Chronic eosinophilic pneumonia

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CASE PRESENTATION

DR. EDWARDS: A 59-year-old woman with a history of asthma and borderline systemic hypertension was admitted to Baylor University Medical Center (BUMC) with increasing dyspnea, cough, fever, and weight loss. She had been well until about 19 months earlier, when she developed a cough and dyspnea. Chest radiograph showed an infiltrate, and she was treated with antibiotics and later prednisone. Dyspnea, however, continued, and she was referred to a pulmonologist 5 months later. Her pulmonary function tests were consistent with asthma, and an albuterol inhaler was prescribed. After 3 months, she presented to a local emergency department with wheezing, cough, and dyspnea, all of which resolved within 45 minutes without treatment. The next month, she was evaluated by another physician, received an injection, and continued on her albuterol inhaler. She felt better for about 3 months. Then she was hospitalized with similar symptoms, and she responded to intermittent positive-pressure breathing treatments and intravenous medications. Throughout that summer, she received several more intramuscular injections, which helped her dyspnea for approximately 1 month at a time.

By late summer, the patient’s dry, hacking cough with dyspnea and weakness had worsened; she used her albuterol inhaler up to 4 puffs, 4 times daily; and a home nebulizer was purchased. Her daily activity was limited by exertional dyspnea. A vacation was cut short due to progressive fatigue, dyspnea, and inability to walk more than short distances. Two weeks before admission, she developed a cough that produced white mucus, approximately 1 teaspoon every 2 hours. She also developed drenching night sweats that alternated with shaking chills and caused restless sleep. She had lost about 10 pounds over several months, with poor appetite but increased thirst. Her symptoms progressed such that she was unable to bathe herself, and she required her husband’s help with transfers from bed to bathroom. Chest radiograph that fall was abnormal, and a computed tomograph (CT) of the chest was obtained. The patient was referred to BUMC for further evaluation and treatment.

Past medical history included bilateral pneumonia in 1973; pneumonia, 1974; endometriosis with hysterectomy, 1983; a neck injury resulting from a fall in 1985; osteoarthritis, 1992; asthma, 1996; and borderline hypertension, 1997. During childhood, she had measles, mumps, whooping cough, and chickenpox. A mammogram (1995) and Pap smear (1997) were normal. She never had evidence of diabetes mellitus, angina pectoris, myocardial infarction, thyroid disease, cancer,
syncope, kidney disease, childhood asthma, emphysema, or tuberculosis. She reported allergic reactions to both erythromycin and aspirin.

Her mother died at age 75 from myocardial infarction, and her father died at age 65 with stroke and adult-onset diabetes mellitus. Her brother died at age 37 from myocardial infarction following a coronary artery bypass graft. Another brother, with a history of alcoholism, committed suicide at age 30. The patient had 2 living sisters, ages 54 and 61, both of whom had hypertension, and 1 had asthma all her life. Her 42-year-old son was in good health.

The patient did not smoke. She drank 1 to 2 glasses of red wine per week. She did not use illicit drugs. She had been married for 43 years. Although now retired, she had worked as a floor tile inspector for a floor tile manufacturing factory, and that position led to regular exposure to heavy dust. She also had worked as a cashier and part-time as a packer for a moving company.

On admission, she was taking cephalexin, 500 mg, twice a day for 1 week; albuterol neubulizer 4 times a day; phenylpropanolamine with guaifenesin for cough as needed; and estradiol daily. She was 62 inches tall and weighed 96 pounds. She had no headaches, syncope, or vision changes. She had occasional tinnitus, hay fever with rhinitis and lacrimation, and nosebleeds. In addition, she described a 3-week history of inspiratory pain below her left breast with local tenderness. The asthmatic symptoms were exacerbated by exercise; cold; and exposure to dust, smoke, pollen, grass, cats, and dogs. There had been no changes in her home environment; she had not had a house cat for 3 years and never had birds or dogs at home. She had no exposure to tuberculosis and never had skin tests. She ate chicken and fish, but had not eaten red meat or eggs for 20 years. Bowel movements were normal. She never had jaundice. She had stress urinary incontinence and increased nocturnal frequency. She never had hematuria, dysuria, vaginal bleeding, or sexually transmitted diseases. She had osteoarthritis of the left hand and knees, but had no redness or swelling. She reported bruising easily most of her life, but she was neither anemic nor had she had transfusions. The peripheral vascular, neurologic, and psychiatric examinations were unremarkable.

