

CASE REPORT

Hypereosinophilia in an infant – case report. The role of eosinophils in selected diseases

Anna Góra¹, Majka Jaszczura¹, Małgorzata Morawiecka-Pietrzak¹, Renata Tomaszewska²,
Edyta Machura¹

¹Department of Paediatrics, School of Medicine with the Division of Dentistry in Zabrze, Medical University of Silesia, Zabrze, Poland

²Department of Paediatric Haematology and Oncology, School of Medicine with the Division of Dentistry in Zabrze, Medical University of Silesia, Zabrze, Poland

ABSTRACT

Eosinophilia is a condition in which the number of eosinophils in the peripheral blood or tissues increases above the normal level. Threshold values for eosinophilia change with age, remaining the highest in infants and young children. Hypereosinophilia is rare and requires detailed diagnosis. The causes of eosinophilia vary. The literature distinguishes its primary form – associated with bone marrow proliferative diseases, and the condition secondary to many diseases, most commonly parasitic infections and allergic reactions. The secondary form of eosinophilia is most frequent in children. Chronic activation of eosinophils can lead to fibrosis and thrombotic changes in tissues affected by infiltration. In the paediatric population, contrary to adults, these pathological processes are more common in the gastrointestinal tract. Hypereosinophilia is rare in infants, which favours diagnostic and therapeutic concerns. In this paper, we present a case of a 10-month-old infant with hypereosinophilia coexisting with lambliosis and food intolerance.

KEY WORDS:

children, allergy, eosinophilia, giardiasis.

INTRODUCTION

Eosinophilia is defined as an increase in the absolute eosinophil count (AEC) in the peripheral blood or tissues above the accepted normal values [1, 2]. We can distinguish mild eosinophilia (AEC within 500–1500 cells/ μ l), moderate (AEC 1500–5000 cells/ μ l), and severe (AEC > 5000 cells/ μ l) [2].

Threshold values of the number of eosinophils change with age, and they are higher in infants and young children [2]. In children, mild eosinophilia (AEC 500–1500

cells/ μ l) is observed relatively frequently, while hypereosinophilia (HE) (AEC \geq 1500 cells/ μ l) is rare and requires careful diagnosis [2, 3]. The aetiology of HE is varied. The increase in the number of eosinophils present in the blood and tissues has been observed primarily in bone marrow proliferative diseases and, as a secondary form, in the course of many disease conditions, including most commonly parasitic infections and allergic diseases [1, 3, 4]. Children most frequently demonstrate secondary HE [2].

HE diagnosis in an infant is related to the necessity to carry out wide testing allowing for the exclusion of co-

ADDRESS FOR CORRESPONDENCE:

Anna Góra, Department of Paediatrics, School of Medicine with the Division of Dentistry in Zabrze, Medical University of Silesia, 13–15 3 Maja St., 41-800 Zabrze, Poland, ORCID: 0000-0002-6294-6147, e-mail: a.szczepanek@o2.pl

existing diseases and organ changes, which often poses a great challenge. Below, we present a case of a 10-month-old infant with HE, coexisting parasitic infestation, and suspected food intolerance.

CASE REPORT

A 10-month-old boy was admitted to the General Paediatric Department (first pregnancy complicated by arterial hypertension, delivery by caesarean section in 39 Hbd with a body weight of 3,170 g, Apgar score 9/10) with normal psychomotor development, not burdened by family history, vaccinated according to the vaccination program, and no foreign trips. The hospitalisation was implemented due to intensive vomiting with stomach content, occurring 3–5 times a day for the preceding 7 days, and leukocytosis with eosinophilia. In addition, for about three months the boy had loose stools 2–3 times per day, without any pathological admixtures. There was no fever, no symptoms of acute respiratory infection, changes in behaviour, or food intake, and no new additional foods were introduced during the intensification of symptoms. Physical examination did not reveal any abnormalities. The body weight of the boy on admission was 9,900 g (75th centile), body length 74 cm (75th centile). In outpatient testing, on the day before admission, leukocytosis was diagnosed with a white blood cell count of 33,000/ μ l (norm 6000–14,000/ μ l).

