

Case study

Progression of asthma in childhood

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In general, asthma runs a variable course. However, there are children with asthma who are at risk for progressive disease that can lead to failure to attain peak lung growth and eventually can result in clinical and functional impairment. We present a case of a 14-year-old girl who has demonstrated a deterioration in lung function at least in the past 6 years. This has been associated with increasing medication requirements, including chronic oral corticosteroid and a steroid-sparing medication, the presence of comorbidities, and the occurrence of frequent exacerbations. The patient has evidence of airway inflammation and remodeling based on biomarkers and biopsy findings. It remains a challenge to determine patients at risk for irreversible airflow obstruction, presumably a result of airway remodeling. Histopathologic studies from biopsy samples provide the best evidence for this. However, bronchoscopy and biopsy require technical expertise and cannot be routinely used. Clinically, once a patient increases medication requirements, this should serve as a marker of disease progression. Biomarkers of airway inflammation such as exhaled nitric oxide, exhaled breath condensates, and induced sputum analysis may have the potential to monitor disease progression. Additional efforts are necessary to understand the mechanisms involved in this phenomenon and to discover specific modalities of treatment to target the structural changes of airway remodeling. (*J Allergy Clin Immunol* 2005;115:700-7.)

Key words: Airway inflammation, airway remodeling, asthma, eosinophils, progression

CASE PRESENTATION

AB is a 14-year-old girl who was first evaluated at the National Jewish Medical and Research Center at 8 years of age. She had had mild to moderate persistent asthma since her diagnosis at 4 years of age, when she had her first hospitalization requiring oxygen supplementation, antibiotic, and systemic corticosteroid. Before age 7 years, she was treated with as-needed albuterol and beclomethasone

Abbreviations used

ADAM33: A disintegrin and metalloproteinase 33
 CAMP: Childhood Asthma Management Program
 FVC: Forced vital capacity
 NRAO: Nonreversible airflow obstruction
 SRP: Subjects who displayed a reduction in lung function

only during periods of exacerbations. She required an additional oral corticosteroid 1 to 2 times a year, especially during the winter season.

At age 7 years, she was again hospitalized for asthma and pneumonia. Cromolyn sodium via metered-dose inhaler (2 inhalations) or nebulizer treatment 4 times daily was initiated. Because of frequent exacerbations especially from 7 to 8 years of age and persistent low peak flow reading, she was referred to National Jewish Medical and Research Center for treatment. At this time, she was reporting wheezing requiring albuterol rescue therapy only twice a week and nocturnal cough and wheeze occurring approximately once per month. Environmental history was notable for the presence of a dog and a hamster in the home since a year before the National Jewish Medical and Research Center assessment and passive smoke exposure since birth.

At her initial evaluation, the physical examination was remarkable for moderate pectus excavatum with no specific ear, nose, throat, eyes, lung, and cardiac findings. Initial spirometry showed a FEV₁ of 1.21 L (69% of predicted), forced vital capacity (FVC) of 1.57 L (77% of predicted), and FEV₁/FVC ratio of 0.77. Postbronchodilator values were FEV₁, 1.47 L (84%); FVC, 1.70 L (84%); and FEV₁/FVC ratio, 0.86. Aeroallergen skin prick tests demonstrated positive reactions to grass, cat, and house dust. Chest radiograph showed moderate to severe pectus excavatum and otherwise essentially normal lung findings. She was initially started on fluticasone propionate 440 µg daily.

AB has been re-evaluated approximately yearly since age 8 years. Spirometric lung function measurements have been obtained serially. Despite significant variability in her pulmonary flow measurements, there was a trend toward a progressive reduction in her prebronchodilator and postbronchodilator FEV₁ percent predicted (Fig 1). At age 8 years, she had maximum lung function measurements with an FEV₁ of 94% of predicted and an FEV₁/FVC ratio of 0.74.

