Asthma Unmasked With Tumor Necrosis Factor- α-Blocking Drugs

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Chest 2011;140;1068-1071
DOI 10.1378/chest.10-2350

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recently described chromosomal abnormalities in proliferative pulmonary lesions in a patient with germline \textit{BMPR2} mutation, which might represent genetic events possibly responsible for cell overgrowth. Nemenoff and colleagues demonstrated that mice with a \textit{Pten} depletion in smooth muscle cells exhibited PASMC hyperplasia, right ventricular hypertrophy, pulmonary vascular remodeling, and histopathology consistent with PAH. Moreover, the normal function of PTEN is to inhibit platelet-derived growth factor receptor (PDGFR) signaling. PDGFR activates the RAS/mitogen activated protein kinase signaling pathway implicated in cell overgrowth and apoptosis. Interestingly, it has been shown that PDGFR was overexpressed in small pulmonary arteries of patients with PAH, and its activation promoted the proliferation and the migration of PASMCs. Thus, we can hypothesize that mutations in the \textit{PTEN} gene may play a role in the development of PAH in the present case by promoting the activation of the PDGFR.

In the present case, the association of PAH with Cowden syndrome could be fortuitous, and PAH could be only due to anorexigen exposure. Our patient was exposed to a 1-year dexfenfluramine intake 20 years before the onset of the first PAH symptoms. The anorexigen exposure, particularly to fenfluramine derivatives taken for >3 months, is known to be a definite risk factor for PAH. Although the majority of dexfenfluramine-associated PAH occurred within the year following the drug exposure, several cases of PAH have been described many years later, but in these cases the implication of anorexigen exposure for the development of PAH is impossible to demonstrate.

The rare occurrence of PAH after anorexigen exposure, the delay between anorexigen intake and the onset of first PAH symptoms, the low prevalence of Cowden syndrome (one in 200,000), and the role of \textit{PTEN} in cell functions and vascular remodeling in experimental models suggest a potential link between Cowden syndrome and PAH.

In conclusion, to our knowledge, this is the first reported case of PAH in a patient with Cowden syndrome. However, the \textit{PTEN} mutation alone is likely insufficient to lead to PAH; it can be hypothesized that \textit{PTEN} mutations may be a predisposing factor for the development of PAH, and anorexigen exposure may be a potential trigger.

ACKNOWLEDGMENTS

Financial/nonfinancial disclosures: The authors have reported to \textit{CHEST} the following conflicts of interest: Drs Simoneau, Humbert, and Sibion have received consulting and lecture fees from Actelion, Bayer, GlaxoSmithKline, Eli Lilly and Co, and Pfizer, Inc. Drs Natali, Girerd, Montani, and Soubrier have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

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Asthma Unmasked With Tumor Necrosis Factor-α-Blocking Drugs

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We report five cases of asthma unmasked by anti-tumor necrosis factor (TNF)-α-blocking drugs. Asthma symptoms appeared within an average of 4 months (range 1-24 months) after starting the anti-TNF-α treatment for inflammatory disease. The patients did not appear to be predisposed to asthma except for one patient who had asthma during childhood. Four patients stopped anti-TNF-α-blocking drugs with an improvement of symptoms within 1 to 5 months. In the patient with a history of childhood asthma, respiratory symptoms recurred when another anti-TNF-α therapy was started. Asthma control was achieved with inhaled steroids, allowing anti-TNF-α treatment to continue. The biotherapy was maintained for the fifth patient in association with inhaled steroids. The pathophysiologic mechanisms are unknown but are probably more complex than the T helper 1/T helper 2 imbalance suggested in the literature, and further studies are required. \textit{CHEST} 2011; 140(4):1068-1071

Abbreviations: BHR = bronchial hyperresponsiveness; Th = T helper; TNF = tumor necrosis factor

CASE REPORTS

Tumor necrosis factor (TNF)-α has been implicated in asthmatic airway inflammation, which makes this cytokine a potential therapeutic target for treating some
subjects with asthma. We report the cases of five patients, three men and two women, who developed intermittent (three patients) or persistent (two patients) asthma after starting anti-TNF-α treatment of inflammatory diseases (three rheumatoid arthritis, one Crohn’s disease, and one ankylosing spondylarthritis). All patients gave their written informed consent for inclusion in this report.

The characteristics of patients are summarized in Table 1. Mean age was 35 years (range 19-66 years). One patient (patient 1) was a former smoker (20 pack-years). TNF-α-blocking drugs were infliximab in patients 3, 4, and 5, and etanercept and adalimumab in patients 1 and 2, respectively. Patient 3 received infliximab and then adalimumab. Anti-TNF-α treatment was used in combination with methotrexate in patient 2 and azathioprine in patient 3. Patients 1 and 5 received prednisone 10 mg/d associated with methotrexate and azathioprine, respectively, as part of the treatment of the inflammatory disease.