In laboratory tests carried out during hospitalisation, the following deviations from the norm were found: leukocytosis – 43,730/ μ l (norm 6000–14,000/ μ l) with the predominance of eosinophils in differential blood count – 47% (norm 1–5%), absolute eosinophilia – 2236 cells/ μ l (norm 80–400 cells/ μ l), high concentration of total IgE – 117 IU/ml (norm 1.3–14.9 IU/ml), and increased fibrinogen levels – 650 mg/dl (norm 200–400 mg/dl).

Examination of faeces for latent blood was positive, and no rotavirus, adenovirus, or norovirus antigens were found in the material. On the 3rd day of hospitalisation, parasitological examinations were performed, detecting numerous lamblia cysts in the faeces, which was confirmed by the ELISA enzyme immunoassay. The parents underwent coproscopic examination, confirming a massive lamblia infection in the child's father. Routine and additional diagnostic examinations were performed: CRP, ESR, ionogram, glycaemia, gasometry, AST, ALT, creatinine, urea, uric acid, LDH, amylase, GGTP, bilirubin, LDH, IgA, IgG, IgM, urinalysis, chest X-ray, and X-ray examination of the abdominal cavity – they all revealed standard values. An abdominal ultrasound examination revealed enlargement of the pyelocaliceal systems of the left kidney up to 3 mm in the AP dimension, otherwise the organ image was normal. In view of the diagnostic doubts and potential organ complications associated with HE, an aspiration biopsy of the bone marrow was performed. Evaluation of myelogram and immunophe-

notyping allowed exclusion of bone marrow proliferative diseases. Based on an MRI of the head, the presence of eosinophilic infiltrates in the brain was excluded. Serological tests for toxocarosis and ascariasis were negative. No specific reagins were found against inhalation and food allergens (norm < 0.35 kU/l).

The oral supply of metronidazole was used therapeutically, but the infant required a change to the parenteral form due to symptoms of oral intolerance. Pharmacotherapy was carried out for a total of 7 days. Nutrition was introduced only on the basis of an elemental formula.

As a result of the treatment, episodes of vomiting and normalisation of stool consistency were observed. In laboratory tests, a gradual decrease in the number of leukocytes to 7,800/ μ l and in the percentage of eosinophils in differential blood count to 6% was noted. Control of faeces for the presence of parasites, lamblia antigen, and latent blood gave negative results. The infant, in a good condition and with an adequate weight gain, was discharged for further outpatient care with the recommendation of feeding with an elemental formula.

On the 14th day after the end of hospitalisation, a complete blood count was performed with the result within standard limits for the age. In differential blood count after one month and after two months from the end of hospitalisation, the percentage of eosinophilia increased to 22%, followed by a decrease to 6%. Decreases in total IgE to 58.21 IU/ml were also reported (norm 1.7–22.7 IU/ml). It was recommended that the basic diet be reinstated. Currently, the boy is under the constant care of gastrological and allergological counselling.

DISCUSSION

As yet, HE in the paediatric population has not been fully characterised [5]. According to the conventional division, HE is distinguished by primary and secondary (reactive) forms – occurring in response to many disease conditions [4]. The primary form of HE in children is rare and is associated with proliferative diseases such as chronic eosinophilic leukaemia, myeloid leukaemia, mastocytic leukaemia, myelodysplastic syndromes, and systemic mastocytosis [1, 2]. Differential diagnosis of secondary eosinophilia includes the following: allergic reactions, metabolic diseases (e.g. adrenocortical insufficiency), connective tissue disorders, primary immunodeficiency diseases, pulmonary eosinophils (e.g. Churg-Strauss syndrome), eosinophils of the gastrointestinal tract, aspergillosis, autoimmune bullous dermatoses, paraneoplastic syndromes, and drug reactions [3–5]. It is also important to exclude the presence of an HE lymphocyte variant associated with the occurrence of clonal T lymphocytes and familial eosinophilia genetically determined [3, 4]. Contrary to adults, in the paediatric population primary immunodeficiency is a more frequent cause of secondary eosinophilia [5]. Severe eosinophilia may be associated with the follow-