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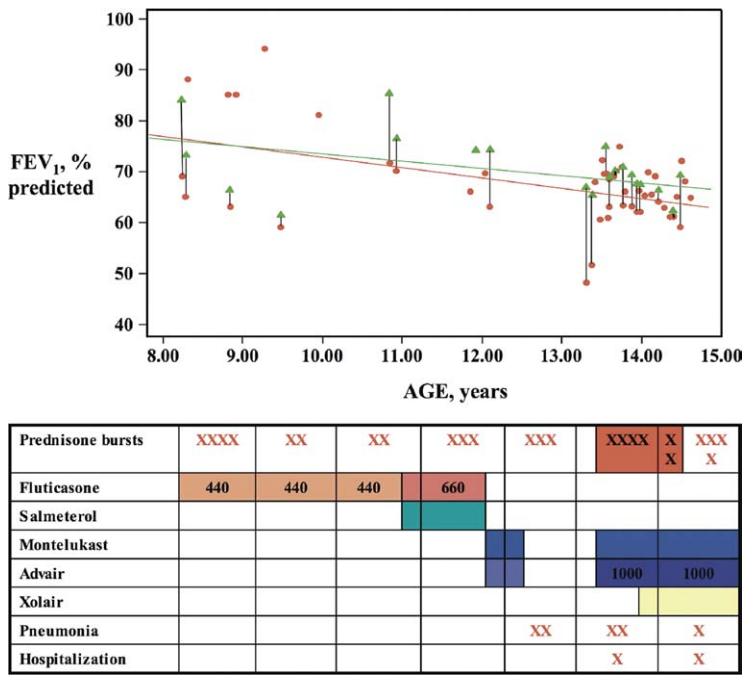


FIG 1. This patient's lung function has diminished over time. Using a regression analysis based on these serial measurements of her prebronchodilator FEV₁ percent predicted (in red circles) and postbronchodilator FEV₁ (in green triangles) over the past 6 years, her slopes of decline were -1.1 and $-2.1\%/y$ ($R^2 = 0.15$ and 0.26 ; P values = $.09$ and $.0002$), respectively.

Consequent escalation of medication requirement over the years was based on episodes of asthma exacerbations associated mainly with respiratory tract infections (requiring 2-3 systemic corticosteroid courses per year) and steady drop in lung function, with very few symptoms between episodes (Fig 1). By 10½ years of age, she was on combination therapy (inhaled corticosteroid and long-acting β_2 -agonist).

The patient returned for a visit at National Jewish Medical and Research Center at age 13 years. She was maintained primarily on as-needed albuterol and oral corticosteroid rescue, without inhaled controller therapy for at least a year. She had frequent day and nighttime symptoms requiring almost daily albuterol rescue use. At that point, she used 1 albuterol canister every 2 to 4 weeks. Peak flow monitoring revealed marked variability from 100 to 250 L/min (compared with a personal best of 350 L/min). She had a prebronchodilator FEV₁ of 48% with a reversibility to 69% of predicted. She acknowledged no major breathing problems. Her mother noted that over the previous year, her perception of degree of airflow obstruction had diminished. She would take albuterol in the middle of the night only when she was sick. Occasionally, she would have no memory of waking up at night when she was well, even if her mother would give her albuterol nebulizer treatments in the middle of the night 1 to 2 times a week.

A 1-week course of prednisone was administered along with reinitiation of combination therapy consisting of fluticasone/salmeterol (Advair; GlaxoSmithKline, Research

Triangle Park, NC) 500/50 μ g twice daily and montelukast (Singulair; Merck, West Point, Pa) 5 mg daily. Despite documentation of response to the initial systemic steroid course, she was able to attain prebronchodilator and postbronchodilator FEV₁ percent predicted only in the 60% to 75% range. She required chronic oral corticosteroid treatment starting at age 13 years. Although her persistent symptoms have improved and peak flow values have increased to the 380 L/min to the 400 L/min range, she had a severe asthma exacerbation associated with pneumonia or atelectasis requiring intensive therapy.

