Journal of Rare Diseases and Orphan Drugs, V3, 2022

Case Report

A FOUR-YEAR-OLD WITH SEVERE IDIOPATHIC HYPEREOSINOPHILIA

Maha Taranish*, Laveena Sehgal, Samer Zaid-Kaylani, Smitha Bhaskaran

Author information: Department of Pediatrics, Texas Tech University Health Sciences Center, Amarillo, Texas, USA

Received: 02-11-2022; Accepted: 06-05-2022; Published: 06-08-2022.

Abstract: Background: Eosinophils are granulocytes that have a role in allergy and immune defense reactions. They represent a small percentage of circulating WBCs and marked increases in their numbers can cause significant detrimental effects. Hypereosinophilia can be allergic, inflammatory, infectious, or malignant in origin. Hypereosinophilic syndrome is an uncommon disorder of eosinophils that can cause significant end-organ damage (Chen YY, Khoury P, Ware JM, et al.)

Case presentation: A 4-year-old female presented with fever and abdominal pain and was found to have cervical and axillary lymphadenopathy spontaneously resolved and with an incidental finding of hypereosinophilia. The patient had an extensive workup, which was negative for common allergic, infectious, inflammatory, and neoplastic etiologies. She continued to show clinical and laboratory improvement and was discharged with the diagnosis of the idiopathic hypereosinophilic syndrome after the exclusion of other etiologies. Her follow-up after discharge showed improvement in eosinophil counts, and she is still being monitored. Given the lack of clear etiology and end-organ damage, she meets the definition of hypereosinophilia of undetermined significance. However, a gastroenterology workup is still considered as future symptoms evolve.

Conclusion: Hypereosinophilia is a relatively uncommon disorder in the pediatric population that could be asymptomatic and discovered incidentally through laboratory workup; however, if it goes unrecognized, it can cause significant morbidity secondary to end-organ damage.

Keywords: absolute eosinophil count, eosinophilia, hypereosinophilic syndrome.

CASE PRESENTATION The patient is a 4-year-old female with no significant past medical history who presented for evaluation for a fever that began around 18 days before admission to the pediatric ward. Before her presentation to the hospital, the temperature ranged from 101-102F daily, with a maximum of 104.9 F. The patient additionally had a sore throat before the presentation that began with the onset of the fever. The sore throat resolved within a week of onset, but the patient was given at least six days of amoxicillin due to her symptoms. The patient was prescribed amoxicillin by her PCP during the first week of her illness when she had a sore throat; although the streptococcal test came out negative, she received at least six days of amoxicillin and did not complete the 10-day course prescribed.

She additionally tested negative for Influenza and COVID-19 during that time. The patient was also noted around her paternal grandfather's farm, which had wild dogs, pigs, and a sick turtle. CBC on admission showed WBC of 20 x10e3/mcL with auto-differential showing 26.9% neutrophils, 16.9% lymphocytes, and 53.1% eosinophils.

Her eosinophils rose rapidly throughout her illness, as her CBC six days prior showed eosinophils at 21% of white blood cells (2.54x10e3/mcL). Her peripheral blood smear showed eosinophilia, mega-platelets, potential lymphoblasts, and reactive lymphocytes (Figure 1, 2A and 2 B). Her physical examination was positive for cervical and axillary lymphadenopathy and anterior cervical lymph nodes that are non-tender and not fixed.

*Corresponding author: Maha Taranish MD, MPH, Department of pediatrics, School of Medicine, Texas Tech University Health Sciences Center, Amarillo, Texas, USA

