A pneumonia that will not go away

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Pneumonia is a common diagnosis with significant morbidity and mortality. However, pneumonia is a commonly overdiagnosed entity, with many similar-appearing conditions. A young, previously healthy woman was misdiagnosed with a variety of respiratory tract infections over the course of five months before establishing the correct diagnosis – chronic eosinophilic pneumonia.

Key Words: Chronic respiratory symptoms; Eosinophilia; Eosinophilic pneumonia

Learning objectives

1. To recognize the presenting symptoms of chronic eosinophilic pneumonia (CEP).
2. To understand the management of CEP.

CanMEDs Competency: Medical Expert

Pretest

- What are the diagnostic criteria of CEP?
- How would you treat a patient who presents with CEP?

CASE PRESENTATION

A 28-year-old woman was admitted with cough and few days' history of progressive shortness of breath and fevers. Her illness started five months previously when she was hospitalized with similar symptoms and was diagnosed with a community-acquired pneumonia. Since that admission, she was diagnosed with bronchitis twice and was treated as an outpatient. Between her acute illnesses, she continued to report dry irritating cough and dyspnea. She denied heartburn symptoms or history of sinusitis. Her medical history was negative and she had no history of smoking. She lived on a ranch in rural West Texas (USA), where she tended cows, goats, chicken and dogs. She was married with two children and none of her family members reported similar symptoms.

On examination, the patient was a healthy-appearing female in no respiratory distress. Vital signs were as follows: temperature 37.8°C; heart rate 95 beats/min (regular); blood pressure 101/58 mmHg; respiratory rate 22 breaths/min; and oxygen saturation 93% while on 2 L/min of oxygen via nasal cannula. Significant physical examination findings included the following: chest, wheezing and prolonged expiration; regular heart sounds without murmurs or gallop and no lymphadenopathy or skin rashes.

Pertinent laboratory findings included the following: white blood cell count $4.4 \times 10^9/L$ (73% neutrophils, 20% lymphocytes and 5% eosinophils); hemoglobin level 129 g/L; platelet count $121 \times 10^9/L$; procalcitonin level 0.2 ng/mL, C-reactive protein level 25.8 mg/L, erythrocyte sedimentation rate 16 mm/h, antinuclear antibodies and rheumatoid factor testing was negative and complement levels were within normal limits; airway cultures and blood cultures were negative;

Une pneumonie persistante

La pneumonie est un diagnostic courant qui s'accompagne d'une morbidité et d'une mortalité importantes. Cependant, elle est souvent surdiagnostiquée, car de nombreuses infections lui ressemblent. Sur une période de cinq mois, une jeune femme auparavant en santé a reçu divers diagnostics erronés d'infections respiratoires avant que le bon diagnostic de pneumonie à éosinophiles chronique soit posé.

HIV test and serologies for Q fever and brucella were negative. Renal function, electrolytes, liver enzyme levels and coagulation studies were within normal limits. Pulmonary function testing (PFT) revealed a forced expiratory volume in 1 s (FEV₁) 45% of predicted, forced vital capacity (FVC) 55% of predicted and FEV₁/FVC ratio of 64. There was a positive bronchodilator response documented by an increase in FVC by 230 mL after the patient received albuterol. Her total lung capacity was 70% of predicted, with a diffusing capacity of carbon monoxide (DLCO) 74% of predicted.

A chest radiograph (CXR) revealed prominent interstitial markings (Figure 1). A computed tomography scan of the chest revealed nonspecific ground-glass opacities (Figure 2). Given the relapsing nature of her complaints and the absence of a definite infectious etiology, an open-lung biopsy (OLB) was performed. The scant and peripherally distributed pulmonary ground-glass opacities, in addition to the patient's low surgical risk supported an OLB as opposed to transbronchial biopsy, and was well tolerated.

The OLB revealed peribronchiolar inflammatory infiltrate composed predominantly of eosinophils in addition to some lymphocytes and plasma cells (Figure 3). No acute inflammation in alveolar spaces, viral changes, foreign bodies, vasculitis or granulomas were identified. The patient was diagnosed with CEP. Empirical antibiotic therapy was discontinued and systemic steroids were started. She was seen in clinic one month after discharge and was completely asymptomatic; a slow, gradual steroid taper was initiated.

DISCUSSION

Eosinophilic lung disorders are a heterogeneous group of pulmonary diseases characterized by the presence of blood and/or lung eosinophilia (1). These ailments can result from a primary eosinophilic lung process including simple pulmonary eosinophilia, acute eosinophilic pneumonia and CEP, Churg-Strauss vasculitis and allergic bronchopulmonary aspergillosis, or a secondary illness caused by drugs, parasites and/or fungi. Thorough history taking including travel and environmental exposures, physical examination, appropriate imaging, PFT and, occasionally, tissue sampling, is essential in establishing a specific diagnosis and determining therapy.

CEP is a rare disease with unknown etiology and insidious onset (2). Patients present with subacute or chronic respiratory symptoms including cough, dyspnea fever and weight loss. The disease is more common in women, with a ratio of 2:1. Most patients are nonsmokers in their third and fourth decades of life (2,3).

