Eosinophilic Pneumonia

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There is a broad spectrum of disease encompassed by the various forms of eosinophilic pneumonia. Variations in both clinical course and histologic picture make these conditions difficult to classify.

A case is reported of an 18-year-old black female, seven weeks postpartum, who presented with distinctive subcutaneous nodules on her extremities. These progressed to include edema and pruritus of both feet and one arm. She had been taking only oral contraceptives for six weeks. While in the hospital, she developed fevers to 104 F, cough, shortness of breath, and eventual respiratory insufficiency requiring intubation and ventilatory assistance. Chest x-ray films revealed diffuse infiltrates. Lung biopsy revealed chronic interstitial organizing pneumonia with vasculitis and marked eosinophilia. She responded dramatically to high dose steroids and recovered.

After careful literature review, this case fits best in the category of Carrington chronic eosinophilic pneumonia. It is unusual in its dermatologic presentation and its fulminant development of respiratory insufficiency.

The spectrum of clinical disease encompassed by the various forms of eosinophilic pneumonia remains broad. Löffler first reported the syndrome of fleeting pulmonary infiltrates and peripheral eosinophilia.[1] Reeder and Goodrich popularized the title "PIE Syndrome" with their series of cases in 1952.[2] Crofton et al presented the first useful classification of the eosinophilic pneumonias also in 1952.[3] In 1969 Carrington presented a detailed review of "chronic eosinophilic pneumonia."[4] Liebow and Carrington have presented a very complete review of the eosinophilic pneumonias.[5] Since then several case reports describing chronic eosinophilic pneumonia have appeared.[6-8] Other conditions entering into the differential diagnosis with the eosinophilic pneumonias include allergic granulomatosis of Churg and Strauss, desquamative interstitial pneumonia, and the eosinophilic granulomas including Hand-Schüller-Christian disease and Letterer-Siwe disease.[9-13] Variations in both the clinical disease course and histologic findings make these conditions difficult to classify.

Case Report

An 18-year-old gravida 1, para 1, black female seven weeks postpartum presented as an outpatient three days prior to admission with a four-day history of subcutaneous nodules on her feet and a one day history of subcutaneous nodules on both elbows which were mildly pruritic. She denied systemic complaints and there was no history of a similar problem. She denied weight loss, fever, chills, malaise, anorexia, myalgia, arthralgia, and any history of trauma or recent illness. The only drug she was taking was the oral contraceptive Ortho-Novum 1/50 (norethindrone 1

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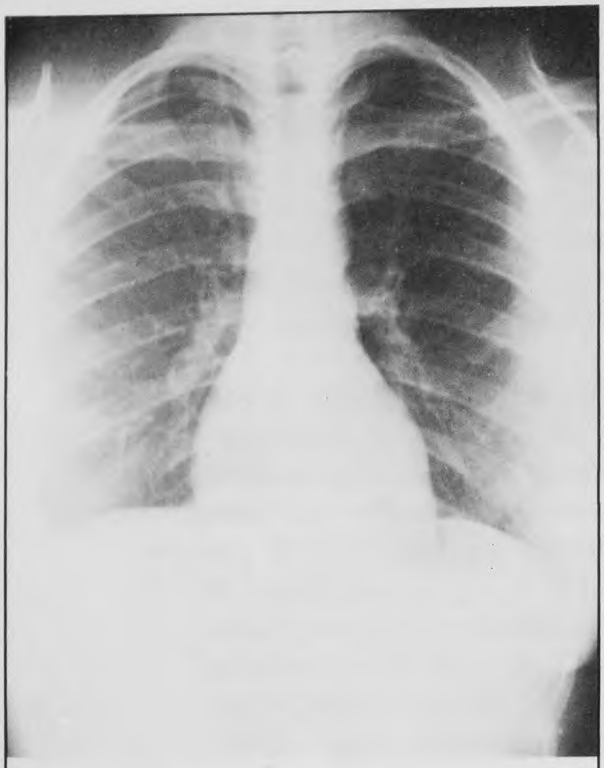

Figure 1. Initial chest x-ray film revealing clear lung fields

mg; mestranol .05 mg) started six weeks earlier. She had neither allergies nor a history of asthma. There were no animals or birds in the home and the travel history was negative. A sister had died at age 25 of disseminated collagen vascular disease.

She had a positive PPD skin test, negative throat culture, negative ASO titer, unremarkable complete blood count, sedimentation rate of 59, and a normal chest x-ray (Figure 1). Two days prior to admission she was seen in the Emergency Room with marked edema of the feet, which disappeared following treatment with diphenhydramine hydrochloride (Benadryl), but significant edema of the left arm occurred. The patient's main complaints on admission to the hospital were pruritus and swelling of the left arm. She denied any urinary symptoms and she continued to be afebrile without cough or sputum production.

