Airway Hyperreactivity in Tropical Pulmonary Eosinophilia*

S. K. Chhabra, M.D.; and S. N. Gaur, M.D., F.C.C.P.

Eosinophils were recently proposed to act as prime inflammation-producing cells in asthma. Tissue eosinophil infiltration is an important feature of another disease, tropical pulmonary eosinophilia. Airway reactivity was determined in two patients with the latter disease and both were found to be hyperreactive.

Airway hyperreactivity is a cardinal feature of asthma. While its cause is not known, the role of airway inflammation in the pathogenesis of hyperreactivity has been emphasized. Recently it was suggested that eosinophils may be important effector cells in asthma, capable of causing inflammation in the airways. An inverse correlation between blood eosinophilia and airway hyperreactivity has been reported in asthmatic patients. Therefore, if the eosinophil can cause airway inflammation, and the latter can produce hyperreactivity, then this may also be expected in tropical pulmonary eosinophilia (TPE) because eosinophil infiltration and airway inflammation is a feature of this disease. Because of the suggested link between eosinophil infiltration, airway inflammation and hyperreactivity, we have assessed airway reactivity in two patients with TPE.

Case Report

The first case was a 16-year-old girl who presented with a one-month history of paroxysmal, irritating cough associated with scanty mucoid sputum and exertional dyspnea. She also felt very weak and had lost nearly 1 kg in weight. She had no pallor, clubbing or cyanosis. There was no family history of atopic disorders and she was a nonsmoker. Examination of the chest revealed no abnormality. Sputum examination revealed a few eosinophils and Charcot-Leyden crystals. Blood examination showed a total leukocyte count of 16,500 cells/μl. Absolute eosinophil count was 11,400 cells/μl. Results of stool and urine examinations were normal. Results of skin tests with common aeroallergens were negative. A chest radiograph showed a fine reticulonodular area in the middle and lower zones. Specific airway conductance (SGaw) at functional residual capacity (FRC), measured using a constant-volume body plethysmograph by a quiet breathing technique was 0.22 s⁻¹ cmH₂O⁻¹ (normal: 0.14-0.37 s⁻¹ cmH₂O⁻¹). Airway reactivity was determined using histamine aerosol inhalation, following the standardized method of Chai et al. The provocative dose required to produce a 35 percent fall in SGaw from the control post-saline SGaw. It was obtained from a log dose response to histamine and found to be 0.94 mg/ml.

The second case was a 20-year-old man who presented with complaints of low-grade continuous fever, paroxysmal cough with scanty mucoid sputum and exertional dyspnea for three weeks. He had lost 1 kg in weight. There was no pallor, clubbing or cyanosis. There was no family history of atopic disorders and he was a nonsmoker. Examination of the chest revealed scattered fine crackles over both bases. Blood examination showed a total leukocyte count of 19,600/μl. Absolute eosinophil count was 12,400 cells/μl. Results of stool and urine examinations were normal. Sputum examination revealed normal oropharyngeal flora, a few eosinophils and Charcot-Leyden crystals. Desquamated epithelial cells (creola bodies) were also seen. Skin test results with common aeroallergens were negative. Radiograph of the chest showed fine reticular shadows in the middle and lower zones, and fine mottling in the right middle zone. SGaw was 0.18 s⁻¹ cmH₂O⁻¹; PD₉₀ SGaw was found to be 0.86 mg/ml.

Discussion

What level of histamine PD₉₀ SGaw cuts off normal subjects from hyperreactive airways has not been reported. However, in our laboratory, no normal subject has reacted to a concentration of histamine less than 5 mg/ml (unpublished observations). Therefore, the histamine PD₉₀ SGaw found in both the patients lies well within the hyperreactive range.

The exact pathogenesis of tropical pulmonary eosinophilia is not known, but it is suspected to be a hypersensitivity reaction to filarial infestation, probably Dirofilaria immitis. Pathologically, eosinophil infiltration and granuloma occur in the alveoli and around terminal bronchioles. Damage to the lining of the mucosa and distortion of lung architecture also occur. Patients with early disease show obstructive ventilatory defects while those with chronic disease may have a restrictive defect. Airway hyperreactivity has never been described in this condition. Tissue eosinophilic infiltration is the hallmark of this disease, and eosinophils are capable of mediating damage to respiratory epithelium and producing airway inflammation by releasing major basic protein (MBP) and other cytotoxic proteins. The presence of eosinophils, Charcot-Leyden crystals and creola bodies in these cases indicated an inflammatory desquamative bronchitis secondary to eosinophilic infiltration. Since airway inflammation may underlie the genesis of hyperreactivity, the observed airway hyperreactivity in TPE can be explained. Wheezing may occur in this disease for the same reason. It is unlikely that these two patients had asthma because clinical, radiologic and laboratory evidence supported the diagnosis of TPE and not that of asthma. No other cause for hyperreactivity was evident.

Both patients were treated with diethyl carbamazine for three weeks which resulted in complete remission of symptoms and normalization of blood eosinophilia. The patients did not return for post-treatment PD₉₀ SGaw measurement and could not be contacted. Symptomatic remission and normalization of eosinophilia suggest that tissue infiltration and the resultant bronchial desquamation must have been reduced. Although the test could not be repeated, we presume this also resulted in a significant increase in PD₉₀ SGaw, since currently Durham and Kay reported an inverse correlation between blood eosinophilia and non-specific airway hyperreactivity.