Wheezing and dyspnea appeared within an average of 4 months (range 1-24 months) after beginning the anti-TNF-α treatment. None of the patients presented with acute severe asthma. None of them had blood eosinophilia or rhinosinusitis during anti-TNF-α treatment. Patients 2 and 4 reported a past history of familial atopy. Patients 3 and 5 had a personal atopy with sensitization to airborne allergen. Lung function tests, performed after the onset of the respiratory symptoms, were normal in patients 1, 2, and 5 (with intermittent asthma). Only patient 2 was tested for bronchial hyperresponsiveness (BHR), and the test was positive with a provocative dose causing a 20% reduction in FEV₁ in 1 s of 173 μg. Lung function tests revealed airway obstruction in patients 3 and 4 with persistent asthma (FEV₁ 80% predicted and 51% predicted, respectively). In patient 4, reversible criteria were not met (FEV₁ increased from 2,960 mL to 3,140 mL, ie, by 8%). He had never smoked, had not been exposed to any significant air pollution, and had never previously suffered from dyspnea. Patient 3 had a reversible obstruction with prebronchodilator FEV₁ of 2,660 mL and postbronchodilator FEV₁ of 3,180 mL (19.5% increase). This patient reported having asthma when she was a child, but she had been asymptomatic for > 5 years. This patient tested positive to dust and cat hair on a prick test, but she did not have a cat at home. Patient 5 had positive prick-test reactions to dust mites, cockroaches, and wormwood. Prick tests using anti-TNF-α were negative in four patients (patients 1, 2, 3, and 5). Total serum IgE levels, assayed before starting asthma treatment, were within the normal range in all patients (3-40 IU/mL). High-resolution CT scan of the lung was normal in all patients.

Respiratory treatment involved inhaled steroids in cases 1, 2, and 4 and an association of inhaled steroid and long-acting β₂-agonist in cases 3 and 5. Steroid dosage for asthma control ranged from 500 μg/d to 2,000 μg/d of beclomethasone equivalent. The anti-TNF-α treatment was stopped in patients 1, 2, 3, and 5 because of the emergence of asthma symptoms. The symptoms disappeared within 1 to 5 months. In patient 4 with persistent asthma (FEV₁, 51%), inhaled corticosteroid treatment was initiated and anti-TNF-α treatment was maintained with improvement of asthma symptoms. Patient 3 initially stopped treatment with infliximab, but the inflammatory disease relapsed. Adalimumab was introduced 6 months after stopping infliximab. After three infusions, dyspnea and wheeze occurred. Spirometry demonstrated a nonreversible bronchial obstruction (an FEV₁ increase of 190 mL, ie, 7%). As anti-TNF-α was considered mandatory to treat the inflammatory bowel disease, the patient remained on biatherapy associated with inhaled steroids, which controlled the asthma symptoms.

The clinical and pulmonary function test follow-up of these patients ranged from 3 to 5 years after the asthma diagnosis. As there were no relapses of respiratory symptoms during this period, the follow-up did not include any further CT scans. Lung function tests, performed on average 3 years after stopping anti-TNF-α treatment, showed normal FEV₁ and FEV₁/FVC in patients 1, 2, and 5. BHR was screened in two patients. Patient 1 had no BHR after stopping anti-TNF-α, but these data were not available during anti-TNF-α treatment. BHR persisted in patient 2 with q provocative dose causing a 20% reduction in FEV₁ in 1 s at 300 μg (compared with 173 μg during anti-TNF-α treatment). During anti-TNF-α treatment, airway obstruction persisted in patients 3 and 5, with FEV₁/FVC of 65% and 66% and FEV₁ of 76% and 51%, respectively. Reversibility criteria were not met for either patient.

The diagnosis of asthma was made on the basis of recurrent wheezing, breathlessness, and coughing, in accordance with the definition of the American Thoracic Society. Only one patient had a history of smoking, and none of the patients had any other detectable underlying respiratory disease.

