with the CD8-positive suppressor/cytotoxic T lymphocytes, resulting in a high CD4/CD8 ratio. In scleroderma, alveolitis usually resembles that in idiopathic pulmonary fibrosis, characterized by increased proportions of neutrophils and/or eosinophils with sometimes moderately elevated lymphocyte proportions. The ratio of CD4- to CD8-positive lymphocytes is usually decreased. In addition, increased CD4 to CD8 ratios have been consistently found in the peripheral blood of patients with scleroderma patients.

In our patient, scleroderma and sarcoidosis were simultaneously present. The occurrence of Raynaud's phenomenon early in his disease suggests the development of a connective tissue disease, in particular scleroderma, when other symptoms are simultaneously present. Biopsy specimens from muscle, lymph node, and lung, however, were compatible with sarcoidosis. We know of no previous report of the coincidence of these diseases. Both of these diseases may cause ILD as well as myositis and differentiation can be difficult. Longitudinal BAL data showed fluctuations of the proportion of lymphocytes, which may indicate waxing and waning of pulmonary sarcoidosis disease activity. The proportions of neutrophils and eosinophils were not increased except for the most recent BAL, where neutrophils and eosinophils together constituted 9 percent of the alveolar cells, considered to be mildly increased. In addition, lymphocyte phenotype analysis of the most recent BAL revealed a very low CD4/CD8 T-lymphocyte ratio, which is compatible with scleroderma lung involvement rather than sarcoidosis disease activity. The progression of scleroderma traits such as sclerodactyly and telangiectasia, also suggests scleroderma disease activity. Whether the myositis, which was sarcoid in origin, became part of scleroderma cannot be ascertained since a repeated biopsy was not performed.

We conclude that BAL with determination of cell differentiation and lymphocyte phenotypes can be a useful diagnostic tool in patients with multiple ILD-associated diseases.

References


Bronchospasm Secondary to Replacement Estrogen Therapy*

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A postmenopausal woman with severe obstructive airways disease and bronchospasm developed increased airflow limitation with the reintroduction of estrogen therapy for osteoporosis. Discontinuation of the estrogen caused symptomatic improvement and decreased her corticosteroid requirement. Readministration of estrogen caused recurrence of her symptoms and a decline in her peak expiratory flow rate and spirometric data, which reversed with withdrawal of the estrogen therapy. Bronchospasm during the luteal phase of the menstrual cycle is well known, but exacerbation of reactive airways disease with the administration of exogenous estrogen has not previously been reported; however, with the increasing practice of reintroducing estrogen in postmenopausal women to reduce the risk of symptomatic osteoporosis, other susceptible women may suffer clinically significant deterioration of their underlying pulmonary disease. (Chest 1993; 104:1300-02)

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During the luteal phase of the menstrual cycle, susceptible asthmatic women manifest increasing symptoms of reactive airways disease, decreased peak expiratory flow rates (PEFRs), and more frequent exacerbations of their reactive airways disease. The pathogenesis of this premenstrual asthma (PMA) is unknown, but it may be due to increased production of prostaglandin F<sub>2α</sub> (PGF<sub>2α</sub>) induced by estrogen. Increased smooth muscle tone due to lower circulation levels of progesterone, altered autonomic tone, allergic factors, increased hydration of airway mucosa, or aspirin sensitivity. The PMA may be poorly controlled by routine therapy with bronchodilators and corticosteroids. We report a case of increased bronchospasm with the reintroduction of estrogen therapy in a postmenopausal woman with severe chronic airflow obstruction.

**Case Report**

A 60-year-old white woman with a 75-pack-year smoking history had dyspnea on exertion with a 10-ft walk, daily cough, and expectoration of white sputum. She was receiving supplemental oxygen at a rate of 2 L/min for desaturation with exercise. Osteoporosis has produced multiple thoracic and lumbar vertebral compression fractures. The patient's pulmonary disease was controlled with oral and aerosolized b-adrenergic agonists; ipratropium bromide, cromolyn sodium, and beclomethasone in metered-dose inhalers; oral therapy with sustained-release theophylline; and prednisone. Her prednisone dose ranged from 20 to 50 mg daily, without seasonal fluctuation. Daily PEFRs and baseline pulmonary function data are shown in Figure 1. The patient denied premenstrual exacerbation of her pulmonary disease, but had been postmenopausal for about 15 years.

Because of symptomatic vertebral compression fractures, treatment with estrogen, 0.625 mg daily for the first 21 days of each month, and progesterone, 10 mg daily for the last 10 days of each month, was instituted. After the first week of estrogen therapy, the patient complained of severely increased dyspnea, clear sputum, and audible wheezing. On examination, she had diffuse high-pitched wheezing throughout both lung fields and trace pedal edema. Her theophylline level was 20.1 μg/ml (therapeutic range, 10 to 20 μg/ml), and the white blood cell count was 13,400/mm<sup>3</sup> without eosinophilia. The patient's corticosteroid dose was increased to 2 mg/kg daily, which lessened her symptoms but did not allow a complete recovery to her baseline status. During the last 10 days of the month, she noted lessening of her symptoms and was able to taper her prednisone therapy back to baseline. Upon restarting the estrogen therapy at the beginning of the second month, the patient had recrudescence of her symptoms. She was unable to register a measurable peak flow on a hand-held peak flowmeter. Her corticosteroid dose was increased again, and she was advised to discontinue the estrogen therapy. Symptoms resolved over the next week. The patient returned for pulmonary function testing at the end of the month and was found to have unchanged spirometric values from her baseline (Fig 1B). Estrogen therapy was restarted, and she returned for repeat testing 1 week later (Fig 1B). Her dyspnea had increased, she wheezed in all lung fields, and her PEFR had decreased (Fig 1A). Her estrogen therapy was stopped, with symptomatic improvement occurring over the ensuing week and with return of her PEFR to baseline (Fig 1A). Repeat pulmonary function testing could not be performed because the patient subsequently suffered a myocardial infarction and died from complications.

