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Eosinophilia and Increased Immunoglobulin E: Is It Really a Primary Immunodeficiency? A Diagnostic Challenge

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Eosinophilia is a common entity in routine practice and is defined as an absolute eosinophil count greater than 500/mm^3 in peripheral blood. Hypereosinophilia is defined as the presence of total eosinophil count >1500/mm^3 and/or evidence of hypereosinophilia in tissues in 2 measurements 1 month apart in peripheral blood.[1] Hereditary eosinophilia syndrome is one of the genetic disorders that fall under the category of primary eosinophilia. The development of secondary eosinophilia occurs most commonly in response to a specific etiology. The potential causes of secondary eosinophilia may include infectious diseases, atopy, rheumatologic disorders, respiratory system disorders, malignancies, drugs, gastrointestinal disorders, lymphocytic disorders, and immunodeficiencies.[2] In this report, primary immunodeficiency was considered in the first stage and referred to our center for diagnosis; this study aims to address the differential diagnosis of hypereosinophilia and increased immunoglobulin E (IgE) in a 3-month-old female pediatric patient presenting with pneumonia, hypereosinophilia, diffuse seborrheic dermatitis, and cytomegalovirus (CMV) viremia.

When the patient was 1.5 months old, she first developed crusted sores with rash and swollen skin; therefore, she was admitted to a secondary healthcare center. Considering atopic dermatitis, recommendations were given in line with this diagnosis. As the lesions exacerbated a month later and the patient became agitated, she was re-admitted to the hospital. Her bloodwork revealed a total eosinophil count of 800/mm^3, while her immunoglobulin G, A, and M levels were within the normal range for her age and her IgE level was 2500 IU/mL (0-64). She also exhibited eosinophilia and elevated IgE levels in addition to skin lesions. Initial considerations included primary immunodeficiency and food allergy. With these prediagnoses, the patient was referred to the pediatric immunology department of our hospital (Figure 1A and 1B).

The patient was 3 months old at the time of her initial admission to our facility. She presented with seborrheic dermatitis on the scalp and diffuse erythematous crusted skin lesions. The patient's physical examination revealed that her height was in the 10-25th percentile, her head circumference was below the 3rd percentile, and her body weight was in the 3rd-10th percentile. Other systemic examinations were normal. It was learned from her personal history that she was previously admitted to a hospital's neonatal intensive care unit, stayed 10 days there, and was treated for congenital pneumonia. Her family history revealed that her parents were second-degree relatives. Moreover, her paternal uncle's 2 daughters both died of unknown causes before 1 year of age. The patient was referred to our dermatology department, where she was diagnosed with atopic dermatitis. Topical steroids were administered to her along with recommendations for moisturizing. Her laboratory studies performed at our facility revealed an eosinophil count of 16 030/mm^3 and a white cell count of 43 100/mm^3. Other parameters were within the normal range. The analysis of the blood smear showed no abnormal cells. Total IgE was 2038 IU/mL. Cytomegalovirus was studied by polymerase chain reaction assay, the result of which was reported as 1.323 copies. Cytomegalovirus was studied in the milk of the patient's mother and it was negative. Cytomegalovirus viremia was treated with foscarnet. Cytomegalovirus copy number regressed under foscarnet treatment,

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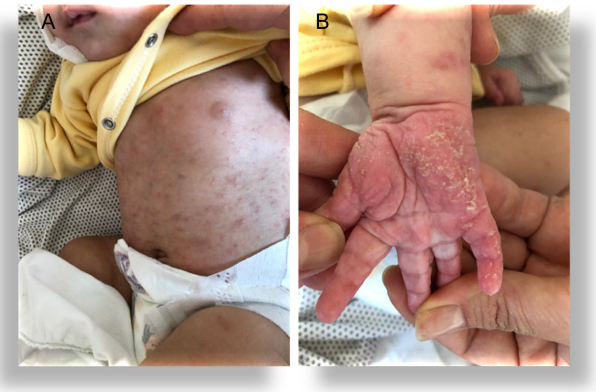

Figure 1. The first lesions of our patient at the time of admission to our hospital. Atopic dermatitis treatment was given to the patient and the patient was called for control.