Her temperature was 38?C (101?F); heart rate, 115 beats per minute; blood pressure, 140/88 mm Hg; and respiratory rate, 24 breaths per minute. Her oxygen saturation was 85% on room air. She was alert and oriented. She was normocephalic with intact extraocular muscles. No scleral icterus was evident. She had a few small, nontender, anterior cervical nodes bilaterally and no supraclavicular nodes. Her pharynx was without exudate or erythema. She had 2 small ulcers on her lower lip and 1 small ulcer on her upper lip, which she developed after taking cephalexin. She had no carotid bruits or jugular venous distention. She had slightly decreased breath sounds over the upper lobes anteriorly with late inspiratory crackles at both bases and scattered late expiratory wheezes. No abnormalities were found on examination of the heart, abdomen, genitalia, rectum, and neurological system. The extremities showed no signs of cyanosis, clubbing, edema, swollen joints, or calf tenderness, and pulses were equal bilaterally. She had no purpura or rashes.

Initial laboratory data revealed the following: arterial blood gases drawn at rest were pH, 7.5; PCO2, 32 mm Hg; PO2, 64 mm Hg; O2 saturation, 94%; HCO3, 26 mEq/L; and FIO2, 0.21. The chemistry profile results were blood glucose, 136 mg/dL; sodium, 136 mEq/L; potassium, 4.7 mEq/L; chloride, 95 mEq/L; CO2, 31 mEq/L; and serum creatinine, 0.7 mg/dL. The cholesterol was 127 mg/dL, and triglycerides, 65 mg/dL. The uric acid was 2.7 mg/dL; phosphorus, 3.0 mg/dL; calcium, 8.7 mg/dL; total protein, 6.4 mg/dL; albumin, 2.9 g/dL; globulin, 3.5 g/dL; total
bilirubin, 0.2 mg/dL; alkaline phosphatase, 98 U/L; γ-glutamyltransferase, 24 U/L; aspartate aminotransferase, 114 U/L; alanine aminotransferase, 125 U/L; lactate dehydrogenase, 229 U/L; and creatine phosphokinase, <20 U/L. Complete blood count results were leukocytes, 13,600/?L; red blood cells, 4.15 ? 10^6/?L; hemoglobin, 10.6 g/dL; hematocrit, 32%; mean corpuscular volume, 78 fl; mean corpuscular hemoglobin, 25 pg; red cell distribution width, 13.4; platelets, 735,000/?L; and mean platelet volume, 10.0 fl. The results of the differential were 12% lymphocytes, 6% monocytes, 59% total polys (1% bands, 58% segmented neutrophils), 23% eosinophils, and 0% basophils. Cell morphology showed 1+ microcytes and 1+ polychromasia. Erythrocyte sedimentation rate was 117 mm/hr. The results of the urinalysis showed specific gravity, 1.010; pH, 6.5, which was dipstick negative; leukocytes, 3/?L to 5/?L; and red blood cells, 0 to 1/?L. There were a few epithelial cells and “light” bacteria.

The electrocardiogram showed a normal sinus rhythm with 94 beats per minute and P-wave abnormalities consistent with atrial enlargement. Initial pulmonary function tests showed prebronchodilator forced vital capacity (FVC), 1.6 L (56%); forced expiratory volume after 1 minute (FEV1), 1.16 L (50%); FEV1/FVC, 91%; and the carbon monoxide diffusing capacity of the lungs (DLCO) was 13.0 per minute/mm Hg (62%). Postbronchodilator pulmonary function test revealed FVC, 1.73 L (60%); FEV1, 1.38 L (60%); and FEV1/FVC, 100%.

**DISCUSSION OF RADIOLOGICAL FINDINGS**

DR. FULMER: A chest radiograph is available ([Figure 1](#)) from several months before the patient’s presenting illness. The findings suggest hyperexpansion of the lungs compatible with asthma. No infiltrates or parenchymal scars are seen. At the time of her admission to BUMC, pulmonary infiltrates were present. They are somewhat peripheral in distribution and in the mid and upper lung fields. A radiograph 2 days later ([Figure 2](#)) showed that the infiltrates were larger, and a cavity may have formed in the left infiltrate.

Computed tomography ([Figure 3](#)) at the level of the aortic arch discloses the peripheral pulmonary parenchymal consolidation. The mediastinal lymph nodes are not enlarged. The radiographs demonstrate a change from a baseline of near normal to that of bilateral mid and upper lung field peripheral pulmonary consolidation without significant lymphadenopathy and no pleural effusions.