Email: Maha.Taranish@ttuhsc.edu

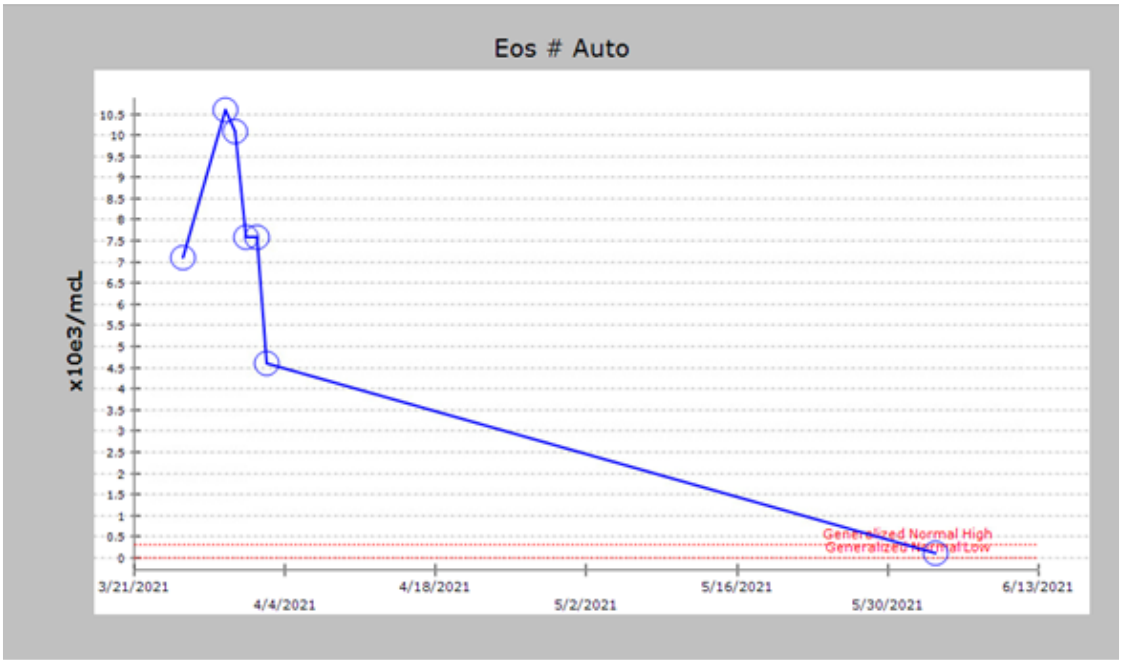

Figure1. Eosinophils count progress for the patient

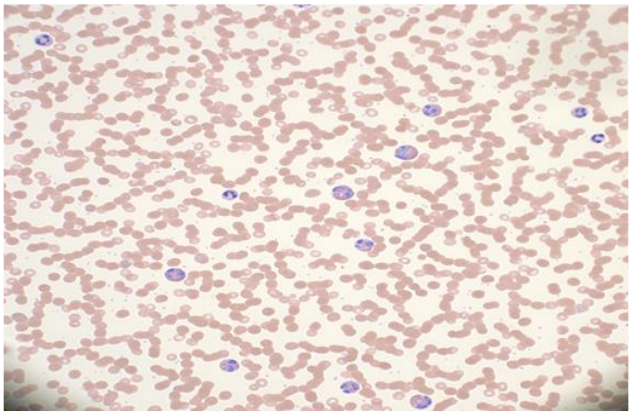

Figure 2 A. Peripheral blood smear from patient showing relative and absolute eosinophilia (53% and 7600 per microliter, respectively). No evidence of acute leukemia

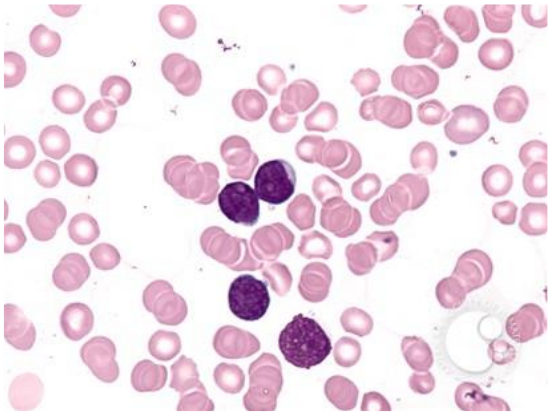

FIgure 2B. Peripheral smear from patient with Acute Lymphoblastic Leukemia (ALL - Peripheral Smear, 2022)

