Previously, Wenzel et al[13] described a series of adult patients with pulmonary function test–proven asthma coupled with granulomatous lesions and lymphoplasmacytic inflammation in lung parenchyma that was obtained by a video-assisted thoracoscopic lung biopsy. Similar to our report, those patients did not meet criteria for a specific rheumatologic entity but responded well to directed therapy. The authors suggested the term "asthmatic granulomatosis" to describe their patients. However, this does not seem appropriate for our patients because granulomas were not uniformly demonstrated (we acknowledge the differences in biopsy methods). As such, we have adopted the term "airway autoimmune inflammatory response syndrome" for our patients. It remains to be seen whether our patients or those described in the previous report will eventually fulfill criteria for a specific rheumatologic entity. Close observation will be important to monitor for any signs of systemic vasculitic disease and, given the findings in the large airway, any signs of early stenosis.

Because of the autoimmune features that were found during evaluations, 2 patients were eventually treated with trimethoprim-sulfamethoxazole, which was accompanied by dramatic improvement in clinical symptoms, autoimmune serology (in patient 2), and bronchoscopic appearance. Although these patients did not fit diagnostic criteria for GPA, previous studies in well-defined patients have demonstrated trimethoprim-sulfamethoxazole to be an effective therapy in achieving and maintaining remission, particularly for patients with pulmonary involvement. In 1 previous study, 82% of patients who received trimethoprim-sulfamethoxazole twice daily remained in remission at 24 months compared with 60% in the control group.[14] These results were similar to a more recent trial in which 75% of patients with antineutrophil cytoplasmic antibody–positive pulmonary vasculitis treated with trimethoprim-sulfamethoxazole 3 times weekly were in remission at 18 months compared with 55% in the placebo group.[15] Although the mechanism of trimethoprim-sulfamethoxazole in patients with GPA is currently unknown, some postulate an antineutrophilic effect, whereas others propose that reduction in infectious triggers leads to improved disease control.

CONCLUSIONS

We describe 3 patients who collectively may represent a novel disorder that we term "airway autoimmune inflammatory response syndrome." We advocate both rheumatologic and bronchoscopic evaluations for patients with persistent respiratory symptoms and failure of high-dose combination asthma therapy. Furthermore, we recommend that suspected patients be referred to a center that is capable of obtaining high-quality mucosal biopsies at the time of bronchoscopy in the event that mucosal nodularity is present.

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ABBREVIATION

GPA: granulomatosis with polyangiitis

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