**CASE DISCUSSION**

DR. LUTERMAN: This is a story of a middle-aged woman who developed asthma in the spring of 1996. As with many patients with asthma, her symptoms worsened with exercise, cold, dust, smoke, grass, pollens, and animal dander. There was a family history of asthma; a sister had lifelong asthma. When first diagnosed, she had an infiltrate on her chest radiograph, and she was treated with antibiotics. Over the ensuing months, she had asthmatic episodes that responded to prednisone. Then she began having symptoms that could be worsening asthma. She had a dry, hacking cough, dyspnea, and weakness. She was using beta-agonists by metered inhaler. Her symptoms were severe enough that a nebulizer was purchased for home therapy. She had dyspnea to the point that she could not walk more than a short distance. Her cough became productive of white mucus. She developed constitutional symptoms of drenching night sweats and shaking chills. She lost approximately 10 pounds in a month. She became so dyspneic that she could not bathe herself or walk to the bathroom.
Two months later, a chest radiograph and CT scan were obtained. She was referred to BUMC. At admission, she was febrile (38°C [101°F]). She had late-inspiratory crackles in the lung bases, suggesting an interstitial process, and scattered expiratory wheezes consistent with asthma. Her digital oximetry showed an O$_2$ saturation of 85%, but her arterial blood gases showed a PO$_2$ of 64 mm Hg and an O$_2$ saturation of 94%. This blood gas did not correlate with the digital oximetry, possibly because the patient had supplemental O$_2$ when the blood gas was obtained. Her white blood cell count was 13,600/?L with 23% eosinophils. She was mildly anemic (hematocrit, 32%). She had thrombocytosis (platelet count, 735,000/?L). Her sedimentation rate was 117 mm/hr. Pulmonary function tests showed both a restrictive and obstructive defect with a bronchospastic component. The diffusion capacity was reduced.

She had pertussis as a child. Childhood pertussis can lead to bronchiectasis. I do not think this is relevant to this case. The patient worked as an inspector at a floor tile manufacturing company between 1965 and 1968. Typically, floor tiles have contained asbestos. The dust was quite heavy in the plant. There was a sufficient latency period to develop an asbestos-related illness. However, I do not think this was her problem.

To summarize, this patient is a middle-aged woman with asthma; a superimposed subacute illness lasting approximately 2 months, with constitutional symptoms, pulmonary infiltrates, progressive dyspnea, hypoxemia; and eosinophilia. Essentially, this is a case of asthma, pulmonary infiltrates, and eosinophilia.

When one considers the triad of asthma, pulmonary infiltrates, and eosinophilia, 2 entities quickly come to mind, Churg-Strauss syndrome and allergic bronchopulmonary aspergillosis. In 1939, Rackemann and Greene (1) reported a subgroup of patients with polyarteritis nodosa and concomitant allergic disease. Similar cases were reported in the 1940s by Harkavy (2, 3). The histopathology and clinical features associated with the entity were first described in 1951 by Jacob Churg and Lotte Strauss (4). They reported a form of necrotizing vasculitis in several organs associated with eosinophilic tissue inflammation and extravascular granulomas that occurred in asthmatics and were associated with fever and peripheral hypereosinophilia. The precise incidence of Churg-Strauss syndrome is uncertain. Case reports are limited to a few small series of approximately 30 cases and many isolated reports. Churg-Strauss syndrome can occur at any age but is most common between the ages of 38 and 50, with a slight predominance in males. Churg-Strauss syndrome usually follows a subacute course, with symptoms ranging from months to years.

There are 3 phases to the Churg-Strauss syndrome: the prodrome phase, the eosinophilic phase, and the vasculitic phase. The prodrome phase is usually characterized by late-onset allergic disease (e.g., allergic rhinitis, sinusitis, drug sensitivity, and asthma) in patients lacking a history of atopy. This phase may occur 8 to 10 years before the clinical recognition of the Churg-Strauss syndrome. The eosinophilic phase is characterized by peripheral blood eosinophilia and eosinophilic infiltration, most commonly in the lung, gastrointestinal tract, and skin. The onset of the vasculitic phase is often heralded by development of constitutional symptoms, including fever, malaise, weight loss, and increased allergic and asthmatic symptoms. Although vasculitis tends to occur years after the onset of the allergic manifestation, in some cases it develops within months of, or concomitant with, the onset of asthma. All patients have asthma at some point during the illness. Upper airways allergic disease, including sinusitis, rhinitis, and polyposis, is seen in up to 85% of the cases.
Churg-Strauss syndrome is similar to Löffler’s syndrome in that eosinophilic infiltrates are present in the lung parenchyma in about 40% of patients. The vasculitic phase can affect the heart, central and peripheral nervous systems, skin, gastrointestinal tract, renal, and other systems. Skin findings are present in 70% of the cases. Although I would have preferred to have diagnosed Churg-Strauss syndrome in this case, there is no evidence of a vasculitis. Therefore, this diagnosis falls short.

Allergic bronchopulmonary aspergillosis, most commonly due to *Aspergillus fumigatus*, is a more common disease. The first cases of allergic bronchopulmonary aspergillosis were reported in England in 1952 (5). Although, typically, allergic bronchopulmonary aspergillosis presents with asthma, fleeting pulmonary infiltrates, and marked eosinophilia, the disease may first manifest in many other ways. Asthma may be extremely mild, there may be no symptoms, and pulmonary infiltrates with eosinophilia may not be noted. The first presentation may be in the form of a collapsed lung or end-stage fibrotic lung disease. End-stage lung disease is rarely seen now, because most cases of allergic bronchopulmonary aspergillosis are recognized, and progression of the disease is prevented.

