Hypereosinophilia and Paraneoplastic Syndrome: An Unusual Presentation with an Unexpected Diagnosis

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Hypereosinophilia is defined as the absolute eosinophilic count of above 1500 × 10^9/L in the peripheral blood on two separate tests taken during one month and/or the pathological confirmation of hypereosinophilia. There are many conditions that are associated with increased eosinophil counts including: parasitic infections, drug reactions, eosinophilic granulomatosis with polyangiitis, allergic reactions, drug reaction with eosinophilia and systemic symptoms (DRESS), primary immunodeficiencies (PID), eosinophilic gastrointestinal diseases (EGID), familial hypereosinophilia, and neoplasms [1]. Molecular classification may be an adjuvant in the classification of hypereosinophilia [2]. Our patient presented with hypereosinophilia as part of a paraneoplastic syndrome.

PATIENT DESCRIPTION

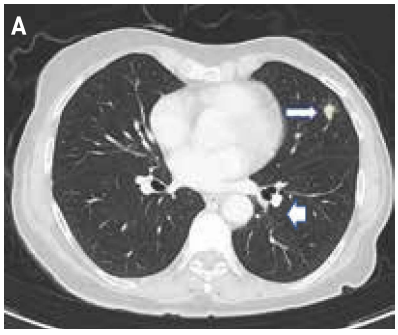
A 75-year-old female with a past medical history of heavy smoking, hypothyroidism, and fibromyalgia, who was treated with opiates and medical cannabis, was admitted to the internal medicine ward for the onset of pain in her neck and right shoulder for 2 weeks accompanied by weight loss of 7 kg over 5 months, and night sweats. Five days prior to admission, she was treated with the antibiotic ofloxacin for suspected urinary tract infection.

On admission, the patient had normal vital signs. On physical examination, the patient had no palpable lymphadenopathy or skin rash. Heart sounds were normal, without murmurs. Lung examination revealed a prolonged expiratory phase, without crackles or wheezing. The patient had abdominal tenderness on palpation in the upper right quadrant and left flank without signs of guarding. The rest of the physical examination was normal.

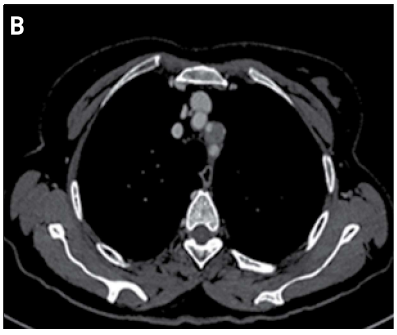
Blood laboratory tests at admission showed leukocytosis 12700 10^9/L (normal range 4.5 to 11.0 × 10^9/L), normochromic normocytic anemia with hemoglobin 12.9 g/dl (normal range 13.5–17.5 g/dl) platelet count 245,000 mm^3 (normal range 150–450 mm3), and an absolute eosinophilic count of 3300× 10^9/L (normal range < 0.5× 10^9/L). A blood smear revealed that 52% of the cells were eosinophils.

The CRP level was 12 mg/dl (normal range 0–0.5 mg/dl). Blood chemistry was normal as was a chest X-ray. Our differential diagnosis included a malignant paraneoplastic syndrome, lymphoma, and drug related eosinophilia. Drug induced eosinophilia was excluded after a close examination of the patient's medication list. Further investigation was performed with a computed tomography (CT) scan of the chest and abdomen that revealed a lymph node in the lingula of 1.1 × 0.8 cm [Figure 1A] and a necrotic space occupying lesion in the left mediastinum of 5.0 × 4.7 × 3.0 cm with left mediastinum necrotic lymphadenopathy [Figure 1B]. The patient underwent mediastinoscopy and the histology was compatible with small cell lung carcinoma. The patient was referred to an oncologist. Unfortunately, the patient was lost to follow-up, and several attempts to contact the patient after hospital discharge failed.

Figure 1. Chest computed tomography axial view of chest and mediastinal findings



[A] The finding of a lymph node of 1.1 × 0.8 cm in the lingual (viewed in a lung window, white arrow)



[B] Left mediastinum necrotic lymphadenopathy (viewed in a mediastinal window, white arrow head)

COMMENT

The diagnosis of hypereosinophilia as part of an occult malignancy (paraneoplastic syndrome) was determined in an older patient due to constitutional symptoms and whole body CT. A higher eosinophilic count is directly correlated to disease severity due to tissue damage [1]. In our patient, the diagnostic workup was delayed and probably the eosinophilia was disregarded as a red flag.

Paraneoplastic hypereosinophilia is most often associated with hematologic malignancies such as Hodgkin's lymphoma, non-Hodgkin's lymphoma, and myeloid leukemias, but has also been reported in solid organ tumors such as squamous cell carcinomas, non-small cell carcinomas, and adenocarcinoma of the lung [1,3]. The association between lung malignancies and paraneoplastic hypereosinophilia usually reflects an aggressive course of disease commonly associated with a metastatic finding at diagnosis, and patients carry a poor prognosis [3]. In our case, the patient did not have metastatic disease.

The implications of paraneoplastic eosinophilia, ranging from asymptomatic to life threatening, are affected by the etiology [4].

All types of lung cancer, and especially anaplastic squamous cell carcinoma, are capable of secreting eosinophil polymorphonuclear leucocyte chemotactic factors, resulting in bone marrow stimulation through circulatory factors which are secreted by the malignant tumor [2,3]. The local inflammatory reaction generated by lymphocytes, mast and dendritic cells against tumor cells are the main cause for eosinophil chemo-attractors by generating interleukin 5 (IL-5) secretions [3].

To date, there are 14 case reports of paraneoplastic hypereosinophilia secondary to lung cancer, including large cell carcinoma, adenocarcinoma, and squamous cell carcinoma of the lung, but none with small cell carcinoma [5]. Hypereosinophilia should be included in the many different paraneoplastic syndromes of small cell carcinoma.

The first line of therapy for patients with paraneoplastic hypereosinophilia is management of the underlying malignancy via a surgical procedure or chemotherapy [4,5]. Corticosteroids may also be added as adjuvant therapy for paraneoplastic hypereosinophilia [4]. IL-5 inhibitors may be an appropriate therapy in hypereosinophilic syndromes [3]. Recurrent hypereosinophilia may suggest disease relapse [2].

CONCLUSIONS

To the best of our knowledge, our case report is the first of a patient who presented with paraneoplastic hypereosinophilia secondary to small cell carcinoma of the lung. Eosinophilia should raise a clinical suspicion of neoplastic disease and necessitate a proper workup.

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Capsule

A potential combination in glioblastoma treatment

Glioblastoma is a highly invasive tumor with poor prognosis. Tumor vasculature and auto phagy are important determinants for glioblastoma progression. **Chryplewicz** and colleagues used mouse models of gliomagenesis to explore inhibitors of vascular endothelial growth factor receptor (VEGFR). A combination of VEGFR inhibitor with the tricyclic antidepressant imipramine, which increases autophagy, significantly delayed tumor growth. It is possible that the therapy-induced increase in autophagy is immunogenic and drives antitumor immunity. The authors observed increased CD8+ and CD4+ T cell infiltration, which was dependent on autophagy in glioblastomas. They also found that imipramine altered the phenotype of macrophages in the glioblastoma microenvironment, skewing them away from immunosuppression. The drug combination appeared to remodel the tumor microenvironment to favor antitumor T cell responses. These responses might be further enhanced by the addition of immune checkpoint inhibitors.

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