



Possible Pulmonary Remodeling in an Adolescent With Allergy and Asthma

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Question:

I am following a 15-year-old male with allergic rhinitis, food allergy, and asthma, followed in our office for the past 5 years. His asthma is intermittent and low risk (never hospitalized or needed systemic steroids). His allergic rhinitis is mild and controlled with loratadine as needed. He participates in school sports (including track) without limitation noted. Spirometric results have been consistently abnormal for several years, with FEV₁ ranging from 30% to 50% and forced vital capacity ranging from 70% to 80% of predicted. Despite several attempts spirometric results were not reversible with albuterol. Fractional exhaled nitric oxide (FENO) levels were markedly elevated at 124 and 129 ppb on two different days several weeks apart (high >50 ppb per American Thoracic Society guidelines). Because of this, a trial of medium-dose inhaled corticosteroid (ICS) (fluticasone propionate 110 µg 2 puffs twice daily) was started which led to a reduction in FENO level to 49 ppb on follow-up; however, he remained asymptomatic and his spirometric findings did not change. Although it was recommended to continue ICS, he returned 3 months later still asymptomatic with continued poor spirometry and FENO 113 ppb, probably because of ICS nonadherence. He is not interested in taking a medication that does not seem to help him. I can sympathize with this because I feel I am basically treating a spirometry number.

My plan is to refer for full pulmonary function testing, chest X-ray, and obtain a complete blood count with differential, perhaps looking for an explanation for his presumed airway eosinophilia and consistently poor and nonreversible spirometry findings for several years. I am conflicted with pursuing an expensive workup for a teenager with intermittent asthma symptoms who can participate in high school track without difficulty. How would you proceed in this case?

Response:

Thank you for your inquiry. We appreciate the opportunity to assist you in the appraisal of this patient's case. It is important to do so because it is a picture that occurs not infrequently in the practice of allergy-immunology.

From my perspective, there are three issues that are highlighted by your patient's presentation:

1. What is the diagnosis? That is, what condition is responsible for the underlying pathology that is producing irreversible obstructive lung disease in your patient?
2. Why is there such a disjunction between objective measurements of pulmonary function and the patient's perception of dyspnea? For example, how can he tolerate vigorous activity in the face of this type of lung function impairment?
3. Is there any potential therapy that might reverse his impairment or prevent further deterioration?

I will give you my opinion regarding the answer to each one of these questions and then share with you the rationale behind these answers.

1. I believe that the diagnosis is asthma per se and that the underlying process that has resulted in his irreversible obstructive disease is pulmonary remodeling. But this degree of obstruction in a teenager without a history of significant asthma, either previously or currently, is impressive and absolutely requires further evaluation. Although this fact is implicit in the recommendations that follow, the bulk of these recommendations are made with the assumption that the patient has fixed obstruction and remodeling and emphasis should be placed on the less controversial assertion that his findings deserve aggressive investigation.
2. We know that pulmonary remodeling in asthma may occur early in life.¹ Therefore, in my opinion, the most probable reason that he is able to tolerate low lung functions so well is that it is highly likely that he was born with diminished lung function or developed such in early childhood and that there has been a very gradual, insidious further loss in both vital capacity and FEV₁ over the duration of his lifetime. The process has been so insidious that he has become accustomed to operating at a level which a patient experiencing a sudden drop in lung function from normal levels would not be able to tolerate.
3. If the above is correct, then the best treatment of which we are aware is maintenance ICSs.

Having shared with you the "punch line," I will try and explain the rationale for these answers.

First, pulmonary remodeling is a rather new entry into our curriculum. The fact that asthma could be an irreversible lung disease was unheard of until the development of fiberoptic bronchoscopy that allowed for frequent biopsies. Between 1980 and 1990, there were only two references in the literature regarding the remodeling process that can occur in asthma. At this date, there are more than 700 articles addressing this issue.

Our appreciation of the frequency of remodeling has also grown. Originally, it was thought not to occur in patients with childhood asthma, but reanalysis of subgroups from the

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Childhood Asthma Management Program proved that hypothesis incorrect.² It occurs in a significant amount of both children and adult asthmatic patients.³ There are a number of pathologic changes that we believe are responsible for the irreversibility noted in patients who do remodel. Perhaps the most salient of these are the deposition of ground substances and collagen in parenchyma, and the destruction of elastic tissue. These can result in findings identical to those seen in your patient. That is, both a loss of forced vital capacity and FEV₁, with the loss in FEV₁ being the greater of the two.