**Discussion**

Our patient demonstrated repeated bronchoconstriction with the reintroduction of exogenous estrogen therapy. During treatment, she was severely symptomatic and had significantly decreased spirometric values. These episodes of bronchoconstriction were poorly responsive to corticosteroid therapy and temporally improved with discontinuation of the estrogen therapy. Although we were unable to document return of her spirometric values to baseline after discontinuing this agent, lessening of her symptoms and an improved PEFR strongly suggest that this occurred.

Premenstrual asthma occurs during the luteal phase and first days of the menstrual cycle, a time associated with a rise in circulating estrogen. The PMA occurs in only some asthmatic women, and there is an additional subset without overt clinical exacerbation in whom decreased PEFR has been demonstrated. The likely cause of bronchoconstriction is the increase in PGF<sub>2α</sub> induced by estrogen. This prostaglandin is a vasoconstrictor and helps to minimize blood flow.
loss during menstruation but is also implicated in the dysmenorrhea and diarrhea suffered by some women. Just as not all asthmatic women experience cyclic fluctuation in their pulmonary disease, not all women experience dysmenorrhea; however, 80 percent of the asthmatic women studied by Ravelo et al. had at least one abnormality of progesterone, estradiol, or cortisol concentration during their menstrual cycle, compared with only 7 percent of the control women having measurable hormonal abnormalities. The reasons for this are unknown, but may reflect an imbalance in bronchodilating/bronchoconstricting prostaglandins and increased production of PGF sub 2α in these women, compared to their peers who do not suffer premenstrual exacerbations; or, a cooling or drying of their airways due to the increased minute ventilation occurring during the late luteal phase. Premenopausal women suffering PMA have been successfully treated with nonsteroidal anti-inflammatory agents and chemical, or even surgical, castration.

Although this is a rare cause of asthmatic exacerbation, the increased practice of reintroducing estrogen therapy in postmenopausal women may precipitate refractory bronchospasm in other susceptible women. Postmenopausal women receiving estrogen supplementation who develop unexplained exacerbation of the pulmonary disease which is refractory to standard bronchodilator and anti-inflammatory therapy may be experiencing this forme fruste of PMA. Under close medical supervision, an estrogen-free trial with pulmonary function testing or PEFR, followed by reinstitution of the drug and retesting, should be done if this phenomenon is suspected.

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The Flow-Volume Loop in Bilateral Vocal Cord Paralysis*

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A 38-year-old man with posttraumatic bilateral vocal cord paralysis and a surgically repaired avulsion of the extrathoracic trachea presented with a slight increase of exertional dyspnea (grade 2). Spirometry showed high normal FEV sub 1 and FVC values, but the F-V loop was characteristic for highly variable UAO with an increased FEV sub 1/PEF ratio of 11 ml/L/min as well as a MEF sub s0/MEF sub 25 of 4.55. Endoscopy during forced respiration showed near total inspiratory obstruction of the larynx due to paradoxical behavior of the vocal cords. In extrathoracic airway obstruction a FEV sub 1/PEF ratio >10 ml/L/min combined with a MEF sub s0/MEF sub 25 ratio >4 is suggestive of variable UAO caused by bilateral vocal cord paralysis rather than by a tracheal lesion.

(Chest 1993; 104:1302-04)

F-V loop = flow-volume loop; MEF sub s0/MEF sub 25 = ratio between maximal expiratory and inspiratory flows at mid-vital capacity; PEF = peak expiratory flow; TLC = total lung capacity; UAO = upper airway obstruction

The value of the flow-volume (F-V) loop in diagnosing upper airway obstruction (UAO) has been demonstrated by several authors. The ratio between maximal expiratory and inspiratory flows at midvital capacity (MEF sub s0/MEF sub 25) is most widely used to differentiate between intrathoracic and extrathoracic airway obstruction. Miller and Hyatt defined three main groups according to this ratio with mean values of 0.32 in variable intrathoracic obstructions, 0.85 in fixed obstructions and 2.2 in variable extrathoracic obstructions. Empey, on the other hand, observed the discrepancy between a markedly decreased peak expiratory flow (PEF) in the presence of a normal FEV sub 1 in patients with variable UAO. He therefore proposed a simple index of FEV sub 1/PEF (ml/L/min) for the assessment of UAO with a value >10 indicating significant obstruction. Bilateral vocal cord paralysis usually results in highly variable UAO with a MEF sub s0/MEF sub 25 >2. In patients with variable UAO due to goiter and normal vocal cord function, Miller et al. found F-V loops that resembled those seen in bilateral vocal cord paralysis but with a mean MEF sub s0/MEF sub 25 of 1.52 only. We present a patient with posttraumatic UAO due to an old high tracheal lesion and bilateral vocal cord paralysis.

CASE REPORT

A 38-year-old man presented with a slight increase in exertional dyspnea that had otherwise been stable (grade 2, NYHA) for 12 years. In 1979, the patient was involved in a car accident that led to a blunt neck injury caused by a safety belt. Severe laryngeal trauma resulted in bilateral vocal cord paralysis and in a complete avulsion of the trachea below the cricoid cartilage necessitating a surgical reanastomosis of the trachea, partial thyroidectomy, and left aryte-

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