Allergic bronchopulmonary aspergillosis is a disease in which the fungus, *Aspergillus fumigatus*, colonizes the sputum plugs in the bronchi of asthmatics, with little or no tissue invasion by the organism. Antigens released from the fungus stimulate an immune response of the host, resulting in formation of IgE, IgG, and IgA antibodies against the organism and an intense production of the nonspecific IgE. The presence in the bronchi of both the *Aspergillus* antigen and the various antibodies is accompanied by an intense inflammatory reaction in the bronchial mucosa and surrounding pulmonary tissues. If it remains undetected, damage to the bronchial mucosa and pulmonary tissue will occur. If the diagnosis of allergic bronchopulmonary aspergillosis is made, treatment with steroids controls the asthma and causes the sputum to disappear. The sputum, being the culture medium for the *Aspergillus*, is now gone, and the organism no longer colonizes the bronchi. Prednisone also eliminates the inflammatory reaction in the bronchi and pulmonary tissues, so the patient’s condition improves clinically, and the radiographic abnormalities disappear.

Allergic bronchopulmonary aspergillosis occurs in 5 stages. In the initial phase, typical findings include pulmonary infiltrates, eosinophilia, asthma, and varying degrees of positive serology. In the second phase, the patient goes into remission following treatment with steroids. The levels of eosinophilia and serum IgE decrease. The asthma disappears and may stay in remission for months or years. In the third stage, the manifestations seen in the first stage recur and the serum IgE rises. Again, the manifestations will reverse with steroid therapy. By the fourth stage, the patient has developed steroid-dependent asthma. In the final stage, fibrotic lung disease is present.

There are other ways to classify the disease. One is serologically. While one can have serologic allergic bronchopulmonary aspergillosis, there may be no other manifestations. Lastly, one can have central bronchiectasis. This may be present in any of stages 1 to 4, but is always present in stage 5.

A diagnosis of allergic bronchopulmonary aspergillosis is easily made in patients presenting with the typical constellation of asthma, fleeting pulmonary infiltrates, *Aspergillus fumigatus* in the sputum culture, increased total IgE, and rapid clearing of the clinical symptoms and radiographic abnormalities with a decrease in serum IgE in response to steroid therapy. In contrast, low-grade, indolent allergic bronchopulmonary aspergillosis with mild asthma and a normal chest radiograph
may be overlooked. In these cases, there must be a high index of suspicion to make the diagnosis.

The skin test for immediate type-hypersensitivity to *Aspergillus fumigatus* is a simple and safe procedure. Initially, a skin-prick test can be done. If negative, an intradermal test may be performed. If skin tests are negative, allergic bronchopulmonary aspergillosis has been ruled out. If either of the skin tests is positive, the patient may have bronchopulmonary aspergillosis. Four serologic tests are used to aid in the diagnosis: 1) serum IgE >1000 ng/mL; 2) serum IgE index > twice the skin-prick test with positive asthmatic controls; 3) serum IgG index > twice the skin-prick test with positive asthmatic controls; and 4) precipitins against *Aspergillus fumigatus*. If 3 of the 4 serologic studies are present, bronchopulmonary aspergillosis is likely. If 2 of the tests are positive, the serologic tests should be repeated in 3 to 6 months. To make things even more difficult, one could have the typical findings of allergic bronchopulmonary aspergillosis due to a variety of other organisms, most commonly *Candida*, *Curvularia*, and *Helminthosporium*.

Although bronchopulmonary aspergillosis is an inviting diagnosis, it also falls short. Our patient has clear sputum, whereas patients with bronchopulmonary aspergillosis usually have yellow or brown sputum due to the *Aspergillus*-laden mucus with its associated inflammation plugging the airways. There is no evidence of mucus plugging in this patient. The infiltrates seen here are not the fleeting infiltrates seen in bronchopulmonary aspergillosis. The radiographic findings are more characteristic of another process. There is no evidence of bronchiectasis, nor is there evidence of bronchial obstruction and atelectasis. I cannot comment on the serology because it is not mentioned in the protocol.

*Chronic eosinophilic pneumonia* is an entity first described by Carrington and coworkers in 1969 (6). Although chronic eosinophilic pneumonia may develop at any age, the peak incidence occurs in people between the ages of 30 and 40 years. Most cases occur in whites. Women are affected approximately twice as often as men; however, this female predominance is less pronounced after age 60. Approximately one third to one half of patients have antecedent atopy, allergic rhinitis, or nasal polyps. Up to two thirds of patients have adult-onset asthma, usually preceded by several months or occurring concurrently with other pulmonary symptoms.