We also know of many risk factors, and one of these is quite clearly atopy and an elevated IgE.⁴ So your patient, even though he does not by history have severe asthma, by virtue of his atopic disease has a very significant risk factor.

We also know that allergen inhalation challenge can result in activation of fibroblasts, production of TGF- β , and a deposition of tenascin as well as thickening of the subepithelial basement membrane.⁵ Biopsies of atopic asthmatic patients also support a role of the remodeling process, and an elevation of IgE itself, as shown in the TENOR study,⁴ can predispose to remodeling.

Thus, we see that this remodeling process can produce pulmonary function findings identical to those seen in your patient, that this process occurs with significant frequency in asthma, and that your patient clearly has at least one significant risk factor for remodeling. Even so, we cannot be certain that your patient has remodeled. It would be helpful if you could plot the pulmonary functions in chronologic order, dating back to your first measurement. The trajectory of the process might become clearer via an analysis of these measurements. This would be important in light of the treatment recommendations mentioned below. However, it should be clear that even if the trajectory is not progressive, it would not rule out the remodeling process because there are not enough data for us to assume that all patients remodel in a steadily progressive manner. For example, we know that exacerbations can accelerate the remodeling process; therefore, there may be changes in the progress of remodeling dependent on the frequency of exacerbations over a period of time. These exacerbations can be due to viral respiratory tract infections⁶⁻⁸ as well as aeroallergen exposure.^{5,9} Thus, because such exposures can be erratic, the remodeling process may not progress in a constant linear fashion.

However, I believe that you are absolutely correct in considering further workup. This workup should be designed to rule out any other cause and also to try and establish that there is an underlying remodeling process.

I think that it is highly unlikely that he has any other underlying process, but those to be considered would be the following:

1. Early onset of chronic obstructive pulmonary disease with emphysematous changes as one might see in α -1 antitrypsin deficiency.
2. Cystic fibrosis.
3. One would also like to assess whether he was experiencing silent reflux, because inhalation of gastric acid at night can institute or aggravate inflammatory changes in the lung.

Thus, the tests that I suggest to further evaluate your patient would be the following:

1. Complete pulmonary function studies with a diffusing capacity of lungs for carbon monoxide. The diffusing capacity

of lungs for carbon monoxide is usually normal relative to the vital capacity in patients with remodeling, but is abnormal in emphysema.

2. A sweat chloride.
3. An α -1 antitrypsin.
4. High-resolution chest computed tomography scan. Patients who exhibit the remodeling process often (but not always) show characteristic fibrotic changes on computed tomography scan of the chest, and it has been shown in some studies that the degree of these changes correlates with the intensity of the remodeling process.
5. Possible assessment for gastroesophageal reflux.
6. You also suggested a complete blood count to look for the presence of eosinophilia. I think this is also an excellent idea because another risk factor for remodeling is an increase in lung as well as blood eosinophils.
7. You can also consider studying pulmonary compliance. In patients who exhibit remodeling, the lung is stiff and the compliance is decreased. The opposite is true in emphysema.
8. You should also consider a cardiopulmonary exercise test.

You might find helpful two references that have recently appeared in this Journal, both of which are germane to your patient. One discusses the differential diagnosis of patients presenting with asthma by Peters¹⁰ and the other, by Bell and Busse,¹¹ discusses severe asthma and has a very nice section on the remodeling process in the context of patients with this disease.

As mentioned previously, if indeed your patient has remodeled, it is not uncommon, at least in our experience, that he would have symptoms that are not commensurate with his lung functions. That is, such patients quite often seem to be able to operate, from their perspective, with lung functions that we would normally associate with more significant impairment of activity as well as quality of life. We see this more commonly in elderly asthmatic patients who seem to be able to get along quite well with an FEV₁ of 0.5 to 0.6 L. However, I have also seen this in adolescent athletes who are able to participate in sports.

This brings us to the final question, perhaps the most important one, and that is, can something be done to reverse or prevent further progression of his disease?

There is no definitive answer to this question, and the issues surrounding it are controversial, but in my opinion there is sufficient evidence to indicate that ICSs can favorably affect the outcome of patients who are undergoing remodeling. Results of the use of corticosteroids for this problem have been mixed, but, again, in my opinion, the weight of evidence supports their use in patients such as the one for whom you are caring.