When she was admitted to the hospital she had a temperature of 97.6 F, a pulse of 72 beats/minute, and respirations of 18/minute. There was a mild lymphadenopathy in the anterior cervical region and the axillae bilaterally. There was a Grade I/VI systolic murmur in the aortic area. Lungs were clear with no rales or wheezes. There was no peripheral cyanosis or clubbing. The left arm was markedly edematous, erythematous, and warm. There was no tenderness in the left elbow joint. There was a 4 cm × 3 cm soft subcutaneous nodule (identical to the lesions on the dorsum of both feet prior to admission) on the extensor surface of the right arm just distal to the elbow. This was erythematous and warm. The lesions on both feet had disappeared. On both palms were erythematous, maculopapular lesions with erythema extending up the middle fingers to the level of the proximal interphalangeal (PIP) joint. This was felt to be consistent with an erythema multiforme-like eruption. There were no lesions on the soles of the feet.

Four days after admission to the hospital the patient began spiking temperatures to 103-104 F. Blood and sputum cultures were obtained and found to be negative. Sputum and gastric aspirate were negative for acid-fast bacilli.

On the fifth day of hospitalization the patient developed a mild cough, but the examination of the chest remained unremarkable. The subcutaneous nodules of both arms and the eruption of both palms resolved at this time. A repeat chest x-ray (12 days after the first normal chest x-ray) revealed bilateral diffuse patchy alveolar infiltrates (Figure 2). Because of the rapidly progressive change in the chest x-ray and the possibility that the edema of the left arm represented a large reaction to the patient's tuberculin skin test, she was given anti-tuberculous therapy, Isoniazid (INH) 300 mg per day.

The patient suffered shortness of breath and tachypnea with arterial blood gases showing a pH of 7.26; PCO_2, 26 mmHg; and PO_2, 54 mmHg. She continued with spiking temperatures, shortness of breath, and increased respiratory rate above 70/minute.

After repeat sputum cultures were obtained, gentamicin sulfate (Garamycin) and cephalothin sodium (Keflin) were begun. The patient's respiratory insufficiency worsened and she required ventilatory assistance with a respirator. A speed drill closed-chest core biopsy of the right lung was performed. Corticosteroid therapy was instituted at

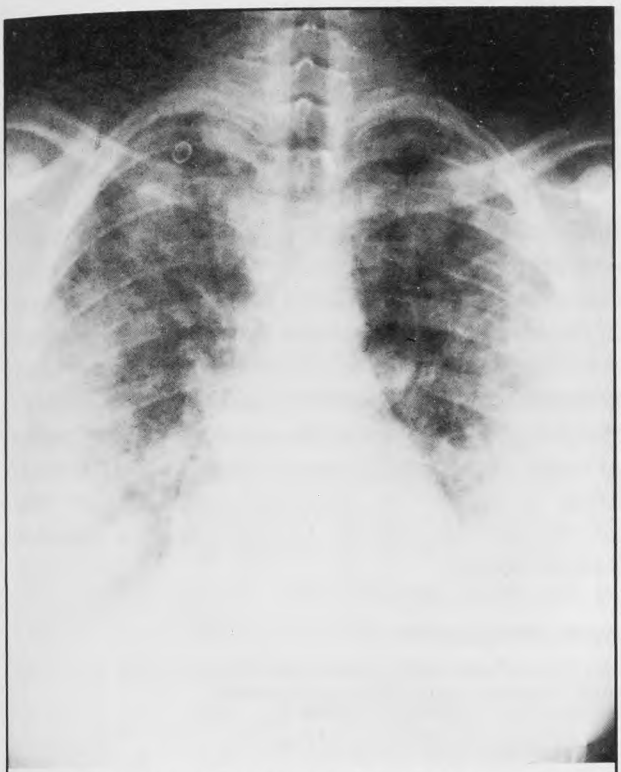

Figure 2. Repeat chest x-ray film 12 days later revealing bilateral diffuse patchy alveolar infiltrates

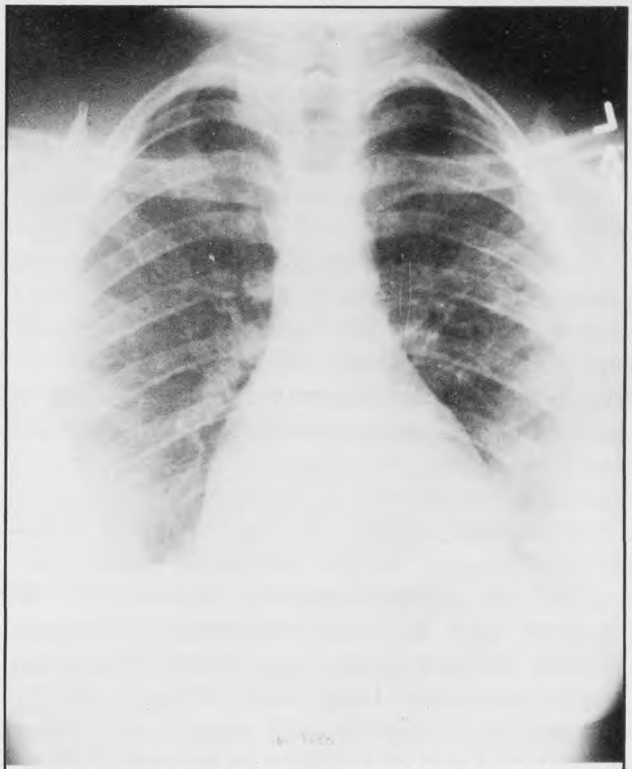

Figure 3. Follow-up chest x-ray film 6 days after initiation of corticosteroids revealing minimal peural reaction at the biopsy site on the right