AB has never lost consciousness, nor has she had a respiratory arrest or hypoxic seizure because of asthma. She has had approximately 5 emergency room visits in her life. She has had several hospitalizations, 3 before 8 years of age before the use of asthma controller therapy, and 1 at age 13 years.

The patient's medical history was significant for 7 episodes of "pneumonia" since age 4 years (3 with apparent radiographic findings), with left-sided or right-sided or bilateral involvement with no positive cultures documented; frequent otitis media in infancy; intermittent sinus infections; and mild levoscoliosis. A typical "pneumonia" and/or asthma exacerbation starts out as a regular cold with or without a low-grade fever. She then proceeds to have a dry cough with nocturnal worsening, general malaise, irritability, wheezing, upper chest tightness, and severe chest pain.

There is a family history of atopy. Her father has "hay fever" and penicillin allergy, and her mother has mild

asthma. The family has had significant economic and emotional stress since her father was diagnosed with a severe form of pemphigus foliaceus in 2002.

Although this patient had minimized the interference of asthma with her school performance and sport activities, she had at least 1 to 2 weeks of missed school days per year in the past 2 years. The parents have maintained close supervision of the patient's compliance with medications and medical follow-ups.

The family used to have a dog in their apartment, which they eventually removed because of the patient's suboptimal response to treatment. At this time, the father has quit smoking. The patient has had no specific problems in this apartment compared with her old environment a year ago.

Review of systems was significant only for intermittent severe chest pain accompanying the respiratory problems; ocular pruritus, especially with exposure to cats; intermittent postnasal drip, snoring, and nasal stuffiness in the winter and late summer; a mild degree of scoliosis and moderate pectus excavatum deformity; and a few episodes of regurgitation but minimal gastroesophageal reflux symptoms. There is no known adverse reaction to non-steroidal anti-inflammatory medications.

DIFFERENTIAL DIAGNOSIS

We have presented a 14-year-old white girl with a history of asthma that started out with mild episodes before school age and over a relatively short period evolved into severe, even refractory, asthma associated with documented deterioration in pulmonary function over a period of 6 years. She has met most of the criteria for refractory asthma proposed by the National Heart Lung Blood Institute in 2000 and adapted from the European Network for Understanding Mechanisms of Severe Asthma.¹

Once the diagnosis of asthma is established, there are other conditions that contribute to refractory asthma in children and should be taken into consideration, including aspiration syndromes (secondary to a swallow dysfunction or gastroesophageal reflux disease or foreign body aspiration, particularly in younger children), sinusitis, ongoing environmental exposure, structural abnormalities (tracheobronchomalacia or compression syndromes), infections (eg, *Mycoplasma* or *Chlamydia*, tuberculosis), vocal cord dysfunction, bronchiolitis, bronchiectasis, cystic fibrosis, hypersensitivity pneumonitis, and allergic bronchopulmonary aspergillosis.² Steroid pharmacokinetic abnormalities or insensitivity may also have a role in suboptimal response to treatment.^{2,3}

LABORATORY AND OTHER TESTING PROCEDURES

This patient has had persistent airflow limitation and recurrent presumed "pneumonias." Her evaluations included pulmonary function tests with body plethysmog-

raphy as well as a cardiology evaluation for possible functional impairment secondary to the pectus excavatum. There was no immediate indication for surgery, other than cosmetic. High resolution chest tomography showed mild changes of airway disease and patchy air trapping of both lower lobes. Exhaled nitric oxide level (at 50 mL/s flow rate) was 53 parts per billion. Sweat test, serum immunoglobulins (except for an elevated IgE of 348 IU/mL), and antibody titers were within normal limits. Evaluation of steroid response included determination of steroid pharmacokinetics⁴ and an *in vitro* assay of steroid insensitivity using the glucocorticoid lymphocyte proliferation assay.⁵ The patient displayed normal prednisone absorption, normal interconversion to prednisolone, and normal clearance of prednisolone. This patient's cellular sensitivity to hydrocortisone, dexamethasone, budesonide, and fluticasone was normal.