There are issues of dosing when one treats with ICSs. At least in two studies,^{12,13} higher doses, that is in one,¹² sufficient to suppress bronchial reactivity (which are higher than Guideline suggested doses) were required to favorably affect histologic changes of remodeling. Thus, I would consider the use of high doses despite that your patient remains asymptomatic. However, this is an area of controversy, and the data are not definitive.

I normally, in such patients, treat with small-particle ICSs because it has been conclusively shown that inflammation and the remodeling process occurs not only in the large but also in the small airways.¹⁴⁻²²

There has also been recent evidence that bronchial constriction per se can result in remodeling through shear forces.²³ There

is some, albeit sparse, data in the literature that support the use of a long-acting bronchodilator in the therapy of remodeling.^{24,25} Furthermore, in your patient, you have been able to show quite convincingly that ICS therapy is able to diminish FENO; therefore, we can at least tentatively conclude that you are thereby able to control the ongoing inflammation (even in the absence of symptoms) that is occurring in your patient. Because the most dominant theory as to the process underlying remodeling proposes that it is due to inflammation, especially eosinophilic inflammation, it would intuitively appear important that you control such inflammation. Thus, there is strong impetus in your case to initiate daily maintenance therapy with an ICS and possibly a long-acting bronchodilator.

I think it is clear, based on the above observations, that a thorough workup should be done before coming to the conclusion that remodeling is the cause of this patient's fixed lung obstruction and relegating him to long-term ICSs. I would also like to add the caveat that the data supporting the use of long-term ICSs has been challenged, and perhaps the best way to express this challenge is to quote the National Asthma Education and Prevention Program 3 Guidelines which state: "The Expert Panel concludes that evidence to date does not support the previously hypothesized contention that early intervention with an ICS, either continuously or intermittently, may alter the underlying severity or progression of the disease."^{26,p.282}

However, even in the face of this caveat, in my opinion, the risk/benefit ratio would favor the use of these drugs once you have ruled out any other cause, as best you can, of this patient's fixed obstruction.

I realize that the things I have suggested are in direct contradistinction with the philosophy expressed in three of the statements contained in your inquiry. I certainly empathize with this philosophy and clearly understand the rationale behind your statements, and also they do make very good sense. However, I would like to play devil's advocate in regard to these statements. The statements were:

1. You sympathize with your patient's reluctance to take daily therapy that does not, in his perception, improve his symptoms.
2. You do not want to be "treating a number."
3. You do not wish to institute an expensive workup for a patient who is relatively asymptomatic.

As mentioned, all of these statements are rational. However, I personally would take a different tack. Perhaps the most important goal regarding any patient's illness is establishing a diagnosis. The treatment in most instances will always be best performed if the diagnosis is firm. In your particular case, unfortunately, the workup will be expensive if you proceed with all of the tests mentioned. But, if you can clearly establish the underlying pathophysiologic process, in my estimation it is worth it.

There is no doubt that the philosophy to "not treat a number" is oftentimes a good one. However, medicine is replete with examples in which that philosophy is not appropriate and actually does the patient harm. For example, outcome studies have shown quite clearly that, if we treat cholesterol by number, regardless of the patient's symptoms, we improve outcome. The same is true for blood pressure. I could cite further examples. Therefore, treating by number is not irrational even when we have to ignore degree of symptoms to do so.

Finally, once again I can empathize with your sentiment regarding your patient's reluctance to take medication. But I think, as with the analogy mentioned above regarding treatment by number, oftentimes we do the patient a service by, as best we can, encouraging adherence to a medical regimen that does not make "sense" to the patient himself. I think in this particular instance, such adherence is extremely important if the diagnosis mentioned is correct, and the remodeling process is active. Although the evidence that we can reverse the process is weak, the evidence that we can reduce the rate of further ongoing remodeling is much better in my opinion.

In closing, I can refer you to two brief and succinct references that are available free online that discuss the remodeling process. The links are <http://f1000.com/prime/reports/m/2/7/4/> and http://www.worldallergy.org/professional/allergic_diseases_center/allergic_remodeling/. These references are not comprehensive, but are selected from the literature to corroborate the statements noted above.

Thank you again for your inquiry, and I hope this response is helpful to you.

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