Chronic Eosinophilic Pneumonia
James A. Bilyeu

Abstract: Chronic eosinophilic pneumonia (CEP) belongs to a group of syndromes manifested by pulmonary infiltrates with peripheral eosinophilia (PIE syndromes). The role of the eosinophil as a destructive agent in CEP is discussed. The degree of manifested eosinophilia at the time of diagnosis, the frequency of relapses of pneumonia, the response to steroid therapy, the status of current physical and x-ray findings, and especially the trend in pulmonary function data, all appear to be critical factors in determining the potential mortality risk of CEP cases.

Address: Medical Underwriting, P.O. Box 2000, 1711 Towanda Avenue, Bloomington, IL 61702-2000

Correspondence: James A. Bilyeu, MD, Medical Director

Keywords: Eosinophilic pneumonia

Received: 9/1/98
Accepted: 9/20/98


Case Presentation
This case involves a 62 year old female, five feet, four inches, 146 pounds, who in late 1997 applied for $150,000 of 10 year level term. Medical information on application includes a five year history of hypertension, shortness of breath from pneumonia 5-6 years ago but fine now, and thyroid check in July, 1997. Current medications are levothyroxin, Premarin, Provera, verapamil, calcium, and a multivitamin. Insurance medical exam information adds a history of shingles in 1992, pneumonia twice in the last 10 years (both episodes treated with outpatient antibiotics, last episode in 1995), and hypertension since 1992 (BP average on exam 156/72). She was said to have a healthy appearance and chest examine findings include clear lungs and no heart murmur. She reports to be a non-smoker, and urine continue screening was negative.

Due to her recurrent pneumonia history, an attending physician statement was obtained which included an extensive history regarding her pulmonary status, a summary of which follows.

In August of 1990 she presented to an emergency room with a persistent cough, dyspnea especially on exertion, white frothy sputum, afebrile, and bilateral basilar crackles on exam. No heart murmur or peripheral edema were present. Her ECG showed non-specific ST-T changes, and chest x-ray displayed left lower lobe and right upper lobe infiltrates. Treatment consisted of Septra and decongestants. She reported feeling considerably better one day later. Two weeks later on follow-up, her cough, sputum production, and dyspnea persisted. Pulmonary exam was normal, however a chest x-ray now displayed left lower lobe and right upper lobe infiltrates. Treatment consisted of Septra and decongestants. Erythromycin was prescribed. ENT evaluation was totally negative. Pulmonary consultation was obtained after two weeks of erythromycin therapy. By then her cough was less, sputum decreased, she was afebrile, and her chest x-ray was improved. She was observed for two more weeks during
which her symptoms and x-ray findings worsened. At this point, the following labs were done with screen, PPD, and anti-neutrophil cytoplasmin antibody. Chest CT showed non-specific bronchopulmonary infiltrates. Bronchoscopy revealed the following: normal upper tracts, lower tract erythema and increased secretions, and normal screens of CD4 levels, CMV, legionella, herpes, AFB, cocciidiomycosis, and cryptococcus. Bronchoalveolar lavage (BAL) was positive for increased eosinophils. Trans-bronchial biopsies yielded chronic interstitial pneumonia with eosinophilia. The diagnosis at this point became CEP. A three week trial of oral steroids was given with marked improvement in symptoms, and slow, steady clearing of infiltrates on x-ray. Six weeks after steroid therapy, her total eosinophil count was 552/µL and her sed rate was 31. It was decided to observe her carefully without further treatment at this point.

Eight months later (Sept., 1991), her chest x-ray was normal, her FEV1 was 1.34 (56% of normal), her FVC 1.54 (53% of normal) and she had a mild, non-productive cough. She was followed carefully by her pulmonologist without displaying significant symptoms until she relapsed in 1994 and again in late 1995 with symptoms and findings similar to those in 1990 - 1991. Repeat bronchoscopy with biopsies and BAL were done in 1995 with the same results as in 1991. Short term steroids were again given with good results, and by February, 1996, her chest x-ray was clear and remained clear until date of application. Repeat pulmonary function tests have not been done to date.

Discussion:
CEP is an idiopathic disease characterized by productive cough, dyspnea, malaise, fever, night sweats, weight loss, and peripheral pulmonary infiltrates. It most commonly affects middle-aged women. Radiographically the classic finding is the “photographic negative of pulmonary edema” or the so called “reverse bat wing” configuration of infiltrates. However, this classic pattern is found in only 1/3 of all cases. Demonstration of eosinophilia is critical in diagnosing CEP. A recent review of CEP cases found that eosinophilia was demonstrated in peripheral blood in 85% of cases, by BAL specimens in 100% of cases, and in transbronchial lung biopsy specimens 64% of the time. All three tests for eosinophilia were positive in 60% of cases. It appears from this study that BAL is the single most reliable indicator of eosinophilia. In cases were symptoms are vague, findings on x-ray are not classic, or inability to demonstrate eosinophilia of CEP. A history of asthma or other atopy is found in approximately 50% of cases. The differential diagnosis primarily includes the other PIE syndromes listed above and bronchiolitis obliterans organizing pneumonia (BOOP), which is also characterized by peripheral pulmonary infiltrates.