Laryngoscopy showed no evidence for vocal cord dysfunction at the time of a positive methacholine test (FEV₁ PC₂₀ 1.16 mg/mL). A 24-hour pH probe study was slightly elevated.

Flexible bronchoscopy using a 4.9-mm external diameter adult digital bronchoscope and endobronchial biopsy were performed because of the history of recurrent pneumonias and to rule out other underlying lung diseases. Gross findings showed mild-moderate global airways inflammation and no anatomic lesion. Bronchoalveolar lavage cytology included 87% macrophages, 2% neutrophils, 8% lymphocytes, and 1% eosinophils; few siderophages; and a lipid laden macrophage index of 20. Cultures for bacteria, fungi, acid-fast bacillus, *Chlamydia*, *Mycoplasma*, *Ureaplasma*, and viruses were negative. Endobronchial biopsy of the right lower lobe main stem carina revealed findings of minimal to moderate chronic inflammation of the submucosa, smooth muscle and goblet cell hyperplasia, and thickened basement membrane with subepithelial collagen deposition (Fig 2).

TENTATIVE DIAGNOSIS WITH DISCUSSION OF PATHOGENESIS

Asthma is generally a variable disease that involves a waxing and waning course. Our patient demonstrated this variable trend in regard to her symptoms and pulmonary function particularly at the time of an acute illness. Yet her disease has run a progressive course over a relatively short period, considering various parameters, including lung function and biopsy findings associated with airway inflammation.

The concept that asthma can be a progressive disease has been supported by findings of airway remodeling in biopsy samples from both adult and, more recently, pediatric subjects with asthma.⁶⁻⁸ In children, progression of asthma becomes a concern for at least 2 reasons: (1) maximal lung or airway growth may not be attained, and consequently, a diminished FEV₁ in childhood can affect the development of fixed airflow obstruction in adulthood⁹; and (2) even at an early age, children may develop

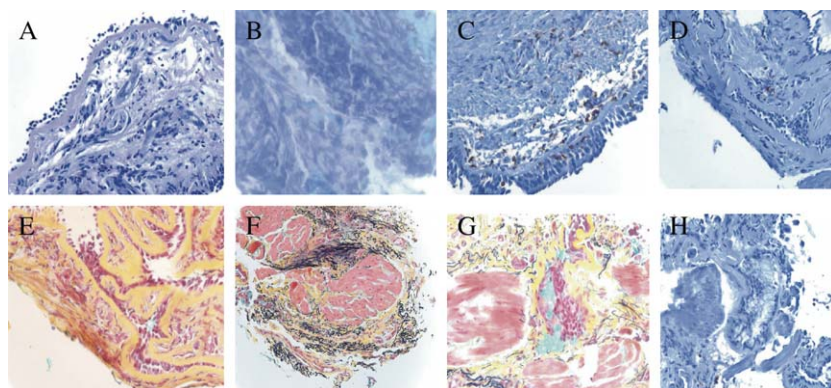


FIG 2. Endobronchial biopsy. **A**, Hematoxylin and eosin–stained section shows the thickened basement membrane and a mild to moderate submucosal inflammation with scattered eosinophils. **B**, Stained mast cells. **C**, CD3 T lymphocytes. **D**, CD20 B lymphocytes. **E**, Pentachrome–stained slide ($\times 400$) demonstrates a greatly thickened basement membrane (collagen stains yellow). **F and G**, Deposition of elastin fibrils (black) and massive smooth muscle hypertrophy (salmon color), and goblet cell hyperplasia (turquoise). **H**, Goblet cells with mucus.

an irreversible airway obstruction to a clinically important degree. This patient now seems to have more asthma exacerbations despite intense therapy.

