Extreme Eosinophilia and Dyspnea as Presenting Signs of a Metastatic Tumor

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Eosinophils are mature myeloid-derived cells, defined by the presence of prominent secondary granules [1]. In peripheral blood, the normal upper limit of absolute eosinophil count (AEC) ranges from 350 to 500 cells/μL. Eosinophilia is defined as an AEC exceeding 500 cells/μL, while hypereosinophilia is characterized by an AEC greater than 1500 cells/μL confirmed on at least two separate occasions [1,2].

Hypereosinophilic syndrome (HES) is defined by the presence of hypereosinophilia accompanied by organ damage or dysfunction attributed to eosinophilic infiltration in the absence of an alternative identifiable cause [1].

Eosinophilia may arise from a broad spectrum of conditions and is generally categorized as either primary (clonal) or secondary (reactive). Primary eosinophilia typically results from myeloid malignancies, whereas secondary eosinophilia is most commonly associated with allergic disorders, helminth infections, drug hypersensitivity reactions, rheumatologic disorders, and, less frequently, paraneoplastic phenomenon [1,3].

PATIENT DESCRIPTION

A 79-year-old female with a medical history of breast cancer at age 36 years and fibromyalgia presented with a 3-week history of progressive dyspnea and a productive cough. She denied systemic symptoms such as fever, weight loss, night sweats, diarrhea, skin rash, arthralgia, or sinusitis.

Two weeks prior to admission, she was diagnosed with pneumonia based on a chest X-ray and treated empirically with oral levofloxacin 500 mg/day for 10 days without clinical improvement.

At admission, the patient exhibited mild speech dyspnea and a respiratory rate of 30 breaths per minute. Her oxygen saturation was 88% on ambient air and 97% with supplemental oxygen via nasal cannula at a rate of 3 L/min. Lung auscultation revealed diffuse bilateral wheezing in the absence of peripheral edema.

Laboratory testing demonstrated leukocytosis with a white blood cell count (WBC) of 31.75 × 10^3/μL and an AEC of 5.15 × 10^3/μL. Renal and hepatic function panels were within normal limits. Lactate dehydrogenase was moderately elevated at 441 U/L. Serum immunoglobulin E was normal at 88 IU/ml. Autoimmune workup revealed an antinuclear antibody titer of 1:160. Cytoplasmic and perinuclear antineutrophil cytoplasmic antibodies were negative.

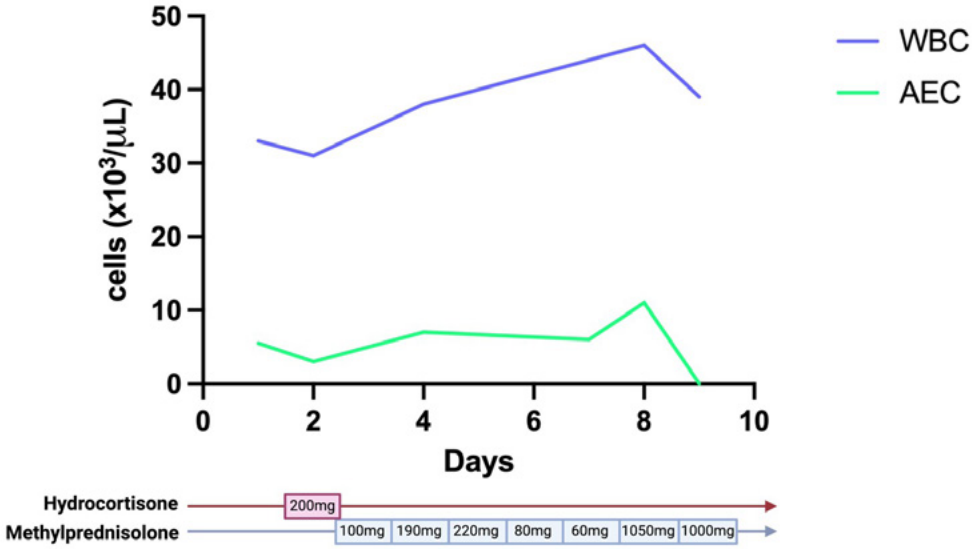
Repeat chest radiography demonstrated multiple bilateral nonspecific infiltrates. Blood cultures were obtained, and empirical treatment was initiated with intravenous ceftriaxone (1 g/day) with inhaled bronchodilators (albuterol and ipratropium). Due to worsening respiratory distress and declining oxygen saturation, the patient received 200 mg intravenous hydrocortisone on hospital day 2, followed by intravenous methylprednisolone at a dose of 2 mg/kg on day 3. Despite therapy, dyspnea progressed, and the AEC continued to rise [Figure 1].

A chest and abdominal-pelvic computed tomography (CT) scan performed on hospital day 5 revealed an 8.6 cm spiculated mass in the right upper lobe invading the right bronchus, mediastinal and hilar lymphadenopathy, and a small pleural effusion. Multiple lesions consistent with metastases were observed in the liver, right adrenal gland, and peritoneum. There was a 2.4 cm subcutaneous mass on the right abdominal wall. Open biopsy obtained from the abdominal wall lesion confirmed metastatic non-small cell carcinoma of unknown primary origin.