Enlarged non-tender, mobile, hard axillary nodes bilaterally measuring about 1.5 cm x 1 cm); Ultrasound of the head and soft neck tissue and the axilla showed multiple enlarged lymph nodes with normal architecture and vascularity, suggesting they were reactive. During the patient's hospital course, she had a fever of 102.4F the night of admission. Blood and fungal cultures were collected, and the patient was started on Cefepime and Tylenol per the hematologist's recommendations. During her hospital course, she underwent extensive workup for her eosinophilia to rule out malignancy and end-organ damage and investigate the etiology of her extensive eosinophilia. B12 was ordered to look for ALPS (Autoimmune Lymphoproliferative Syndrome), which was normal; HIV negative GI PCR, normal Saccharomyces Cerevisiae, negative Bartonella Henselae and Quintana IgG/IgM, anti-centromere/antichromatin/anti-DNA/anti-Jo 1/antiscleroderma- 70/RNP/Smith/Sjogren's anti-SS A and anti-SS B antibodies were all normal.

Cytogenetics was negative. The lymphocyte subset was negative. The patient had a CT chest/abdomen and pelvis with no obvious lesions seen for biopsy. The patient's bone marrow aspiration did not show obvious malignant cells (Figure 3 A and Figure 3 B, which shows bone marrow biopsy in acute leukemia). Throughout the patient's stay in the hospital, her eosinophil counts downtrend and was 38.9% of WBCs on day 5, the day of discharge. Her other labs also downtrend, with her final labs before discharge showing a WBC of 11.9x10e3/mcL, ESR of 69 mm/hour, and CRP of 17.20 mg/L. Upon being afebrile for 24 hours, the patient was discharged home with an outpatient follow-up scheduled with hematology. PDGFR gene testing was sent to check if the patient was a candidate for Imatinib therapy; however, the result was normal. A gastroenterologist assessed the patient after discharge, and the specialist did not believe there was an indication for endoscopy. Her fecal calprotectin, a noninvasive biomarker for intestinal inflammation, was initially elevated but normal after one week.

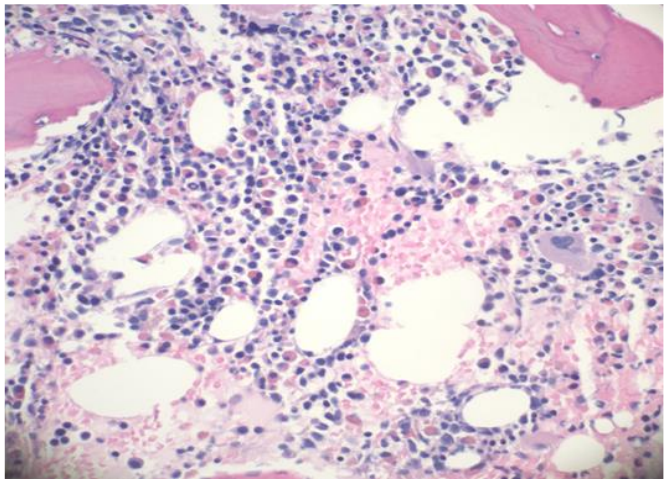

Figure 3 A. Bone marrow biopsy for the patient with no morphologic evidence of acute leukemia. There are increased eosinophils and eosinophil precursors throughout the marrow

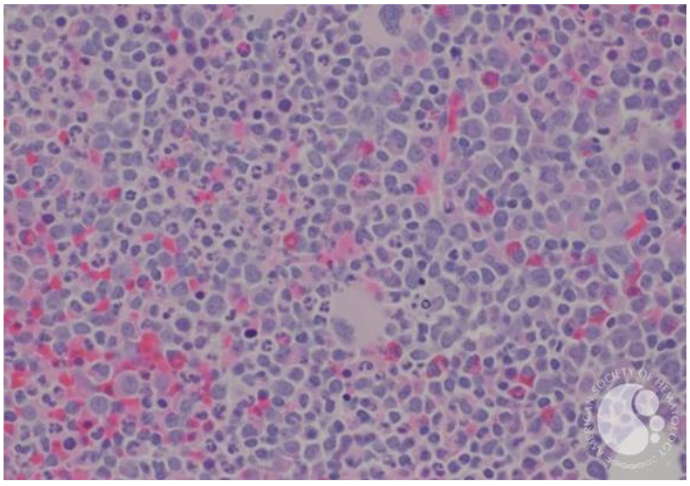

Figure 3 B: Comparison, Acute Myeloid Leukemia (Girish Venkataraman, 2022)