Cross-sectional studies in children with mild to moderate and those with severe asthma demonstrate lung function decline of varying rates. The baseline data of children with mild to moderate persistent asthma in the Childhood Asthma Management Program (CAMP) suggest a reduction of 0.9% prebronchodilator FEV₁ percent predicted per year of asthma duration by using a simple regression analysis,¹⁰ whereas among children with severe asthma evaluated at National Jewish Medical and Research Center, a greater reduction of 1.8% per year in prebronchodilator FEV₁ percent predicted was evident.⁶

It is well recognized that adult patients with asthma lose lung function at a greater rate than subjects without asthma over time.¹¹ In contrast with adults who incur a decline in absolute FEV₁ values as a normal process, children have an increase in absolute FEV₁ and FVC until the second decade. Hence, there is an inherent difficulty in tracking lung function decline in the context of the normal process of lung development. One way to evaluate loss of lung function is to use comparative values such as *z* scores (ie, each subject's lung function measure is compared with age-specific and sex-specific means and expressed as standard deviation score from the mean) or percent of predicted values to account for age, sex, and height differences.

From the Tucson Children's Respiratory Study, in which lung function measurements using maximal forced expiratory flow at functional residual capacity from infancy in several subjects were obtained, the persistent wheezing group incurred a decline in lung function from infancy to 6 years using *z* scores compared with the transient, late-onset, and never-wheezing groups.¹² Although speculative, could this be a result of an ongoing airway inflammatory process in a susceptible group during a period of rapid lung growth?

We have additional insights from the CAMP study. This study involved more than 1000 children and was

intended to evaluate the effects of 3 inhaled treatments—budesonide, nedocromil, and placebo—in children originally 5 to 12 years old with mild to moderate asthma. These children started out with lung function in the normal range and with a significant degree of airway reactivity.¹³ In the main CAMP outcome paper, no significant change in postbronchodilator or prebronchodilator FEV₁ percent predicted during the treatment period was observed, regardless of treatment groups.¹³ However, this included a group of patients who had a steady reduction in FEV₁ percent predicted over time. Covar et al¹⁴ explored this further by setting a reasonable definition of lung function reduction. A regression slope or change in postbronchodilator FEV₁ percent predicted on the basis of repeated measures of lung function per individual patient throughout the treatment phase of CAMP was determined. A reduction in lung function was considered significant if the regression slope was less than $-1\%/y$ associated with a *P* value of $\leq .1$ and an *R*² of at least 0.14. Using this definition, 25% of the CAMP subjects studied had progressive reduction in postbronchodilator FEV₁ percent predicted throughout the treatment phase. Predictors of a significant reduction in lung function included younger age, male sex, and higher lung function at randomization. This patient's calculated postbronchodilator and prebronchodilator FEV₁ percent predicted regression slopes over the past 6 years were consistent with the previous definition: $-1.1\%/y$ and $-2.1\%/y$ (*R*² = 0.15 and 0.26; *P* values = .09 and .0002), respectively (Fig 1).

Another way of evaluating lung function reduction is to track the absolute spirometric values along the normal lung growth curves from reputable reference values. This process is similar to the pediatric practice of monitoring somatic growth on the basis of height and weight for age. Fig 3 compares the patient's absolute FEV₁ values with an available database of predicted values.¹⁵

The FEV₁/FVC ratio has also been used as a surrogate marker of airway remodeling (ie, postbronchodilator FEV₁/FVC ratio -1.96 SD from the age-specific and

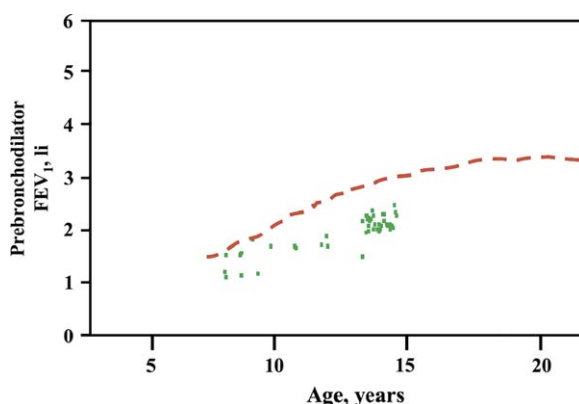


FIG 3. This patient's serial measures of FEV₁ (L) with age are plotted against the predicted values determined from the National Health and Nutrition Examination Survey III normal children of the same age and sex.¹⁶