On hospital day 6, the patient underwent a single 8 Gy palliative chest radiotherapy session. Despite this,

Figure 1. Daily leukocyte and absolute eosinophil count during hospitalization

AEC = absolute eosinophil count, WBC = white blood cell count
The lower bars show administrated doses of corticosteroids. Both leukocyte and eosinophil counts continued to rise despite treatment, with a decline observed only after the second day of pulse corticosteroid therapy.



her respiratory condition deteriorated, and pulse steroid therapy with 1 gram intravenous methylprednisolone daily for 3 days was initiated on day 8. A decline in AEC was noted 2 days into pulse therapy [Figure 1]. Nevertheless, her clinical condition continued to worsen, and her functional status rapidly declined. The patient died on hospital day 13.

COMMENT

Paraneoplastic hypereosinophilia is predominantly associated with hematological malignancies and, to a lesser extent, with solid tumors [2,3]. A clinical review conducted in 2021 documented 100 cases of paraneoplastic hypereosinophilia secondary to solid tumors, with lung cancer identified as the most prevalent malignancy. Additional reported cases included gastrointestinal malignancies (including pancreas, colon, liver, and rectum), renal cell carcinoma, and thyroid carcinoma, although these were described only anecdotally [4].

Paraneoplastic hypereosinophilia is a diagnosis of exclusion [3-5], carries an unfavorable prognosis and increased mortality, particularly in cases of metastatic malignancies originating from the lung, thyroid, kidney, liver, and pancreas [4].

Paraneoplastic hypereosinophilia is frequently asymptomatic [3]; however, when symptoms do emerge, they commonly include fatigue (26%), coughing (24%), and dyspnea (16%) [2].

While definitive treatment with anticancer therapies usually resolves hypereosinophilia, symptomatic patients require bridging treatment to alleviate and stabilize symptoms [3].

In such cases, corticosteroids represent first-line intervention, with dosing ranging from 1 mg/kg to 1 gram of methylprednisolone, depending on the clinical severity [1-3]. The therapeutic effect of corticosteroids is attributed to multiple mechanisms, including suppression of eosinophil production in the bone marrow, inhibition of their release into the circulation, promotion of eosinophil apoptosis, and attenuation of eosinophil chemotaxis [4].

Hydroxyurea is also considered an effective first-line agent and may be used either in combination with corticosteroids or as an alternative in patients who do not respond to steroid therapy. The methylprednisolone initial dose ranges from 500 to 1000 mg per day [1,2,3,5]. Second- and third-line treatment options include vincristine, cyclophosphamide, and etoposide [2,5].

In the present case, the patient's severe symptomatic paraneoplastic hypereosinophilia was managed with corticosteroid therapy. How-

ever, despite escalating doses, no clinical improvement or reduction in WBC or AEC was observed. Supportive measures, including inhalation therapy for dyspnea, were similarly ineffective. The patient's functional status deteriorated rapidly during hospitalization, precluding the initiation of hydroxyurea. Although administration of two doses of 1gram methylprednisolone resulted in a reduction in AEC, the patient ultimately opted for only palliative measures.

CONCLUSIONS

Paraneoplastic hypereosinophilia represents a rare manifestation of solid tumors. While definitive oncologic therapies typically resolve hypereosinophilia, corticosteroids and hydroxyurea serve as bridging therapies, particularly in symptomatic individuals. Elevated eosinophil counts that are refractory to corticosteroid therapy should prompt consideration of an underlying malignancy and are typically associated with a poor prognosis.

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Capsule

Noninferiority of one HPV vaccine dose to two doses

A total of 20,330 participants were enrolled in a survey by **Kreimer** et al. and underwent randomization, including 3005 unvaccinated participants. The noninferiority analysis showed that one vaccine dose was noninferior to two doses in preventing HPV16 or HPV18 infection. The rate difference between one and two doses of the bivalent vaccine was -0.13 infections per 100 participants (95% confidence interval [95%CI], -0.45 to 0.15; $P < 0.001$ for noninferiority). The difference between one and two doses of the nonavalent vaccine was 0.21 infections per 100 participants (95%CI, -0.09 to 0.51; $P < 0.001$ for noninferiority). The vaccine effectiveness was at least 97% in each of the four trial groups. No safety concerns were identified.

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Capsule

Reverse vaccinology in action

Two recent outbreaks of mpox, caused by monkeypox virus (MPXV), underscore the urgent need to develop and stockpile effective vaccines and therapeutics. **Paciello** and colleagues applied reverse vaccinology combined with AlphaFold3-based structural modeling to identify an MPXV protein targeted by human B cells to enable the development of antibody therapeutics and vaccines. The authors recombinantly expressed MPXV-neutralizing antibodies derived from B cells of individuals who had a history of MPXV infection or vaccination. They then used modeling and cryo–electron microscopy to identify the target of a subset of potent, broadly neutralizing antibodies as the protein encoded by the conserved orthopoxviral gene 153 (*OPG153*). Immunization of mice with an adjuvanted MPXV OPG153 vaccine elicited neutralizing antibodies, suggesting that OPG153 represents both a candidate vaccine antigen and a therapeutic antibody target. Together, these findings highlight the power of leveraging human immunity to design therapeutics and vaccines.

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