This report, although it includes only two cases, is of interest because it is the first time airway hyperreactivity has been observed in TPE.

References

3. Frigas E, Gleich GJ. The eosinophil and the pathophysiology of asthma. J Allergy Clin Immunol 1986; 77:527-37

*From the Clinical Research Centre, Vallabhbaai Patel Chest Institute, University of Delhi, Delhi, India.
Pulmonary Complications of Hormone Treatment in Prostate Carcinoma*

Joel Seigneur, M.D.†; Philippe F. Trechot, Ph.D.‡; Jacques Hubert, M.D.;§ and Pierre Lamy, M.D.†

Fever, dyspnea, dry cough and interstitial fibrosis occurred in a patient with prostate carcinoma treated with nilutamide and buserlin for two and one-half months. The diagnosis of drug-induced fibrosis was established on the basis of chronologic and semilogic events. This is the first such case reported.

We report a case of pulmonary fibrosis following therapy with the combination of an analog of LHRH and a true nonsteroidal antiandrogen.

CASE REPORT

The patient, age 74, was admitted for treatment of serious prostatectomy with change in general health within two months (weight loss: 2.5 kg).

The pathologic history is relatively minor (inguinal hernia). Rectal examination revealed an enlarged prostate gland and drill biopsy showed a stage 3 adenocarcinoma (Bocking's classification). Further examination mainly showed a left supraclavicular node; cytologic puncture revealed metastasis of the adenocarcinoma. The bone scan showed only partial hyperemia of the right 7th dorsal vertebrae. The initial biologic examination revealed no evidence of abnormality. Chest x-ray film findings are quite normal.

The hormonal therapy was initiated on June 14, 1986; it combines nilutamide (Anadrolon, Laboratoire Cassene), 300 mg/day and an analog of LHRH, buserlin (Suprefact, Laboratory Hoechst), 500 µg/day subcutaneously.† The only other therapy administered was the combination of ethoxazoxuridoxide, ascorbic acid and papaverine.

This treatment was given at the same dosage for two and one-half months. Improvement in micturition and regression of the supraclavicular node were reported on each visit to the urology department.

On September 11, 1986, thoracic changes appeared and the patient developed fever (37.5°-37.8°C), dyspnea and dry cough with normal pulmonary auscultation. Patches of perihilar heterogenous condensation in the upper lobes of the lung are found on the chest tomogram. The left supraclavicular node was completely regressed.

RESULTS

Among the likely diagnoses, metastatic lung cancer was first considered, but the unsuggestive pulmonary findings and regression of the left supraclavicular node only partly supported this etiology; then, we considered an opportunistic lung infection because of bilateral involvement noted on chest film, the reticulonodular aspect, and the immunodeficiency resulting from metastatic cancer; finally, iatrogenic disease was not considered unlikely. On September 18, several transbronchial biopsies were taken for optical, electron and immunohistochemical analysis. Bronchoalveolar lavage was performed for study of the cell populations and bacterial, viral and parasitic analysis. Interstitial fibrosis was revealed by light microscopy. The immunohistochemical study showed a T-cell infiltration mainly with suppressive, cytotoxic phenotypes and the bronchoalveolar lavage showed hypercellularity (380,000 cells/cu mm) with 45 percent hyperlymphocytosis, 28 percent hypereosinophilia, and a CD4/CD8 ratio at 0.47.

The various blood and bronchial analyses were not consistent with an opportunistic infectious disease, metastatic lung disease, or granulomatosis. The arterial blood gas determinations showed hypoxemia of 74 mm Hg; results of biologic evaluations were not conclusive (the number of blood eosinophils in particular were 450/cu mm). Drug-induced lung disease was then likely.

On September 29, 1986, therapy with the analog of LHRH (buserlin) was withdrawn. Simultaneously, the nilutamide dosage was reduced to 150 mg/day after being discontinued one day for testicular pulpectomy (October 1, 1986).

It should be noted that no corticosteroid or antibiotic therapy was ever instituted between the first thoracic clinical symptoms and the change in the hormone treatment.

On October 23, 1986, the bilateral reticulonodular pulmonary signs had significantly regressed; further bronchoalveolar lavage showed hypocellularity (24,000 cells/cu mm) and a CD4/CD8 ratio at 0.21. Minor fibrosis on the subbronchiolar alveolar parenchyma was revealed by electron microscopy. Respiratory function tests and arterial blood gas levels were within normal ranges. On October 28, the rate of IgE was about 732 KU/L, the circulating immune complexes were normal, and the human basophils on degranulation test with buserlin were negative.

On November 17, 1986, the clinical investigation and the chest x-ray film findings gave normal results and the hormone analysis was satisfactory.

DISCUSSION

This case strongly suggests a drug-induced lung disease because of the sequence of events; the absence of pulmonary history; the exclusion of cancerous or infectious pulmonary pathology; and the spontaneous regression of pulmonary opacities and the use of no corticosteroid or antibiotic therapy.

As to the fibrosis, it seems reasonable to consider drug-induced etiology combining therapy with a nonsteroidal antiandrogen and an analog of LHRH.

REFERENCE


*From the Centre Hospitalier Regional et Universitaire, Nancy, France.
†Pneumology Service.
‡Pharmacology Service.
§Urology Service.

Reprint requests: Dr. Seigneur, Hopital Villemain, 42 Rue de Nabecon, 54000 Nancy, France