**Discussion**

The causality of anti-TNF-α in respiratory symptoms can be evaluated on the basis of the classic pharmacologic imputability criteria using the model suggested by Edwards and Aronson. Asthma symptoms appeared after...
Table 1—Characteristics of Patients With Asthma Unmasked by Anti-TNF-α Treatment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Age, y</td>
<td>55</td>
<td>66</td>
<td>19</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Inflammatory disease</td>
<td>Rheumatoid arthritis</td>
<td>Rheumatoid arthritis</td>
<td>Crohn's disease</td>
<td>Ankylosing spondylitis</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Anti-TNF-α</td>
<td>Etanercept</td>
<td>Adalimumab</td>
<td>Infliximab then adalimumab</td>
<td>Infliximab</td>
<td>Infliximab</td>
</tr>
<tr>
<td>Immunosuppressive treatment</td>
<td>Methotrexate, prednisone 10 mg/d</td>
<td>Methotrexate</td>
<td>Azathioprine</td>
<td>Nonsteroidal antiinflammatory</td>
<td>Azathioprine, prednisone 10 mg/d</td>
</tr>
<tr>
<td>Familial atopy</td>
<td>No</td>
<td>Contact dermatitis and asthma in father</td>
<td>No</td>
<td>Asthma in brothers</td>
<td>No</td>
</tr>
<tr>
<td>Personal atopy</td>
<td>No atopy symptoms, skin tests negative</td>
<td>No atopy symptoms, skin tests negative</td>
<td>Allergic rhinitis, asthma in childhood, prick test positive to dust and cat hair</td>
<td>NA</td>
<td>Prick test positive to dust mites, cockroaches, and wormwood</td>
</tr>
<tr>
<td>Anti-TNF-α prick test</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>NA</td>
<td>Negative</td>
</tr>
<tr>
<td>IgE, IU/mL</td>
<td>NA</td>
<td>10</td>
<td>NA</td>
<td>3</td>
<td>40</td>
</tr>
<tr>
<td>Lung function</td>
<td>FEV1/FVC 77%</td>
<td>FEV1/FVC 72%</td>
<td>FEV1/FVC 68%</td>
<td>FEV1/FVC 66%</td>
<td>FEV1/FVC 75%</td>
</tr>
<tr>
<td>FEV1, 116%</td>
<td></td>
<td></td>
<td>FEV1, 80%</td>
<td>FEV1, 51%</td>
<td>FEV1, 74%</td>
</tr>
<tr>
<td>Kco, mmol/min/kPa/L</td>
<td>93</td>
<td>91</td>
<td>4 mo and after each infusion</td>
<td>NA</td>
<td>82</td>
</tr>
<tr>
<td>Time to asthma onset</td>
<td>2 y</td>
<td>3 no</td>
<td>2 y</td>
<td>1 no</td>
<td>1 no</td>
</tr>
<tr>
<td>Asthma treatment</td>
<td>Fluticasone 500 µg/d</td>
<td>Beclomethasone 500 µg/d</td>
<td>Fluticasone 1,000 µg/d and salmeterol</td>
<td>Fluticasone 1,000 µg/d</td>
<td>Fluticasone 1,000 µg/d and salmeterol</td>
</tr>
<tr>
<td>Anti-TNF-α stopped</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Clinical evolution</td>
<td>Respiratory symptoms disappeared</td>
<td>Respiratory symptoms disappeared</td>
<td>Improvement after stopping Infliximab, relapse under adalimumab</td>
<td>Clinical symptoms decreased after receiving inhaled corticosteroids</td>
<td>Respiratory symptoms disappeared</td>
</tr>
<tr>
<td>Lung function evolution</td>
<td>FEV1/FVC 73%</td>
<td>FEV1/FVC 70%</td>
<td>FEV1/FVC 65%</td>
<td>FEV1/FVC 66%</td>
<td>FEV1/FVC 81%</td>
</tr>
<tr>
<td>FEV1, 117%</td>
<td></td>
<td></td>
<td>Not reversible</td>
<td>Not reversible</td>
<td>FEV1, 98%</td>
</tr>
<tr>
<td>No BHR</td>
<td>BHR</td>
<td></td>
<td>FEV1, 76% under adalimumab</td>
<td>FEV1, 51% under infliximab</td>
<td></td>
</tr>
</tbody>
</table>

BHR = nonspecific bronchial hyperresponsiveness; Kco = carbon monoxide transfer coefficient; NA = not available; TNF = tumor necrosis factor.
introduction of anti-TNF-α in patients who did not appear to be predisposed to the disease. One patient had presented with asthma symptoms >5 years prior to beginning anti-TNF-α treatment. No other causes of dyspnea were found, and the pathophysiologic mechanism of asthma unmasked by anti-TNF-α are unknown, but several hypotheses can be put forward. Our cases make the hypothesis of an allergic reaction to anti-TNF-α unlikely. No skin or anaphylactic symptoms were observed after anti-TNF-α treatment. Bennett et al.⁵ suggested an involvement of T helper (Th) 1/Th2 balance in the side effects of anti-TNF-α, with a Th1 cytokine decrease, allowing Th2 to be expressed, leading to asthma symptoms. However, this mechanism is also not consistent with the low IgE rate in our patients. Immune mechanisms may be more complex than the simple Th1/Th2 balance, and two hypotheses could be considered. Th17 cells, which have been demonstrated to play a role in asthmatic airways,⁷ might be involved in asthma unmasked by anti-TNF-α. TNF-α-blocking drugs might also decrease immunity, playing a role in asthma onset.⁸ Anti-TNF-α, associated with methotrexate or azathioprine use, could worsen viral infection known to exacerbate asthma.⁹ Indeed, the induced immunodeficiency could lead to a virus cytopathogenic effect in patients with deficient innate immunity. At the same time, release of other proinflammatory mediators secondary to TNF-α inhibition might damage respiratory epithelial cells.

To better understand the relationship between anti-TNF-α and the onset of asthma, a prospective follow-up of patients receiving this treatment, including immunologic and virologic tests, might be considered. In cases of severe asthma, anti-TNF-α withdrawal should be considered, whereas anti-TNF-α may be maintained in milder cases of asthma controlled by steroid inhalation.

ACKNOWLEDGMENTS

Financial/nonfinancial disclosures: The authors have reported to CHEST that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

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