Chronic eosinophilic pneumonia after trastuzumab and radiation therapy for breast cancer

A case report

Fan Jin, MD\textsuperscript{a}, Shao-ting Wang, MD\textsuperscript{b},\textsuperscript{*}

Abstract

Rationale: Chronic eosinophilic pneumonia (CEP) is rare and an idiopathic disorder. The disease has been associated with drugs, infection, or irradiation, and its relationship with asthma remains unclear.

Patient concerns: We reported a case of a 49-year-old female patient after trastuzumab and radiation therapy for breast cancer. Two months after radiation treatment, the patient complained of productive cough, progressive breathlessness, occasional wheezing, and left pectoralgia.

Diagnoses: Computed tomography (CT) scan revealed infiltrates in lungs. Without evidence of infection, marked increased eosinophils in a transbronchial biopsy performed from the left upper lobe confirmed the diagnosis of CEP after trastuzumab and radiation therapy.

Interventions: The patient was started with oral prednisone at 0.5 mg/kg/day.

Outcomes: A CT scan of the chest obtained 2 weeks after steroid treatment showed diminishment of the lesions, and at the 6-month follow-up, the patient had no complaints of discomfort with no relapse of pulmonary lesions.

Lessons: Physicians should consider CEP as a diagnosis in patients who have had previous exposure to trastuzumab and radiation therapy, especially with a history of asthma. Timely diagnosis and treatment may benefit these patients.

Abbreviations: CEP = chronic eosinophilic pneumonia, CT = computed tomography.

Keywords: breast cancer, chronic eosinophilic pneumonia, radiation therapy, trastuzumab

1. Introduction

Chronic eosinophilic pneumonia (CEP) is an idiopathic disorder characterized by an abnormal and marked accumulation of eosinophils in the interstitium and alveolar spaces of the lung.\textsuperscript{1} CEP is a rare disorder, in registries of interstitial lung disease (ILD) in Europe, which accounts for up to 2.5\% of cases of ILD.\textsuperscript{2} Clinical manifestations are nonspecific with subacute to chronic respiratory symptoms. It is usually idiopathic, however, it has been associated with drugs or toxin, parasite or fungi, irradiation for cancer, and rheumatoid arthritis.\textsuperscript{3–5} In this case, a female patient with a history of asthma and breast cancer developed CEP two months after she completed radiation and trastuzumab therapy.

2. Case report

A 49-year-old female with a medical history significant for left-sided breast cancer underwent lumpectomy in 2017, for which the pathology was ductal carcinoma, HER2 positive. Then, she was treated with trastuzumab (8 mg/kg loading dose, then 6 mg/kg every 3 weeks intravenously) and oral capcitabine (1000 mg/m\textsuperscript{2} twice a day on days 1–14 every 3 weeks) for 7 cycles from September 2017 to February 2018. During chemotherapy, a course of radiotherapy was performed, delivering 50 Gy in 25 fractions to left chest wall and supraclavicular fossa (2 Gy every fraction and 5 fractions per week) from November 17 to December 22, 2017. Two months after radiation treatment, the patient complained of productive cough and progressive breathlessness, occasional wheezing, and left pectoralgia. Her chest X-ray showed infiltrates in the left apical segment and was prescribed ipratropium inhalers and antibiotics. With no improvement in her symptoms, the computed tomography (CT) scan of the chest (Fig. 1A) revealed a left upper lobe consolidation. Half a month later, the range and density of the consolidation increased, and the left pleural effusion was newly seen (Fig. 1B).

\textsuperscript{a} Department of Internal Medicine, \textsuperscript{b} Department of Respiratory Medicine, Peking Union Medical College, Beijing, China.\textsuperscript{*} Correspondence: Shao-ting Wang, Department of Respiratory Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, No. 1 Shuaifuyuan, Dongcheng District, Beijing 100730, China (e-mail: bird0162@163.com).

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\textsuperscript{4} Availability of data and materials: All data generated or analyzed during this study are included in this article.

\textsuperscript{5} Ethics approval and consent to participate: In accordance with the Declaration of Helsinki, informed consent was obtained from the patient.

\textsuperscript{6} Conflict of interest: The authors declare that they have no competing interests.
On review of systems, the patient reported suffering from nocturnal sweats but no fevers, no change in appetite, and no weight loss. She had a full-time job as an office worker and denied any significant environmental exposure history. She is a never smoker with a 6-year past medical history of well-controlled asthma.