Chronic eosinophilic pneumonia usually has a subacute presentation with symptoms typically present for several months before the diagnosis. Common presenting symptoms include low-grade fever, drenching night sweats, and moderate weight loss. The cough, virtually a universal finding, is initially dry and becomes productive with a small amount of mucoid sputum. Patients ultimately develop progressive dyspnea that may be associated with wheezing in patients with adult-onset asthma. Although a subacute presentation is typical, some patients present with severe, acute respiratory failure, similar to acute respiratory distress syndrome, with severe hypoxemia requiring mechanical ventilation. There are no major extrapulmonary manifestations.

Patients with chronic eosinophilic pneumonia frequently manifest a moderate leukocytosis. Most, 60% to 90%, have peripheral blood eosinophilia, with eosinophils constituting >6% of their leukocyte differential. Leukocyte differentials of up to 90% eosinophils have been reported in this disorder. A lack of eosinophilia in the peripheral blood, however, does not rule out the diagnosis, because eosinophilia is absent in about one third of the cases originally described (7). A moderate normochromic, normocytic anemia and thrombocytosis may be present. The erythrocyte sedimentation rate is elevated. The IgE levels are up in about one third of the cases. The severity of the pulmonary function abnormalities depends on the stage and severity of the disease when
diagnosed. Typically, there is a moderate-to-severe restrictive defect, a reduced diffusing capacity, and a widened alveolar-arterial oxygen gradient. Patients with asthma will also have obstructive defects on spirometry.

Carrington and colleagues (6) described 3 radiographic features characteristic of chronic eosinophilic pneumonia: 1) a progressive, peripherally based, dense infiltrate; 2) rapid resolution of the infiltrate following corticosteroid treatment, with recurrences in the identical location; and 3) the appearance of an infiltrate as a photographic negative of pulmonary edema. Infiltrates associated with chronic eosinophilic pneumonia are not migratory and typically affect the outer two thirds of the lung field. These areas of consolidation are patchy, dense, and have ill-defined margins. They are frequently nonsegmental, nonlobular, and are adjacent to the pleura. Infiltrates are more commonly bilateral and located in the mid-to-upper lung zones. They may even mimic loculated pleural effusions. Computed tomography scans vary, depending on the timing of the scan relative to the symptoms. Typically, there are areas of dense, peripheral air space consolidation. Streaky bands of opacities may be evident when symptoms have been present for 2 months. Mediastinal adenopathy may be evident on routine chest radiographs and on CT scans. The classic presentation occurs approximately 25% of the time. Up to 33% of the cases do not have peripherally located infiltrates.

Pathologically, the pulmonary lesions are characterized by varying degrees of leukocyte infiltrates in the alveolar air spaces and interstitium, predominantly eosinophilic with some associated macrophages, a small number of lymphocytes, and, occasionally, plasma cells. Although the precise immunopathogenesis of chronic eosinophilic pneumonia is unknown, various lines of evidence suggest that the eosinophils play a primary role in the pathogenesis of the pulmonary tissue damage. Increased numbers of eosinophils appear in the peripheral blood and bone marrow before the onset of clinical disease. Eosinophilia is the prominent abnormality in bronchoalveolar-lavage fluid. The diagnosis of chronic eosinophilic pneumonia is based on clinical, radiographic, and bronchoalveolar-lavage findings as well as the inability to document pulmonary or systemic infection. Bronchoalveolar-lavage eosinophilia of 30% to 50% is typical. However, a range of bronchoalveolar-lavage eosinophilia from 14% to 75% has been reported (7, 8). Usually, lung biopsy is required only in atypical cases. Transbronchial biopsy is performed to rule out other diagnostic entities and may reveal the eosinophilic infiltrate.

Corticosteroids, the mainstay of therapy, result in rapid and dramatic response with clearing of the infiltrates. In fact, a therapeutic trial of systemic steroids often is useful in establishing the diagnosis. Failure to document a rapid clinical improvement should alert the physician to consider another diagnosis. Even patients presenting with severe respiratory failure may respond well to systemic steroids. In most cases, treatment with prednisone leads to defervescence within 6 hours; reduced dyspnea, cough, and blood eosinophils within 24 to 48 hours; and resolution of hypoxemia within 2 to 3 days. Radiographic improvement should occur within 1 to 2 weeks, with a complete resolution of symptoms within 2 to 3 weeks. Normalization of the chest radiograph usually occurs within 2 months.

The prognosis of chronic eosinophilic pneumonia is generally favorable. Spontaneous remissions seldom occur in untreated patients. In patients treated with steroids, morbidity and mortality related to chronic eosinophilic pneumonia are low. However, clinical, hematologic, and radiologic evidence of relapse occurs in many patients. From 50% to 80% of patients will relapse when steroids are either tapered or discontinued. Some patients may require 1 to 3 years of steroid
treatment to control the disease, and up to 25% may require long-term maintenance steroid therapy.