sex-specific means for subjects without a history of wheezing or smoking) in the New Zealand Dunedin Health and Development birth cohort followed serially until the last analysis at 26 years of age.¹⁶ Low FEV₁/FVC ratio was found in 7.4% and 6.4% of study members at ages 18 years and 26 years, respectively, whereas 4.6% had low ratios at both ages. Only approximately 25% of male subjects and 10% of female subjects with asthma developed low ratios. Subjects with a low ratio also had a more rapid decline in FEV₁ and FEV₁/FVC ratio from age 9 years to age 26 years, and they were less responsive to β -agonists at 26 years. More than half of subjects with a diminished ratio were on inhaled corticosteroids, compared with $\frac{1}{3}$ of those with a normal ratio. This study suggests that clinically relevant airway remodeling does not occur in all patients with asthma and airway remodeling, and loss of β -agonist reversibility can occur despite inhaled corticosteroid therapy.

An important observation from this patient that mirrors significant findings in adults with severe asthma was her initial display of significant reversibility in lung function and, more recently, a less reversible pattern (Fig 1). Nonreversible airflow obstruction (NRAO; defined as postbronchodilator FEV₁ < 80% predicted and β -agonist response < 9%) as a surrogate for disease progression was found in 23% of 92 adult lifelong nonsmoking subjects with moderate to severe asthma after 10 years.¹⁷ They all were on high doses of inhaled corticosteroid, and $\frac{2}{3}$ were oral steroid-dependent. Despite this, they had a steeper decline in FEV₁ over time. Patients with NRAO had a higher degree of FEV₁ reversibility at enrollment compared with patients who had reversible airflow obstruction. Thus, the risk of NRAO may be highest in patients with variable airflow obstruction, which might be related to airway inflammation, albeit no markers of airway inflammation were obtained.

The contribution of airway inflammation to changes in lung function and airway remodeling is not clearly established, yet it is essential to our understanding and

search for immunomodulator interventions. In nonsmoking adults with severe symptomatic asthma despite therapy with high-dose inhaled corticosteroids and long-acting bronchodilators, ten Brinke et al¹⁸ found that persistent airflow limitation (defined as either postbronchodilator FEV₁ < 75% predicted or FEV₁/FVC ratio < 0.75) occurred almost 9 times more often in patients with severe asthma with sputum eosinophilia. The authors suggested that airway inflammation underlies the development of persistent airflow limitation. Wenzel et al¹⁹ performed bronchoscopy with endobronchial biopsies on patients with severe, moderate, and mild asthma and controls without asthma. They found that patients with severe asthma with airway eosinophilia not only had elevated numbers of T lymphocytes, mast cells, and macrophages in their airway but also had thicker basement membrane compared with the eosinophil-negative patients with severe asthma. Payne et al⁷ evaluated the relationship between exhaled nitric oxide and airway eosinophilia in children with refractory asthma after a course of prednisolone. In a small number of patients who remained symptomatic despite the steroid course, a significant correlation was found between exhaled nitric oxide and tissue eosinophils. The Denver site had the opportunity to evaluate markers of inflammation during the CAMP closeout visits.¹⁴ Participants who had a reduction in lung function had greater sputum and circulating eosinophil counts during the washout period. Whether eosinophilia is a marker or the factor causing fibrotic changes in the airway that lead to persistent airflow limitation is still uncertain. The findings from these studies emphasize the need to monitor inflammatory markers in addition to lung function and symptoms to determine whether asthma progression indeed is driven by active inflammation that may not be steroid-responsive.

