



## Bronchogenic Adenocarcinoma with Severe Eosinophilia

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### ABSTRACT

Hypereosinophilia is defined as eosinophil count more than 1500 per microliter that can be associated with tissue and organ damage, regardless of the underlying cause. There are various categories of diseases that are able to cause eosinophilia. Solid tumor-associated hypereosinophilia is an unusual manifestation in patients with cancer. Cytokines namely granulocytes macrophages stimulating factor (GM-CSF), interleukin 3 (IL-3), and interleukin 5 (IL-5) may play an important role in the pathogenesis of eosinophilia development. Here, we describe a 70-year-old man with metastatic adenocarcinoma of the lung presenting with fever, weight loss, shortness of breath, and severe hypereosinophilia. In patients with compatible clinical findings and associated risk factor(s), it is important to consider lung adenocarcinoma as a differential diagnosis in patients with unexplained eosinophilia and lung symptoms with associated risk factors.

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### Introduction

**H**ypereosinophilia in peripheral blood (defined as eosinophil levels more than 1500 per microliter) could be associated with tissue and organ damage, regardless of the underlying cause (1). The causes of secondary hypereosinophilia include infectious diseases, allergic disorders,

medications, toxins, autoimmune diseases, and endocrine disorders. Hypereosinophilia has been also reported in some malignancies, including metastatic cancers (1, 2). Tumor-associated hypereosinophilia has been reported in cervix, vagina, penis, skin, nasopharynx, stomach, large bowel, uterine body, and bladder carcinomas (3), but it is

rare in bronchial carcinomas (4). Despite several reported cases, the precise pathogenesis of tumor-associated hypereosinophilia is not well known. Here, we report a case of lung adenocarcinoma with metastasis into bone and lymph nodes with associated severe hypereosinophilia.

### Case Report

A 70-year-old man presented to the emergency department with fever, chills, night sweats, bone pain, shortness of breath, and dry cough for one month period. Due to insufficient response to intravenous antibiotic therapy for suspected pneumonia and presence of massive pleural effusion in radiologic findings, he was admitted to general hospital affiliated to Tehran University of Medical Sciences, Iran, for further work-up and management.

The patient also reported anorexia and weight loss of 20 kg during 2 months before presentation. There was no history of hemoptysis and hoarseness of voice. He had no known history of allergies or atopic diseases and was heavy smoker (one pack of cigarettes per day for 50 years). He was greengrocer since young age and he denied any exposure to asbestos containing material in the late past. There was no previous history of any medical illness including pulmonary disease, cardiovascular disease, or diabetes mellitus. Similarly, he had no history of medication use other than recent 10-day course of antibiotics for suspected multidrug-resistant pneumonia in another center including meropenem (1 g every 8 hours), ciprofloxacin (400 mg every 8 hours), and vancomycin (1 g every 12 hours).

On physical examination, he was somewhat ill but cooperative with mild distress in sitting position. Respiratory rate was 18 per minute, pulse rate 80 per minute, and blood pressure was 100/60 mmHg. The oxygen saturation was less than 90% on room air. He was given 3-5 l/minute nasal oxygen. On chest auscultation, breath sounds were decreased in right lung base. There was no

clubbing and cyanosis. No other significant finding was evident on general examination.

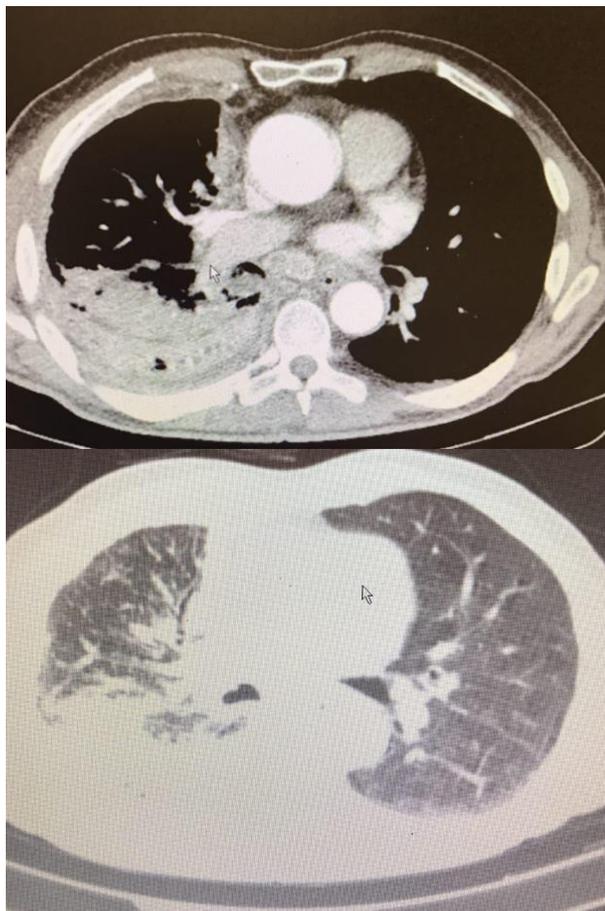
Basic laboratory data revealed the following results: white blood cell (WBC): 16300 cells/ $\mu$ l with 22% eosinophil, and absolute eosinophil count of 3600 cells/ $\mu$ l, hemoglobin (Hb): 13.6 g/dl, platelets count: 267000 cells/ $\mu$ l, erythrocyte sedimentation rate (ESR): 27 mm/hour, and C-reactive protein (CRP): 88.6 mg/l.