This patient has a classic presentation of chronic eosinophilic pneumonia. The chest radiograph can be considered pathognomonic for chronic eosinophilic pneumonia. Because this presentation is classic, I believe it warrants a trial of systemic steroids with no further diagnostic procedures performed. If one looked at the bronchoalveolar-lavage fluid, one should see a predominance of eosinophils. Transbronchial biopsy should show chronic eosinophilic infiltrates; however, due to a possible sampling error of the transbronchial biopsy, it may not. If it does not, it would not deter this diagnosis because this is such a classic presentation. If treated with steroids, this patient should have rapid defervescence and marked improvement in both symptoms and radiograph.

**PATHOLOGY**

DR. HOOVER: From the transbronchial biopsy, we received several fragments of alveolar tissue and smaller portions of bronchiolar and bronchus tissue. *Figure 4* shows alveolar spaces and alveolar septae. There are rare lymphoid aggregates, and some of the alveolar spaces are filled with loosely organized connective tissue. *Figure 5* again shows alveolar spaces and alveolar septae, some of which are markedly thickened due to mixed inflammatory infiltrates composed of plasma cells, lymphocytes, and eosinophils. The eosinophils are best seen near the periphery of the infiltrate. They are easily identified by their brightly eosinophilic cytoplasm and, typically, a bilobed nucleus. The flattened, type I pneumocytes have undergone metaplasia to become rounded, plump, type II pneumocytes. As seen in *Figure 6*, the disease process is centered primarily on the interstitium, with increased numbers of eosinophils. Very rare eosinophils are identified in some of the alveolar spaces, but no eosinophilic abscesses or products were identified here.

To summarize, as seen in *Figure 7*, the disease process centers primarily on the interstitium, with increased numbers of eosinophils that occasionally appear in groups or clusters, possibly representing early eosinophilic microabscesses within the alveolar septa. No eosinophilic abscesses are seen in the alveolar spaces. No increased numbers of eosinophils or eosinophilic products are seen in the alveolar spaces. No evidence of granulomas, vasculitis, or parasites is seen. Special stains for fungi and acid-fast organisms are negative.

**FOLLOW-UP DISCUSSION**

DR. EDWARDS: The topic I would like to review briefly is *eosinophilic lung disease*, with emphasis on the *eosinophilic pneumonias*. The eosinophilic lung diseases are a diverse group of disorders linked by the common finding of increased numbers of eosinophils in circulation or tissues. In addition to the presence of eosinophils, mixed inflammatory changes usually are seen. These diseases may be predominantly airways based, parenchymal based, or both.

These diseases may be classified as eosinophilic lung disease by 1 of 3 means. First, there may be eosinophilia with infiltrates on chest radiographs. This is known as *pulmonary infiltrates with eosinophilia* (PIE) syndrome. The second way is by lung biopsy, which is a much more direct means, because the majority of the eosinophils migrate from blood to tissues and reside with a ratio of >100 to 1. The third way of defining eosinophilic lung disease is by bronchoalveolar lavage (9).

Numerous classification syndromes have been proposed since PIE syndrome was first introduced in the early 1950s (10). Crofton et al (11) divided these diseases into 5 groups: simple pulmonary
eosinophilia, also known as Löffler’s syndrome; prolonged pulmonary eosinophilia; tropical eosinophilia; pulmonary eosinophilia with asthma; and polyarteritis nodosa. This initial classification system has provided a useful framework that has been modified and expanded.

Although many conditions are associated with pulmonary eosinophilia, there is a distinct group in which eosinophils are believed to be an integral and consistent part of the lung inflammation. Within this broad category are the eosinophilic pneumonias, allergic bronchopulmonary aspergillosis, Churg-Strauss syndrome, tropical eosinophilia, and certain parasitic and drug reactions.

Simple pulmonary eosinophilia

In 1932, Löffler first described simple pulmonary eosinophilia (12). This disease is characterized by migratory infiltrates accompanied by eosinophilia, with minimal symptoms. The chest radiograph shows transient infiltrates. In Löffler’s original series, most patients likely had an Ascaris infection (9). Other parasites that might cause Löffler’s syndrome include Ascaris suum or lumbricoides, Entamoeba histolytica, Fasciola hepatica, Necator americanus, and Strongyloides stercoralis (15, p. 1916).

Most patients initially diagnosed with simple pulmonary eosinophilia ultimately will be found to have parasitic infections or drug reactions. No cause can be found, however, in as many as one third of patients (9). When symptoms are present, they are mild and can include fever, cough, and dyspnea. Usually, no abnormalities are found during physical examination. All patients have moderate-to-extreme eosinophilia. Serum IgE levels usually are normal. Patients with simple pulmonary eosinophilia have an excellent prognosis. Treatment is rarely required, because the infiltrate from the eosinophilia resolves spontaneously within a few days to a few weeks. In severe episodes, steroids are highly effective. When Ascaris is the cause, treatment is albendazole.