Although still speculative, there may be genetic mechanisms that contribute to this phenomenon of disease progression. One proposed pathway relates to A Disintegrin And Metalloproteinase 33 (ADAM33), a member of the zinc-dependent matrix metalloproteinases, which possess proteolytic and adhesion activities. This study of 152 Dutch white subjects is the first genetic study disclosing an association between polymorphisms in a gene and longitudinal decline in lung function.²⁰ Individuals who were homozygous for the rare alleles of the SNPs S2, T1, and T2 of the ADAM 33 gene had about a 30 mL/y excess decline compared with the nonrisk genotypes. Because ADAM33 is expressed by lung fibroblasts and bronchial smooth muscle cells, it is plausible that ADAM33 is related to airway remodeling if an increase in its functional properties causes a proliferation of smooth muscle cells and fibroblasts. A proposed alternative explanation is that if normal ADAM33 function protects the airways from increased repair processes, loss of its function could lead to remodeling.²⁰

Peculiar to this patient is the presence of a congenital pectus excavatum (the most common congenital deformity of the chest wall) that potentially could have affected her lung function abnormalities. In a recent report of 103

children (5-19 years of age) with idiopathic pectus excavatum, 54% had lung function within the normal range, whereas 41% and 5% had evidence of obstructive and restrictive lung disease, respectively.²¹ A clinical diagnosis of reactive airway disease was present equally in 20% of those in the normal, obstructive, and restrictive groups. What could be more relevant in this case was their observation that with increasing age, there was no convincing evidence that the pectus deformity was associated with progressive worsening of lung function.

FINAL DIAGNOSIS WITH TREATMENT/ MANAGEMENT PLANS

Although this patient has been on inhaled corticosteroids for most of her illness, it was during the time that treatment was disrupted when she developed more symptoms and variable peak flow readings. Thus, it is apparent that significant components of the disease are still responsive to this form of anti-inflammatory treatment. This finding is consistent with studies showing that inhaled corticosteroid therapy affords protective effects on lung function decline and bronchial hyperresponsiveness, which become obvious on discontinuation.²² The effect of inhaled corticosteroid therapy on features of not only airway inflammation but also airway remodeling has been evaluated by measuring basement membrane thickness in adult patients with mild to moderate asthma.^{8,23} In these studies, although the basement membrane thickness before and after placebo remained constant, there was a partial yet significant decrease in the basement membrane thickness after treatment with the corticosteroid associated with a reduction in the number and activation of inflammatory cells in the bronchial mucosa. These studies indicate that inhaled corticosteroid therapy affords some protective effect on airway remodeling.

Although the benefits from corticosteroids on several aspects of asthma control and severity are well established, there are still components of the disease such as loss of lung function in certain individuals for which this intervention is not adequate. This patient required escalating doses of inhaled corticosteroid and even recently has been on chronic oral corticosteroid therapy. In the CAMP cohort, similar percentages of children had a reduction in postbronchodilator FEV₁ percent predicted over time (labeled SRP) in the different treatment groups: budesonide, nedocromil, and placebo.¹⁴ In addition, among the SRP, there was no statistical difference in the slopes found between the 3 different treatments. Does this reflect overwhelming inflammation that requires higher doses of steroid? Alternatively, does the inflammatory process create various cellular and immunologic mechanisms of steroid insensitivity?³ Is this evolving into a different disease entity? What seems obvious now from the patient's biopsy are findings of significant structural changes that may conceivably be unaltered by steroid therapy. Clinically, this raises the dilemma of establishing a balance of the right dose of corticosteroid to curtail

steroid-sensitive inflammation against that which can enhance steroid adverse effects. It may be that a patient's increased controller medication requirement should prompt closer surveillance and evaluation, because it indeed can serve as a marker of progression.