The role of the eosinophil in CEP is being pursued extensively. There are two basic theories as to the main function of eosinophils in general. One holds that the eosinophil is a protective killer cell specifically involved in defense against metazoan parasites. The alternative theory pictures the eosinophil as an anti-inflammatory modulator of hypersensitivity reactions, acting to constrain and minimize the immune response and possible unnecessary spread. Both theories are supported by experimental data. Regardless of which hypothesis is primarily correct, the fact that eosinophils can be harmful rather than beneficial is clear.

Electron microscopic examination of DEP specimens reveals increased numbers of lymphocytes and macrophages, degeneration and necrosis of pneumocytes, denuded basement membranes, destroyed alveolar structures, edema of the stroma, and fibrin deposition. Eosinophils and released eosinophil granules, along with macrophages phagocytosizing them, are frequently found in the necrotic alveolar tissues. It appears that eosinophil cationic protein, released by eosinophil granules, plays a large role in tissue injury. Immunoglobulin A may play a role in the degranulation of eosinophils. A chemokine...
named RANTES, which is chemotactic for eosinophils, is found in markedly increased quantities in the BAL specimens from CEP patients. It appears that RANTES is produced locally in the lungs of CEP patients. Eosinophil-active cytokines designated interleukin-5, interleukin-6, and interleukin-10 have been found in strikingly elevated levels in the involved lung segments of CEP patients but are either absent or minimally present in uninvolved lung segments in the same patients. This evidence strongly suggests a role for these cytokines in the pathophysiology of CEP.0

Spontaneous remission of CEP occur in approximately 10% of cases. The remaining 90% require steroid therapy, which is generally quite satisfactory. The main complication of therapy is relapse of disease when treatment is tapered or discontinued. Length of steroid treatment is quite variable and is generally guided by the disappearance of symptoms and infiltrates on x-ray. In cases of CEP that tend to relapse, administration of therapy for as long as five years is common. Increased IgE levels have been found in some cases of CEP. This appears to be a nonspecific finding; however, measuring decreasing levels of IgE during steroid therapy, may play a role in guiding dosage and duration of such therapy.

Risk Classification
For life underwriting purposes, the long-term prognosis of CEP is paramount. A recent study of nineteen CEP patients followed for a minimum of twelve months and a maximum of one hundred and forty-two months found in the following. Lung function tests performed at the time of diagnosis were normal in six, restrictive in nine, and obstructive in four. Relapses had occurred in nine patients. When last evaluated, eight of the nineteen patients showed complete recovery, one had developed bilateral apical fibrosis and ten exhibited obstructive pulmonary function of various degrees without relapse of CEP. In these ten, despite the absence of x-ray or symptom relapse signs, chronic obstructive lung disease had developed. Also of prognostic value in this study was that the level of eosinophils in BAL specimens at the time of diagnosis tended to be higher in the ten patients that developed obstruction than in those that did not develop obstruction on follow-up. In appraising the mortality risk of a CEP applicant, one therefore must carefully consider the clinical status and lab data at time of diagnosis, the relapse history, the duration of follow-up, treatment history (duration and response), quality of medical follow-up, and current physical findings, x-ray findings, and especially pulmonary function data.

Those CEP patients with favorable results of the above considerations appear to be acceptable at moderately increased mortality risk. Those displaying marked eosinophilia at diagnosis, those with frequent relapse history, those not responding adequately to steroids, and those displaying worsening pulmonary function, even without relapse history, must be very critically underwritten. Our discussion case displays both good and somewhat worrisome features of her CEP. She responded quite well to brief courses of steroids, and her x-ray cleared completely and has remained clear for a substantial length of time. However, she exhibited considerable peripheral blood and BAL eosinophilia at the time of diagnosis, she has relapsed twice in a six to seven year follow up, and she displayed considerably abnormal pulmonary function during a symptom free period in 1991 with no subsequent pulmonary function testing done to date. In light of these facts, it is necessary to evaluate her mortality risk cautiously.

Conclusion
CEP is a relatively rare, somewhat mysterious disease, as are all the PIE syndromes. Much as been learned about the pathophysiology, especially the role of the eosinophil, in this disease. Active research continues in this area. From an underwriting standpoint it appears feasible to separate out certain CEP applicants with favorable characteristics who are likely to experience modestly increased mortality risk.
References