Paraneoplastic hypereosinophilia associated with lung squamous cell carcinoma

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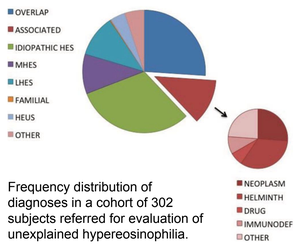
BACKGROUND

- Eosinophilia poses a unique diagnostic challenge due to association with a wide range of clinical presentations and underlying pathophysiology.
- Paraneoplastic syndromes represent an exceptionally rare cause for eosinophilia, though should be considered in association with solid tumors where infectious, parasitic, inflammatory, hematologic, and hypersensitivity evaluations are otherwise unrevealing.



Frequency distribution of diagnoses in a cohort of 302 subjects referred for evaluation of unexplained hypereosinophilia.

Adapted from Klion *et al*, Blood 2015.

CASE PRESENTATION

A 69 year old man with history of cardiovascular disease, type 2 diabetes, and tobacco use was admitted to the hospital after sustaining a fall while on Plavix. He also reported about one month of preceding right upper quadrant abdominal pain, weight loss, and fatigue with more recent altered mental status. Head imaging was unremarkable, however chest and abdominal imaging noted spiculated lung and innumerable liver lesions concerning for malignant process, with biopsy demonstrating primary squamous cell lung carcinoma (**A**) with extensive liver metastases (**B**) and PD-L1 expression <1%. During admission he developed intermittent fever and rigors with leukocytosis (WBC 44.8K/μL) and progressive eosinophilia (peak 5.9K/μL from ~2K/μL) as well as elevated absolute neutrophil, monocyte, and granulocyte counts without blasts. Quantitative lymphocyte subsets reflected normal absolute counts with elevated CD4:CD8 ratio (3.08). Additional infectious evaluation included negative bacterial, fungal, and AFB cultures; negative respiratory virus, HIV, and HSV PCR; negative fungal antigens and serologies; and negative parasitic serologies; with no culture growth from IR-guided aspiration of liver lesions. Further targeted evaluation of eosinophilia reflected negative ANCA and MPO/PR3, stable troponin, normal tryptase level, negative peripheral KIT D816V mutational and clonal TRG rearrangement analyses, and eosinophilia FISH panel without evidence of FIP1LI::PDGFRA gene fusion or PDGFRA/PDGFRB/FGFR1/JAK2 rearrangements.

EVALUATION & CLINICAL COURSE

Summary of laboratory evaluation:

Infectious:
- Serum culture, AFB PCR, Quantiferon, HIV antigen-antibody screen and PCR, HSV qPCR, Coxiella serology, cryptococcal antigen, galactomannan, fungitell, and fungal serology panel negative
- Urine histoplasma antigen, blastomyces antigen, Legionella pneumophila serogroup 1 antigen, and streptococcus pneumoniae antigen negative
- Sputum AFB culture and PCR negative

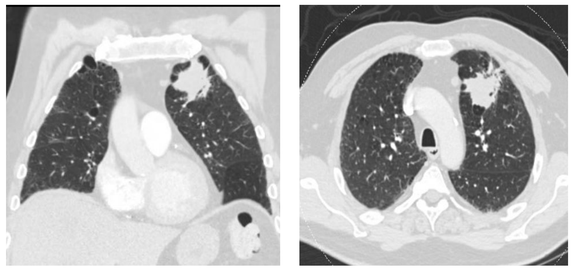
Parasitic:
- Serum Echinococcus serology, Strongyloides serology, and Toxocara serology negative
- Stool O&P negative

Immune/Inflammatory:
- Quantitative T/B/NK panel by flow cytometry normal except for elevated CD4:CD8 ratio of 3.08
- P-ANCA, C-ANCA negative

Hematologic:
- Tryptase 5.4 ng/mL (RR < 11.5 ng/mL)
- PCR for KIT c.2447A>T (D816V) mutation negative
- Monoclonal gammopathy evaluation negative
- FISH panel for the FIP1L1::PDGFRA gene fusion, or rearrangements of PDGFRA, PDGFRB, FGFR1, or JAK2 genes negative
- PCR for TCR rearrangement negative

Clinical course:
- Given negative laboratory evaluation, lack of rash or defining features of EGPA, and inconsistent temporal association with any specific medications, persistently rising eosinophil count was felt most likely secondary to underlying squamous cell carcinoma.
- Multidisciplinary discussion surrounding corticosteroid treatment was initiated in light of concurrent malignancy and septic presentation, though while infectious evaluation remained pending focus of care was ultimately transitioned to comfort so this had thus far been deferred.

A.



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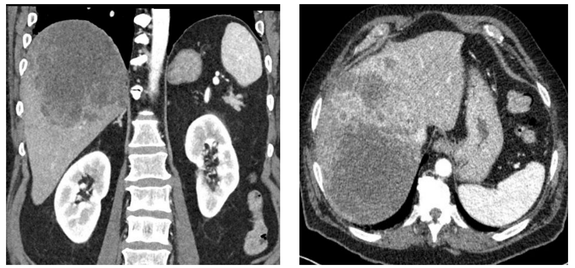

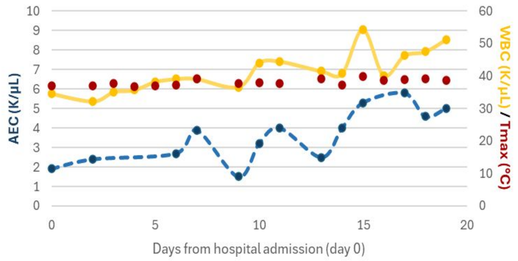

LITERATURE REVIEW

While pathophysiology of paraneoplastic eosinophilia is not well understood, some cases have reported increased serum and primary tumor intracellular IL-5 with resolution of eosinophilia following chemotherapy and/or tumor resection (Pandit *et al*, 2005), suggesting that tumor-associated cytokine production may drive eosinophil production in bone marrow. Pre-treatment paraneoplastic eosinophilia has been associated with more aggressive tumors, extensive metastases, and limited response to therapy in lung adenocarcinoma, together suggestive of overall worse outcomes (Pereira *et al*, 2024; Wehbe *et al*, 2021). This has prompted investigation into eosinophilia as a prognostic marker within this setting, though predictive value is controversial as some studies have also observed positive correlation to outcomes, in particular following immune checkpoint inhibitor initiation (Takeuchi *et al*, 2024).

DISCUSSION

- This case represents a rare but recognized phenomenon among the literature, particularly associated with carcinomas arising from mucin-secreting epithelium such as that found in the bronchus and gastrointestinal tract, which should be considered among the differential for eosinophilia and may portend more aggressive or advanced disease.
- This phenomenon should also be considered following treatment initiation in order to differentiate paraneoplastic syndromes from drug reactions, which may limit definitive therapy for malignancy.
- Conclusions regarding diagnostic and prognostic utility have been limited by relative rarity, and would benefit from continued case reporting and dedicated systematic review.

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