Laboratory studies revealed 56% eosinophils (6.16 × 10^3/L) in peripheral blood, IgE 154.0 kU/L. Her blood biochemical profiles as well as serum immunoglobulins were all unremarkable. Infectious disease etiologies workup including serologies for aspergillus, flarial worms, lungworms, cysticercosis, and trichinella spiralis was negative. Stool examinations for ova and parasites were negative. Vasculitides and connective tissue diseases workup including antinuclear antibody, anti-double-stranded DNA, rheumatoid factor, and anti-neutrophil cytoplasmic antibody was negative. Bone marrow biopsy and FIP1L1-PDGFR alpha test excluded hematological diseases such as myeloproliferative neoplasms and hypereosinophilic syndrome. Pulmonary function tests revealed forced expiratory volume in the first second of 2.88 L (97.0% predicted), FEV1/FVC ratio of 73.73%, total lung capacity of 4.68 L (96.9% predicted), and diffusing capacity for carbon monoxide of 6.41 mmol/min/kPa (79.8% predicted). She underwent bronchoscopy, and bronchoalveolar lavage (BAL) fluid demonstrated eosinophil count of 83%. A transbronchial biopsy performed from the left upper lobe was suggestive of eosinophilic pneumonia with the consolidations diminished after steroid treatment for 2 weeks. (D) At 6-month follow-up, CT showing no relapse of pulmonary lesions.

Figure 1. (A) CT showing a left upper lobe consolidation. (B) CT showing the consolidation increased and newly seen small-sized pleural effusion. (C) CT showing the consolidations diminished after steroid treatment for 2 weeks. (D) At 6-month follow-up, CT showing no relapse of pulmonary lesions.

Figure 2. Transbronchial biopsy showing eosinophilic infiltrates within lung parenchyma. No vasculitis or microorganisms were seen; H&E, ×200 magnification.

3. Discussion

The pathophysiology of CEP remains incompletely delineated, though elevations of several cytokine, chemokine, and immunomodulatory products in studies of BAL fluid existed. Women develop CEP about twice as often as men and a majority of patients are nonsmokers. A third to a half of affected patients have a history of asthma. The diagnosis of CEP is typically based on the combination of clinical presentation, and typical symptoms include a productive cough, fever, breathlessness, weight loss, and night sweats, occurring over 2 months. Chest imaging may show predominantly peripheral or pleural-based opacities. The BAL eosinophil count is always more than 25% in CEP. CEP is usually a diagnosis of exclusion and the differential diagnosis includes acute eosinophilic pneumonia, allergic bronchopulmonary aspergillosis, infectious causes, eosinophilic granulomatosis with polyangiitis, or hypereosinophilic syndrome. Lung biopsy is not necessary unless the BAL does not show eosinophilia, the chest imaging features are atypical, or the patient does not respond promptly to systemic glucocorticoid therapy. Response to steroids aids in confirming the diagnosis and is usually with dramatic improvement in symptoms within 24–48 h.

Therapy is indicated once the diagnosis of CEP has been made, as fewer than 10% of patients with CEP spontaneously recover. In addition, CEP occasionally leads to irreversible fibrosis, although death secondary to CEP is extremely unusual. Initial therapy consists of oral prednisone at a dose of 0.5 mg/kg per day. We usually continue the initial dose for 2 weeks after the complete resolution of symptoms and abnormal plain chest radiographic (usually 4–6 weeks). Symptomatic or radiographic recurrence is common (50–80% of cases) either after cessation of therapy, or less commonly, with tapering of the glucocorticoid dose. In managing a relapse, the prednisone dose can be restored to 0.5 mg/kg per day. Treatment usually lasts at least 3 months, usually 6–9 months.
Occasionally, glucocorticoid therapy continues indefinitely.\[9\] Alternative therapies have been explored for patients with recurrent flares of CEP that are associated with radiographic opacities, including high-dose inhaled glucocorticoids and omalizumab (monoclonal antibody to IgE).\[10,11\] Inhaled glucocorticoids (1000–1500 mg per 24h) have been reported to be effective in CEP. Inhaled glucocorticoids are not recommended as an initial or monotherapy, but may help in reducing the maintenance dose of oral glucocorticoid.\[10\]

Our patient met the diagnosis of CEP, and the therapeutic effects of glucocorticoid have proved the diagnosis. After exclusion of other causes, the pneumonitis appeared to be the consequence of trastuzumab or radiotherapy. Radiation therapy has been associated with the development of eosinophilic pneumonia, especially in those who have underlying allergies such as asthma.\[12,13\] Cottin and Chaaban successively reported cases of patient with CEP in breast patients post-radiation therapy, and all patients rapidly improved with oral corticosteroids without sequelae.\[13,14\] In addition to radiotherapy, triggers, such as drugs, toxins, and environmental exposure, are usually needed.\[13,15\] No case of trastuzumab causing CEP has been reported, but there are reports of trastuzumab related to pulmonary interstitial disease in the NSABP B-31 and N9831 trials, which revealed that 9 patients in the trastuzumab group had interstitial pneumonitis.\[10\] Physicians should be aware of a causative association between trastuzumab and pulmonary toxicity, and consider CEP as a diagnosis in patients who have had previous exposure to trastuzumab and radiation therapy for breast cancer.

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