60 mg of prednisone per day, because of the suspicion of an allergic process. The patient showed marked improvement with the corticosteroids and was extubated in 24 hours. The chest x-ray films showed remarkable improvement in 48 hours, and six days later it was clear except for the minimal pleural reaction at the biopsy site (Figure 3).

Leukocyte count ranged from 9,800 on admission to 14,400 at the height of the illness with the eosinophil count ranging from zero percent on admission to seven to eight percent at the height of the illness. Hemoglobin value was 11.9 gm/100 ml, sedimentation rate 69 mm/hr, and an antinuclear antibody test was negative. Six blood cultures for anaerobes and aerobes showed no growth. Six sputum cultures showed normal flora. Three sputum specimens and gastric aspirates for acid-fast bacilli smear and cultures were negative. Bone marrow biopsy, done to rule out marrow tuberculosis, showed moderate marrow eosinophilia. Cold and febrile agglutinins were negative. Titers for fungal and Legionnaire disease were negative. The patient's sera contained no identifiable precipitins to 12 of the more common pulmonary hypersensitivity antigens (performed at the University of Iowa Allergy Laboratories). The lung biopsy revealed chronic interstitial, organizing, and organized pneumonia with vasculitis and marked eosinophilia.

Comment

Allergic granulomatosis as described by Churg and Strauss in 1950 was considered in the differential diagnosis in this patient.[9] Their review of 18 patients showed a clinical syndrome of fever, dyspnea, recurrent pneumonia, severe asthma, and hypereosinophilia. All their patients had asthma preceding their illness from a few months to ten years. All had marked leukocytosis and most had intense peripheral eosinophilia. The

majority did exhibit a variety of cutaneous lesions. The lesion in seven cases that merited special attention was a deep cutaneous or subcutaneous nodule occurring on the head, trunk, and extremities. However, the typical pulmonary pathologic findings included granuloma formation which this patient did not have.

Carrington and associates described chronic eosinophilic pneumonia in nine women who presented with chronic life threatening illnesses with high fever, night sweats, weight loss, and severe dyspnea.[4] Tuberculosis was the initial diagnosis in most cases. Six patients developed asthma for the first time during their illness. Three patients had neither asthma nor blood eosinophilia. Chest x-ray films showed rapidly progressive dense pneumonic infiltrates in the peripheral pattern described as a "photographic negative of the shadows seen in pulmonary edema." Corticosteroids brought prompt clinical and roentgenographic resolution. Lung biopsy revealed numerous mature eosinophils, mild angiitis, and sparse organization and proliferation of interstitial fibroblasts. Clinically and histologically, this case fits well with those of the Carrington series.

The prompt response but variable dependency on corticosteroid therapy has been further illustrated in cases reported by Perrault et al,[6] Morrissey et al,[7] and in a series of eight cases by Pearson and Rosenow.[8] Morrissey presents a practical classification schema including: (1) simple eosinophilic pneumonia (Löffler syndrome), (2) allergic bronchopulmonary aspergillosis (ABPA), (3) chronic eosinophilic pneumonia (CEP), (4) asthmatic type (non-ABPA), (5) drug induced type, (6) parasitic-tropical type, and (7) other.

Conclusion

An intensive environmental and drug exposure history revealed the only drugs the patient had received were one time doses of alphaprodine hydrochloride (Nisentil), testosterone enanthate/estradiol valerate (Deladumone), and mepivacaine hydrochloride (Carbocaine) during her prior labor and delivery, and six weeks of oral contraceptive pills. Oral contraceptives have been reported related to erythema nodosum; however, this patient's dermatologic lesions were not consistent with erythema nodosum.[14]

This patient was gradually withdrawn from prednisone over the next six months and has done well over the ensuing six months with no recurrent episodes of asthma or other allergic diathesis. She remains on Isoniazid for her positive PPD reaction. She has not been challenged with oral contraceptives again.

The uniqueness of this case certainly involves the unusual dermatologic presentation. The rapid and fulminant development of respiratory insufficiency was more profound then others described in the literature. Aside from the deep cutaneous or subcutaneous nodules described by Churg and Strauss, which this patient's nodules did resemble, the case does best fit in the category of Carrington chronic eosinophilic pneumonia. To our knowledge, it is the first reported case in which oral contraceptives may be implicated as a possible causal agent.

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