Pharmacologic options for asthma refractory to corticosteroids include add-on medications recommended in the National Asthma Education and Prevention Program guidelines²⁴ such as long-acting β -agonists, leukotriene-modifying agents, and theophylline. Alternative therapies such as oral gold, methotrexate, cyclosporine A, intravenous immunoglobulin, and most recently anti-IgE are available primarily as steroid-sparing agents, but their observed effects have been limited, especially in children, for various reasons, including the presence of unwanted side effects or numerous contraindications, lack of information about long-term response, lack of available predictors of response, lack of placebo-controlled studies, and expense.^{2,25} This patient was started on omalizumab (Xolair; Genentech, Inc, and Novartis Pharmaceuticals Corporation) in the fall of 2003 while she was on chronic oral corticosteroid. She was able to discontinue her chronic oral corticosteroid requirement 6 months after starting Xolair, but she has still required several short bursts indicated for exacerbations, usually associated with respiratory tract infections. A repeat set of pulmonary function with body plethysmography 5 months after her first Xolair injection showed a modest decrease in the degree of air trapping, with essentially similar spirometric measures.

Given that most patients with refractory asthma have coexisting morbidities and confounders such as gastroesophageal reflux disease, sinusitis, environmental exposures, and associated adverse effects from high-dose inhaled and/or oral corticosteroid, these should be monitored and managed accordingly. This patient has had good control of her reflux symptoms on a proton pump inhibitor and dietary and behavioral modifications. She has not developed significant steroid adverse effects. Surveillance for steroid adverse effects has included ophthalmologic evaluation, monitoring of growth and development plus adrenal function, and determination of bone mineral density. The occurrence of a severe chronic illness at any age can be emotionally and psychologically debilitating, because it can affect the quality of life. The patient has also been evaluated by a clinical psychologist.

Can early intervention alter disease progression? There are some interesting insights from the START (inhaled Steroid Treatment As Regular Therapy in early asthma study) trial.²⁶ This large, international, randomized, placebo-controlled study was undertaken to evaluate whether early intervention with a low-dose inhaled corticosteroid for 3 years in patients with less than 2 years of mild persistent asthma would prevent not only severe asthma-related events but also an accelerated decline in lung function. Patients on active drug had fewer asthma exacerbations and courses of systemic corticosteroids and more symptom-free days than patients on placebo. A

rather unexpected finding was that despite low-dose inhaled corticosteroid, a deterioration in postbronchodilator FEV₁ percent predicted after 3 years occurred in all age groups (5-10 years, 11-17 years, and 18-66 years). These observations suggest that inhaled corticosteroid therapy has disease-modifying effects in reduction in symptoms and exacerbations, but there may be components of the disease (such as aberrant repair processes) that are not targeted by these medications and that manifest in progressive deterioration in lung function.

SUMMARY STATEMENT WITH CLINICAL PEARLS

In children with asthma, progressive worsening of symptoms and lung function can occur, but not all children with mild to moderate asthma will develop this.

Progressive reduction in lung function in children can eventually result in clinical and functional impairment.

It remains a challenge to determine patients at risk for irreversible airflow obstruction. Research directed at predictors for irreversible airflow obstruction is of great importance. The etiology of the reduction in lung function, which may reflect reduced lung growth or airway remodeling, is still not apparent.

Histopathologic studies from biopsy samples provide the best evidence for airway remodeling and disease progression. However, bronchoscopy and biopsy carry some risk and require technical expertise that make their routine use difficult. Evaluation of disease progression can be clinically assessed by monitoring escalation of symptoms, frequency of exacerbations, and medication requirement over time, or tracking loss of lung function, which is the most objective measure of asthma to date. Clinically, once a patient starts to require increased medications, this should serve as a marker of disease progression. To expand on the asthma profile, investigations are necessary into the use of noninvasive tools to monitor disease activity and progression, such as exhaled nitric oxide, exhaled breath condensates, and induced sputum analysis.

Asthma progression in some patients occurs despite high-dose inhaled and/or systemic corticosteroid therapy. Additional investigations are necessary to understand the mechanisms involved in this phenomenon and to discover specific modalities of treatment to prevent or reverse airway remodeling.

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