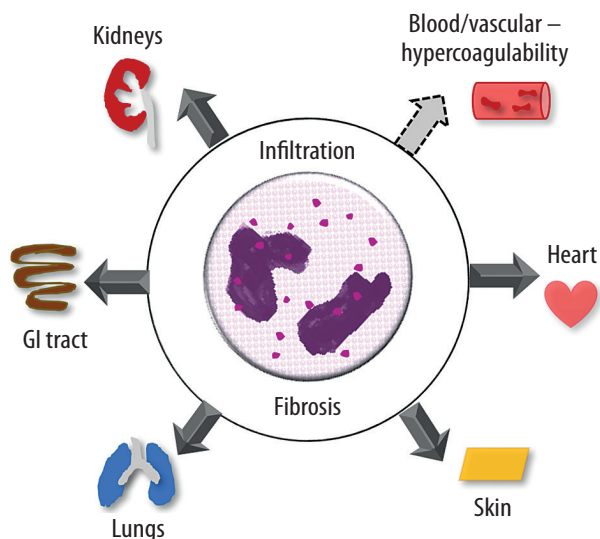


FIGURE 1. Eosinophilic infiltrates can occur in most tissues and organs. The action of stimulated eosinophils through fibrosis and blood clotting disorders can lead to organ damage (based on [10])

ing primary immunodeficiencies: Job syndrome, Omenn syndrome, Wiskott-Aldrich syndrome, Comel-Netherton syndrome, Kostmann disease, DOCK8 deficiency, PGM3 deficiency, ADA-SCID, autoimmune lymphoproliferative syndrome, and immunodysregulation polyendocrinopathy enteropathy X-linked syndrome [6, 7]. In some cases, the cause of the lesions cannot be determined, which leads to the diagnosis of the idiopathic form [4].

Diagnosis of eosinophilia in children, due to its usual secondary character, consists of the recognition of the underlying disease. It is suggested routine complete blood count be performed with differential, ESR, CRP, hepatic tests, vitamin B12 concentration, tryptase, troponins, urinalysis, faecal culture, parasitological tests (coproscopic assessment, immunoenzymatic testing), and imaging studies for organ changes depending on medical history and physical examination. After excluding secondary causes, the diagnosis should be made for clonal eosinophilia, including bone marrow biopsy with an immunophenotyping, morphological and cytogenetic evaluation [2, 3]. The treatment of secondary eosinophilia consists of the elimination of the disease that underlies the change. In some cases, glucocorticosteroids are an essential part of the therapy [3, 4].

Eosinophils play an important role in the functioning of the immune system, as well as tissue regeneration and remodelling processes [2]. These cells have specific mechanisms of degranulation associated with the creation of a network – the so-called eosinophil extracellular traps (EET), which may be important in the pathogen immune response [8, 9]. Stimulated eosinophils release inflammatory mediators and procoagulants, which may lead to the development of thrombotic processes and tissue fibrosis [1, 3, 5]. Elevated fibrinogen levels, fibrin degradation products, and thrombocytosis are observed in patients with eosinophilia [10], which also occurred in

our patient. Organ damage, depending on the location of eosinophilic infiltration, most often affects the skin, circulatory system, respiratory system, gastrointestinal tract, and nervous system [11] (Fig. 1).

The clinical picture of HE in both groups is similar, with adults being dominated by respiratory symptoms (with the exception of bronchial asthma). Children are more likely to reveal symptoms of the gastrointestinal tract [5]. It is well known that the increase in the percentage of eosinophilia is related to the tissue invasion of parasites [4, 12]. This refers especially to helminths, including of strongyloidiasis, schistosomiasis, filariasis, ascariasis, trichinosis, and toxocariasis. Eosinophilia may also occur due to the action of other parasites, such as scabies [2, 4]. Protozoa such as *Giardia lamblia*, *Cryptosporidium*, or *Entamoeba* usually do not evoke this kind of response [2]. However, it is worth noting that individual cases of giardiasis with HE have been described [13–15].

Giardiasis is common both in developing as well as in highly developed countries [12, 16–18]. The infestation may occur as a result of direct contact with a person infected with *Giardia lamblia* (faecal-oral route, sexual contact), contact with a sick animal, or in case of consumption of contaminated water or food [14, 17, 19]. The incidence of giardiasis in Poland in 2017 was estimated at 3.2/100,000 inhabitants. In the indicated period, almost 25% of cases of the disease concerned children under the age of four years, while 0.9% of patients were children under one year of age [20].