COURSE AFTER DISCHARGE The patient was seen within a week of her discharge in the hematology clinic and continues to follow up. She has done well since discharge. She has not had any fevers. Her mother mentions that she has been active, with no new symptoms except abdominal pain in the epigastric area. H. pylori test was sent for that, and it was negative. She has not had any nausea, vomiting, or hematochezia. Her eosinophil counts have continued to drop since discharge, with the last counts being normal. Her appetite has been stable, with a healthy increase. Mom reports that she has still complained of intermittent diffuse abdominal pain and bloating sensation but denies any diarrhea or constipation.

DISCUSSION Eosinophils are blood cells originating from CD34 positive hematopoietic cells in the bone marrow; several cytokines, predominantly IL-3, IL-5, and GM-CSF control their differentiation [1,2].

They have a half-life of hours (around 6-10 hours) in the peripheral blood and several weeks in tissues [3]. In addition to peripheral blood and bone marrow, eosinophils can be found in the spleen, lymph nodes, thymus, GI tract, and uterus. Eosinophils normally represent 3-5 % of the white blood cell count. They play a role in allergic reactions -particularly atopy, such as asthma and eosinophilic esophagitis -and body defense against helminthic infection. The number of circulating eosinophils is strictly regulated. A significant increase can cause adverse reactions, such as those seen in gastrointestinal eosinophilic conditions and severe inflammatory responses during helminthic infection [4-11].

In the peripheral blood, eosinophil counts typically range between 0.05 and 0.5 x 10^3/ml^3. Hypereosinophilia in the pediatric population has an incidence of 54.4 per 100,000 children annually; most affected patients are less than one

year or 6 to 11 years old [9]. Blood eosinophilia is defined as eosinophil count > 0.5 x 10^3/ml^3.

Based on severity, eosinophilia can be classified into mild eosinophilia with an absolute eosinophil count of 500-1500/ml^3, Marked eosinophilia with AEC 1500-500/ml^3, and massive eosinophilia with AEC more than 5000/ml^3. The term hypereosinophilia is used when marked, or persistent eosinophilia has been documented (AEC >1.5 × 10^9/L blood on two occasions ≥1 month apart) and/or marked tissue eosinophilia is observed [1]. According to The Year 2011 Working Conference on Eosinophil Disorders and Syndromes, tissue hypereosinophilia applies when one or more of the following criteria is met: (1) Eosinophils percentage is more than 20% of all nucleated cells in bone marrow sections ; (2) tissue infiltration by eosinophils is massively based on pathologist review compared with other inflammatory cells, or (3) extensive extracellular disposition of eosinophils indicated by a stain specific for an eosinophil granule protein such as MBP (major basic protein) reveals extensive extracellular deposition of eosinophil-derived proteins indicative of local eosinophil activation [1].

Another term used in the categorization of the severity of eosinophilia is Hypereosinophilic syndrome which requires all of the following three criteria: (1) blood eosinophilia, (2) Hypereosinophilia-related end-organ damage, and (3) absence of an alternative explanation for the end-organ damage.

Our patient meets the definition of hypereosinophilia since she had an AEC of more than 1500/ml^3 on two separate occasions with a ≥ 4 weeks interval. However, she does not fulfill the criteria for diagnosis of HES given her lack of end-organ damage.

The aim of the extensive workup the patient had was to rule out serious etiologies such as malignancies, exclude end-organ damage, and identify the etiology of her eosinophilia.

When dealing with significant hypereosinophilia, we need to consider categories of etiologies. Based on the clinical picture and etiology, hypereosinophilia (HE) can be classified into [1]: 1. Hereditary/familial HE: There is familial clustering of cases, and pathogenesis is unknown. 2. Primary/neoplastic HE: in which there is underlying neoplasm. 3. Secondary/reactive HE: in which HE is usually cytokine driven. Common causes or reactive HE includes atopic diseases, helminthic infections, and drug reactions. 4. Hypereosinophilia of undetermined significance: in this category of hypereosinophilia, patients have no hereditary, reactive, or malignant process, and no evidence of end-organ damage is identified.