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Figure 1) Chest radiograph showing prominent bilateral lower lobe interstitial pulmonary markings

The majority of patients have peripheral blood eosinophilia and an elevated erythrocyte sedimentation rate (3). Immunoglobulin E levels are elevated in 50% of patients. PFT can be normal, obstructive or restrictive, and DLCO is usually reduced. Peripheral parenchymal infiltrates are common on CXR and mimic the photographic negative of acute pulmonary edema (4). Computed tomography of the chest will confirm the parenchymal opacities but may reveal ground-glass opacities that are not apparent on CXR. Pleural effusions are rare; however, the typical pattern is not present in the majority of patients and are apparent in other interstitial lung diseases (4). The percentage of eosinophils is elevated in bronchoalveolar lavage (BAL) fluid. Lung biopsy shows eosinophilic infiltration of intra-alveolar septa and alveolar spaces.

Oral corticosteroids are the mainstay of therapy for CEP (3). The clinical response is rapid and most patients will experience complete resolution of their symptoms. The usual dose of prednisone is between 0.5 mg/kg/day and 1 mg/kg/day followed by gradual tapering over a six- to 12-month period (3). Relapse of CEP is very common and some patients will require long-term maintenance therapy with steroids.

In contrast to the above, acute eosinophilic pneumonia presents with rapid-onset respiratory failure that may require intubation and mechanical ventilation. Patients present with fever, myalgia and shortness of breath accompanied by severe hypoxemia and bilateral lung airspace opacities with rapid progression to severe respiratory failure (5). In contrast to CEP, there is no peripheral eosinophilia, but the percentage of eosinophils in BAL is elevated (5). There is rapid and dramatic clinical and radiographic response to corticosteroids. Most patients remain disease free with no recurrence after the discontinuation of corticosteroids.

Simple pulmonary eosinophilia is a self-limiting disease that presents with mild respiratory symptoms, migratory lung opacities and peripheral eosinophilia. Parasitic and fungal infections as well as drug reactions should be ruled out before diagnosing this entity (1).

Churg-Strauss syndrome is a systemic vasculitis that commonly develops in the setting of antecedent asthma, allergic rhinitis or sinusitis. Patients usually present with peripheral eosinophilia, migratory pulmonary opacities, purpuric rash, fever and arthralgia (6). Complaints related to cardiac, gastrointestinal or renal involvement are less common. P-ANCA is positive in 40% of patients (6). Tissue biopsy establishes the diagnosis (6). Most patients respond quickly to

Figure 2) A and B Chest computed tomography scans demonstrating scattered ground-glass pulmonary opacities without pleural effusions or lymphadenopathy

Figure 3) Lung wedge biopsy showing peribronchiolar eosinophilic inflammatory infiltrate (hematoxylin and eosin stain, original magnification $\times 400$)

high-dose steroids. Severe cases may require cyclophosphamide. Relapses are frequent; therefore, suppressive therapy with azathioprine or methotrexate for 12 to 18 months is recommended (6).

Allergic bronchopulmonary aspergillosis is a hypersensitivity lung disease associated with inflammatory destruction of airways in response to *Aspergillus* species. This disease's diagnostic criteria include: asthma, central bronchiectasis, *Aspergillus fumigatus* hyper-reactivity documented by elevated specific immunoglobulin levels or, on skin testing, fleeting pulmonary opacities and peripheral eosinophilia (7). Corticosteroids are a cornerstone of therapy; itraconazole has a demonstrable steroid-sparing effect (7).

Idiopathic hypereosinophilic syndrome is a rare myeloproliferative disorder characterized by peripheral eosinophilia that has been present for >6 months associated with evidence of end-organ damage caused by eosinophilic infiltration without any other identifiable etiology (1). Pulmonary manifestations include chronic cough, asthma and pulmonary fibrosis. Cardiac involvement is a main cause of mortality in patients with this disease (1).

Secondary eosinophilic lung diseases result from certain parasitic and fungal infections or the exposure to certain drugs. In North America, *Strongyloides*, *Ascaris*, *Toxocara* and *Ancylostoma* are the most common parasitic causes of eosinophilic lung disease (8,9). In primary coccidioidomycosis, an endemic fungus in the southwestern corner of the United States, peripheral blood eosinophilia is noted in the majority of cases and pulmonary eosinophilic infiltrates may be demonstrated on lung biopsy or BAL examination (10). Drugs commonly reported to cause eosinophilic lung disease include amiodarone, cocaine, nonsteroidal anti-inflammatory drugs, penicillins and sulpha compounds (11).

Post-test

- What are the diagnostic criteria for CEP?

Patients with CEP present with chronic respiratory symptoms, peripheral blood eosinophilia, abnormal PFT and peripheral lung infiltrates. Diagnosing CEP requires the presence of a consistent clinical picture in addition to the identification of eosinophilic pulmonary infiltrate on bronchoscopy or lung biopsy, in combination with excluding other eosinophilic disorders, especially parasitic infections.

- How would you treat a patient who presents with CEP?

Systemic corticosteroids are the mainstay therapy for CEP. The disease is steroid responsive but requires prolonged therapy. Given the high prevalence in women and the need for chronic corticosteroid therapy, special measures should be taken to prevent osteoporosis.

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