Chronic eosinophilic pneumonia

Unlike Löffler’s syndrome, chronic eosinophilic pneumonia is a serious disease requiring specific treatment. The first 2 cases were described in 1960 (13); however, Carrington et al are generally credited with the first large study of patients in 1969 and coined the term “chronic eosinophilic pneumonia” (6). This disease most commonly affects middle-aged women, and females are afflicted twice as often as males. The onset is insidious, with symptoms lasting >2 weeks and averaging 7 months in duration before diagnosis (14). Patients may be moderately-to-severely ill. The patient’s history may reveal minor remissions and exacerbations, but symptoms are generally progressive. Asthma is present in approximately 50% of cases, usually with a recent onset of less than 5 years (9).

In Carrington’s initial study of 9 female patients, he described classic symptoms of fever, drenching night sweats, cough, dyspnea, and weight loss ranging from 10 to 45 pounds (6). He also reported leukocytosis and eosinophilia, in addition to the prompt clearing of infiltrates on radiographs with the treatment of steroids and the tendency for relapse. The most common symptoms were cough, fever, dyspnea, and weight loss. Other symptoms included mucoid sputum, night sweats, and chest pain.

Leukocytosis with eosinophilia is typical and may be accompanied by anemia and thrombocytosis.
The average leukocyte count is 13,000/?L, and average eosinophilia is 26% (14). The erythrocyte sedimentation rate usually is elevated, often to around 100 mm/hr. Serum IgE levels usually are normal or only mildly elevated (15, p. 1923). Pulmonary function studies usually show restrictive defects with a reduced diffusing capacity. Essentially all patients will have hypoxemia. Following therapy, indices of gas exchange are notably improved.

Chest radiographs demonstrate peripheral infiltrates in the outer two thirds of the lung fields in about 60% of cases. Dense, extensive, bilateral, peripheral infiltrates most apparent toward the apices and axilla are referred to as the “photographic negative of pulmonary edema.” This classic radiographic feature is seen in one fourth of cases (9, 14). The shadows may be isolated or widely spread and often do not conform to segmental or lobar boundaries. Often, the infiltrate progresses or regresses in one area, and during relapse may recur in the same location. One half of patients have mediastinal adenopathy on CT that is not apparent on chest radiograph (16).

Steroids rapidly suppress both clinical and radiographic abnormalities. Prednisone results in dramatic and diagnostic resolution of symptoms within 24 to 48 hours, improvement in chest radiographs within 3 days, and complete resolution of the disease within 10 days to 3 weeks (15, p. 1923). There usually is sudden defervescence and decline in the eosinophilia level within 12 to 24 hours. Complete clinical response usually occurs within 2 weeks to 1 month. Most patients will have relapse of symptoms and chest radiograph abnormalities if corticosteroids are discontinued in the first 6 months. Relapses can be prevented by continued treatment with small doses of prednisone. Fewer than 10% of patients will have spontaneous resolution (9).

**Acute eosinophilic pneumonia**

Acute eosinophilic pneumonia was first described in 1989 and is characterized by an acute febrile illness lasting 1 to 5 days, with myalgias, pleuritic chest pain, and hypoxemic respiratory failure within 7 days of initial symptoms (9; 15, p. 1923). Patients may be of any age or sex. The earliest finding on chest radiograph usually is a subtle interstitial infiltrate, followed within several hours to 2 days by extensive alveolar and interstitial infiltrates involving all lung lobes. Unlike chronic eosinophilic pneumonia, peripheral infiltrates are rare, and small, bilateral pleural effusions are frequent. Eosinophilia usually is absent, but there is a very high percentage of eosinophils in bronchoalveolar lavage fluid. Serum IgE levels may be elevated. Pulmonary function studies show a restrictive pattern and a low diffusion capacity with normalization after treatment. Lung biopsy demonstrates eosinophils and edema, and vasculitis is absent. Patients with acute eosinophilic pneumonia can progress rapidly to severe respiratory failure within hours and can respond rapidly to high-dose steroids within 24 to 48 hours. Treatment is methylprednisolone every 6 hours until respiratory failure resolves, followed by steroid tapering over 2 to 4 weeks. Unlike patients with chronic eosinophilic pneumonia, patients with acute eosinophilic pneumonia do not relapse after the discontinuation of steroids (9).