Based on this classification of etiologies, our patient likely falls in the category of hypereosinophilia of undetermined significance given no underlying cause of her HE was identified, lack of positive family history, no evidence of neoplasm or reactive (infectious or inflammatory) process, and no end-organ damage secondary to HE was recognized.

Our patient continued to show improving eosinophil counts, as demonstrated in the curve above. Most infectious, inflammatory, and neoplastic etiologies have been excluded through the extensive workup done during her hospital admission. The only diagnosis that is still not completely excluded is gastrointestinal eosinophilic disorders, although less likely given the lack of convincing clinical symptoms, which made gastroenterologists defer endoscopy. The patient is still following up with the hematologist.

CONCLUSION Although uncommon in the pediatric population, HE syndrome should be considered in differentials of HE of unknown etiology due to potential organ damage. Children with hypereosinophilia need evaluation to rule out end-organ damage, which may require treatment, especially with many patients who have had a subtle clinical course. In addition, secondary causes of hypereosinophilia need to be ruled out, as many of those can be treated. It is critical to investigate these cases to confirm that the origin of HE is not malignant. More research is needed to classify eosinophilia further and define etiologies for HE with unknown etiologies. Patients like our patient, with unknown etiology, will need to be followed outpatient to monitor for possible complications of hypereosinophilia.

Disclosure:
The author declares no conflicts of interest.

REFERENCES

1.Valent P, Klion AD, Horny H-P, *et al.* Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. The Journal of Allergy and Clinical Immunology, 2012, 130(3), 607-612.e9. doi.org/10.1016/j.jaci.2012.02.019

2. Lanzkowsky, P., Lipton, J. M., & Fish, J. D. Lanzkowsky's manual of pediatric hematology and oncology. Academic Press Is An Imprint Of Elsevier; 2016.
3. Simon HU, Yousefi S, Germic N, *et al*. The Cellular Functions of Eosinophils: Collegium Internationale Allergologicum (CIA) Update 2020. International archives of allergy and immunology, 2020; 181(1), 11–23. doi.org/10.1159/000504847
4. Burris D, Rosenberg CE, Schwartz JT*, et al*. Pediatric hypereosinophilia: Characteristics, clinical manifestations, and diagnoses. J Allergy Clin Immunol Pract. 2019; 7(8):2750-2758.e2. doi: 10.1016/j.jaip.2019.05.011
5. Schwartz JT, Fulkerson PC. An Approach to the Evaluation of Persistent Hypereosinophilia in Pediatric Patients. Front Immunol. 2018; 9:1944.doi.org/10.3389/fimmu.2018.01944
6. Wagelie-Steffen, A., Aceves SS. Eosinophilic disorders in children. Current Allergy and Asthma Reports, 2006; 6(6), 475–482. doi.org/10.1007/s11882-006-0024-5
7. Khoury P, Makiya M, Klion AD. Clinical and Biological Markers in Hypereosinophilic Syndromes. Frontiers in Medicine, 2017; 4, 240. doi.org/10.3389/fmed.2017.00240
8. Burris D, Rosenberg CE, Schwartz JT, *et al*. Pediatric Hypereosinophilia: Characteristics, Clinical Manifestations, and Diagnoses. J Allergy Clin Immunol Pract. 2019;7(8):2750-2758.e2. doi: 10.1016/j.jaip.2019.05.011.
9. Rosenwasser LJ. Approach to patients with eosinophilia. Mo Med. 2011;108(5):358-360.
10. ALL - Peripheral Smear. imagebank.hematology.org. Accessed May 31, 2022. https://imagebank.hematology.org/imageset/362/all--peripheral-smear
11. Girish Venkataraman, M., 2022. *Bone marrow biopsy*. [online] Imagebank.hematology.org. Available at: <https://imagebank.hematology.org/image/63909/bone-marrow-biopsy> [Accessed 31 May 2022].