Immunoglobulin E (IgE) level was 188 IU/ml (Normal range: 150 and 300 UI/ml). Peripheral blood smear examination revealed severe eosinophilia (31% eosinophils, 3% lymphocytes, 65% neutrophils, and 1% monocytes), and no atypical cells were found. Fasting blood sugar, renal function tests, liver enzymes, and lactate dehydrogenase (LDH) were within normal ranges. Human immunodeficiency virus (HIV) serology was negative. Three consecutive stool exams for evaluation of ova and parasite were all negative. Serology results for parasitic infections were all negative. Sputum smear examination for acid fast bacilli was negative in three occasions.

Pulmonary function tests (PFT) revealed forced vital capacity (FVC) of 41%pred, forced expiratory volume in one second (FEV<sub>1</sub>) of 43%pred, FEV<sub>1</sub>/FVC of 0.7, total lung capacity (TLC-b) of 68%pred, and residual volume (RV-b) of 103%pred. Echocardiography showed normal left ventricular ejection fraction (LVEF = %55), and systolic pulmonary artery pressure of 35 mmHg.

No significant pathology was found in abdominopelvic computed tomography (CT) scan. Thoracic CT-scan revealed diffuse significant pleural thickening and surface nodularity, interlobular septal thickening in right lung apex, consolidation and collapse in right middle lobe (RML) and right lower lobe (RLL), lobar and segmental branches of left bronchi, multiple mediastinal lymphadenopathy with the largest lymph node measuring 12 mm, moderate pleural effusion in right side, and some air bubble in pleural surface (Figure 1). Whole body bone scan showed

multiple bone metastases. Bronchoscopy showed no endobronchial lesion.



**Figure 1.** Mediastinal and parenchymal window of thoracic computed tomography (CT) scan showing right plural effusion/thickening and adjacent pulmonary infiltration

Biochemical analysis of the pleural fluid confirmed that it was an exudative effusion (pleural fluid: WBC: 3200 cell/ $\mu$ l, albumin: 1.7 g/dl, total protein: 2.4 g/dl, LDH: 2100 IU/l, and adenosine deaminase (ADA): 29 U/l, serum: albumin: 2.6 g/dl, total protein: 4.1 g/dl, and LDH: 429 IU/l). Pleural fluid culture for usual bacteria was negative. Chest tube was inserted through the right side of chest wall to drain the effusion and relieving the symptoms.

Initially, the patient was treated with bronchodilators, analgesics, and symptomatic therapy. But, his general condition deteriorated and he did not respond significantly to

supportive treatments. A thoracoscopic biopsy of the pleura was performed and pathology revealed poorly differentiated adenocarcinoma of the lung, immunohistochemically positive for cytokeratin 7 (CK7), thyroid transcription factor 1 (TTF-1), and napsin, but negative for calretinin, p63, caudal type homeobox 2 (CDX2), CK20, and prostate specific antigen (PSA).

### Discussion

There are various complex initial presentations in patients with new or pre-existing malignancies that could cause delay in initial diagnosis (5, 6). Among these presentations, numerous paraneoplastic syndromes have been defined including the hematologic ones. Different etiologies can increase eosinophil count in peripheral blood (7). The terms of hypereosinophilia and severe hypereosinophilia defined as blood eosinophil count exceeding more than 1500 and 5000 per microliter, respectively. The skin, airways, and gastrointestinal tract are the common target organs of eosinophilic diseases, and hypereosinophilia most commonly represents allergy, parasitic infections, adverse drug reactions, and hematologic malignancies (8, 9). Severe hypereosinophilia has been reported in various solid tumors and malignancies -may be as a paraneoplastic syndrome- including gastrointestinal tumors, renal cell carcinoma, prostate cancer, and sarcomas (10-14). But paraneoplastic hypereosinophilia is a very rare finding in lung adenocarcinoma. There are few published case reports of adult patients with lung adenocarcinoma presenting hypereosinophilia, as well as our patient (15-19). In majority of these reports, hypereosinophilia correlated with extensive metastasis and poor survival.

Following producing several cytokines, namely granulocytes macrophages stimulating factor (GM-CSF), interleukin 5, (IL-5) and interleukin 3 (IL-3) by primary tumor cells, proliferation and differentiation of myeloid

stem cells occur and as a result, the number of neutrophils, eosinophils, and monocytes may increase in bone marrow (20-22).

Although all causes of secondary hypereosinophilia including allergic disorders, infectious diseases, medications, and toxins were excluded for our patient, bone marrow biopsy was not performed to rule out myeloid leukemia. However, it is extremely unlikely for this patient to have primary leukemia and lung adenocarcinoma simultaneously. The patient was discharged and referred to the oncology clinic. However, due to rapid progression of disease, he died in a short time before initiation of any chemotherapy drugs.

In conclusion, although hypereosinophilia is an unusual manifestation in patients with cancer, it should be considered as an important clue in patients suspected with adenocarcinoma. We suggest to consider lung adenocarcinoma as a differential diagnosis in patients with unexplained eosinophilia and lung symptoms with according risk factor(s). Furthermore, patients with lung cancer and associated hypereosinophilia could be more advanced cases with adverse prognosis.

### Conflict of Interests

Authors have no conflict of interests.

### Acknowledgments

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