**Allergic bronchopulmonary aspergillosis**

Allergic bronchopulmonary aspergillosis is probably the most common cause of pulmonary eosinophilia. In most cases, patients have a history of childhood asthma. This disease is most commonly diagnosed in adults <35 years of age. Major diagnostic criteria include asthma, eosinophilia, chest radiograph shadowing, and a positive skin-prick test for Aspergillus. Other findings can include increased serum IgE levels >1000 mg/dL and Aspergillus in the sputum. IgG-
precipitating Aspergillus antibodies are present in >90% of cases. Dyspnea, cough, and wheezing are the most common symptoms. About two thirds of patients have a cough productive of bronchial casts. Only 10% of cases have systemic features such as night sweats, fever, or malaise. Frequently, the diagnosis is made by routine chest radiograph in asthmatic patients. Central bronchiectasis is found in 85% of patients at the time of diagnosis. Features include tram-line shadows, ring shadows, and gloved finger shadows due to dilated bronchi and trapped secretions (15, p. 1920). There may be segmental collapse after mucus plugging, resulting in scarring in the upper lobes. Typical treatment is prednisone. Relapses usually can be prevented, and serum IgE levels may be monitored for an index of activity.

**Churg-Strauss syndrome**

Churg-Strauss syndrome was originally described in 1951 (4). All patients have a history of asthma, and most have allergic rhinitis. They often develop dramatic levels of eosinophilia and infiltration of a variety of tissues, followed by vasculitis and extravascular granulomas. Men and women are affected equally (9). Systemic illness is characterized by fever, weight loss, and malaise. There is often involvement of the upper airway and skin, in addition to gastrointestinal, cardiac, renal, and central nervous system involvement. The chest radiograph shows transient infiltrates and occasionally large and small noncavitary nodules. Pleural effusions and hilar adenopathy may occur. There is leukocytosis with eosinophilia and anemia. The serum IgE level and erythrocyte sedimentation rate are elevated, and patients may have a positive perinuclear anticytoplasmic antibody test. Lung histology demonstrates necrotizing giant cell vasculitis, especially of the small arteries and veins, and eosinophilic pneumonia in various combinations. Interstitial and perivascular granulomas are common. Corticosteroids dramatically alter the natural progression of this disease. Prednisone is the mainstay of therapy. In patients who fail to respond to prednisone, methylprednisolone, azathioprine, or cyclophosphamide may be effective (9).

**Tropical pulmonary eosinophilia**

Tropical pulmonary eosinophilia, as first described in 1943 (15, p. 1917), is caused by filarial worms, mosquito-borne parasites that infest lymphatic tissue. Once there, they release microfilariae that travel to the lung and create an intense inflammatory reaction. Eighty percent of patients are male, usually between the ages of 20 and 40. Most cases have been reported in India, Africa, South America, and Southeast Asia. Cases in North America are acquired from endemic areas. Patients commonly present insidiously with nocturnal cough, dyspnea, wheezing, low-grade fever, and weight loss. Usually, extremely high eosinophilia levels, high titers of antifilarial antibodies, and high serum IgE levels are present. Chest radiographs typically show a diffuse nodular pattern, often involving the lower lung fields. Pulmonary function tests classically show restrictive changes and reduced diffusion capacity with long-standing or severe disease. Treatment with diethylcarbamazine results in improvement within a few days. Unlike Löffler’s syndrome, however, residual mild symptoms and relapses are common following initial improvement. Without treatment, symptoms may persist, remit, and then recur years later.

**Other causes of pulmonary eosinophilia**

In addition to parasitic infections associated with Löffler’s syndrome and tropical pulmonary eosinophilia, many other parasitic infections cause PIE syndrome. Prevalence of these infections varies among geographic regions. In the USA, parasites that can cause infection include
Strongyloides, Toxocara, and Ancylostoma (9; 15, p. 1917).

Different drugs have been associated with the development of PIE syndrome. Presentations are varied. Reactions may start within hours of taking a drug, although they more commonly occur after several days of treatment. Dry cough, dyspnea, and fever are typical. In some cases, there may be a rash or generalized lymphadenopathy. Although many patients will improve by simply discontinuing the medication, in severe cases, short courses of steroids may hasten recovery. Interestingly, a number of commonly used drugs have been implicated as causing eosinophilic lung disease, including ampicillin, ibuprofen, naproxen, phenytoin, sulfasalazine, and tetracycline. Nitrofurantoin is unique, causing acute, subacute, and chronic reactions (15, p. 1917).

In summary, this patient was diagnosed with chronic eosinophilic pneumonia. In addition to the diagnostic features already presented, she had an elevated IgE of 572 U/mL, and Aspergillus precipitins were negative. She was initially treated with methylprednisolone that was followed by prednisone, with rapid clinical response. She was discharged on prednisone, 40 mg a day. At her 3-week follow-up she was doing well on 30 mg daily. Repeat pulmonary function tests showed significant improvement in the forced vital capacity and the forced expiratory volume after 1 minute, with some mild airways obstruction (post-FVC, 2.44 L [87%]; FEV1, 1.78 L [79%]; FEV1/FVC, 89%). The patient’s steroid dose was tapered to 20 mg of prednisone daily, and severeent and a triamcinolone inhaler were prescribed. The goal was to taper the steroid dose to the lowest amount that would maintain remission. Follow-up chest radiograph showed near resolution of the peripheral infiltrate.

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References


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