Figure 2. The patient's last condition at the follow-up. (A) The patient was 6 months old. (B) The patient was 11 months old.

and CMV copy number became negative in the first month of treatment. Her chest x-ray showed a thymus shadow. She was given ampicillin sulbactam after the blood culture studied in another center tested positive for *Staphylococcus aureus*. However, her thoracic tomography revealed consolidation areas on the upper lobe and lower lobe superior segment of the right lung along with atelectasis, and dependent ground-glass opacities on the posterior parts of both lungs, after which the treatment was switched to piperacillin-tazobactam. It was thought that the infiltrative appearance detected in the chest x-ray and computed tomography of the patient might be due to CMV pneumonia; however, it was stated by the pediatric radiologist that this appearance is not typical for CMV pneumonia.

Our initial diagnosis was primary immunodeficiency; however, the results of her lymphocyte subgroup panel were normal. The estimated score for the hyper IgE syndrome was 28, while DOCK-8 expression was normal. She was given a hypoallergenic formula when her milk-specific IgE was found to be 2+. Her stool microscopy and parasite examinations were reported as normal. No sign consistent with Langerhans cell histiocytosis was noted on her skin biopsy. Despite being referred to our center with a pre-diagnosis of primary immunodeficiency, the causes of secondary hypereosinophilia were investigated upon these initial test results. The patient underwent bone marrow aspiration, which revealed no infiltrative pathology. Her cardiac assessment also revealed no pathology other than an increase in trabeculation in the apical part of the right ventricle. Her abdominal ultrasound examination was insignificant.

When topical steroid treatment prescribed for skin rash during her admission was discontinued, the patient's rash recurred. Our dermatology department reassessed the patient and sillions were identified in her palms and on her back. Based on these findings, sulfur-containing creams were prescribed to the patient and her family, considering a pre-diagnosis of scabies. The patient's skin lesions regressed after using the treatment for a month. Her follow-up complete blood count analysis showed a decrease in total eosinophil count to 1030/mm^3 and in IgE level to 74.2 IU/mL (Figure 2A and 2B). In the follow-up, the rash regressed after scabies treatment, the CMV copy number became negative, pneumonia disappeared, and the patient was discharged. No genetic disorder was detected as a result of the genetic evaluation sent to an external center in terms of primary immunodeficiencies that may accompany it. In the follow-ups after discharge, it was observed that the patient's growth and development were compatible with those of his peers. The microcephaly of the patient, whose head circumference growth was regular, improved, and the last percentile of head circumference was measured as 25-50th percentile.

The causes of secondary hypereosinophilia may include oncological, pulmonary, dermatological, and gastrointestinal disorders as well as fungal, bacterial, parasitic, viral infections, hyper IgE syndrome, and primary immunodeficiencies such as T cell immunodeficiency. As of 2022, over 450 gene deficiencies have been classified under 10 categories, where numbers are constantly increasing. The range of inborn errors of immunity varies considerably, from mild infections to serious multisystemic diseases.[3] One of the well-known causes of eosinophilia is parasitic infections.[4,5] As in our patient, scabies, a parasitic infestation caused by *Sarcoptes scabiei* var. hominis, should be kept in mind when investigating the etiology of secondary hypereosinophilia in patients presenting with atypical skin rash. Krüger et al[6] reported a case of scabies infection in a 2-month-old infant who presented with hypereosinophilia, elevated levels of total immunoglobulin, eczema, and recurrent skin abscesses and was diagnosed after necessary tests.[6] The limitations of the diagnosis were that the rash of the patient was not compatible with scabies at the first admission and that the laboratory facilities of the first hospital were not developed enough to make a differential diagnosis.

In conclusion, parasitic infections especially scabies should absolutely be kept in mind in patients presenting with hypereosinophilia and increased levels of IgE, even though such patients might have atypical clinical findings.

Informed Consent: Verbal and written consent was obtained from the family for the use of the patient's photographs.

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