The course of the disease is accompanied by enterocyte apoptosis and intestinal barrier disruption, which leads to disturbances of intestinal microbiota, disappearance of microvilli, and development of inflammatory reaction [21]. The consequence of the mentioned changes may be disturbances of intestinal absorption, which in turn leads to malnutrition [12]. The clinical picture of giardiasis varies [14, 22]. The most common symptoms include diarrhoea, abdominal pain, abdominal distension, weakness, loss of appetite, and weight loss, while vomiting and fever are less common [12, 19, 22]. The early period of the disease is accompanied by gushing stools, usually without bloody admixtures. Ailments may increase after eating foods rich in lactose [19]. Two-thirds of infected patients are estimated to have asymptomatic giardiasis [14, 23].

Diagnosis of giardiasis is based on clinical symptoms and additional tests consisting in microscopic examination of stool specimens for the presence of eggs, cysts, and trophozoites, and based on immunoenzymatic methods confirming the presence of lamblia antigen [19, 22, 24, 25].

First-line treatment of giardiasis includes metronidazole [23] administered in the following doses: adults and children over 10 years of age – 2000 mg daily for 3 days or 500 mg twice daily for 7 to 10 days; children from 7 to 10 years old – 1000 mg once daily for 3 days; children from 3 to 7 years old – from 600 mg to 800 mg

once daily for 3 days; and children from 1 year to 3 years old – 500 mg once daily for 3 days (alternative dosage is from 15 to 40 mg/kg daily divided into 2–3 doses) [26]. Tinidazole (50 mg/kg – single dose) can also be used in treatment. Second-line agents such as benzimidazoles (albendazole, mebendazole), nitazoxanide, furazolidone, paromomycin, or quinacrine are less commonly used [22, 23]. Tinidazole and albendazole have similar efficacy to metronidazole [23]. Although previous studies suggest high efficacy of azithromycin in the treatment of giardiasis, current reports do not confirm this [22, 27, 28].

Secondary eosinophilia develops as a result of a reaction dependent on the action of inflammatory cytokines, including IL-3, IL-5, and GM-CSF, which can indirectly lead to an increase in total IgE concentration [2–4]. Importantly, the population of children with giardiasis, in contrast to healthy controls, demonstrates higher levels of total IgE in serum and a tendency for an increased IgE-mediated response to common allergens. It is suspected that this condition combined with abnormal exposure to antigens in the diseased small intestine and mast cell proliferation may contribute to the development of allergic diseases [18]. It is worth mentioning that in developed countries, secondary eosinophilia accounts for patients with allergic reactions in up to 80% of cases [4]. At the same time, it is estimated that food allergy occurs in as many as 15–20% of infants and young children [29]. The development of food allergy in this group is largely related to the immaturity and permeability of the intestinal barrier [29]. Although the methods of food allergy diagnostics are constantly improving, the final diagnosis requires a test of elimination and provocation with the allergen with the subsequent clinical evaluation of the patient [30].

Gastrointestinal symptoms of food intolerance are highly diverse due to their mechanism. The course of IgE-dependent allergy may be accompanied by discomfort in the mouth, itching of the mouth and tongue, nausea, vomiting, diarrhoea, and spasmic abdominal pain. Bloody stools, malabsorption, malnutrition, constipation, and stunted development speak for the diagnosis of IgE-independent food allergy [29].

IgE-independent food allergy mechanisms may manifest themselves in the form of many disease, e.g. atopic dermatitis, food protein-induced enterocolitis syndrome, eosinophilic gastrointestinal disorders (EGID), or celiac disease [29].

Peripheral eosinophilia affects approximately 50% of patients with EGID [29]. This is a group of diseases in which eosinophil infiltrates are found in the gastrointestinal tract wall with no other known causes of tissue eosinophilia [31]. Eosinophilic enteritis is supposed to be more common in children than in adults [5]. The aetiology of EGID and its relationship to food allergy have not been clearly established until now [29]. Depending on the location, the clinical manifestation is varied;

when the mucosa of the stomach and small intestine is involved, vomiting, diarrhoea, abdominal pain, iron-deficiency anaemia, bleeding from the gastrointestinal tract, enteropathy with protein loss, growth disorders, weight loss, and in extreme cases malnutrition are observed [31]. Diagnosis is based on histopathological examination of the gastrointestinal wall biopsy [29]. EGID therapy is carried out by eliminating the allergen and local or systemic supply of glucocorticoids [31]. Imaging and laboratory diagnostics in connection with clinical data allowed the exclusion of the majority of diseases with secondary eosinophilia and the presence of bone marrow proliferative diseases. Bearing in mind the non-specific gastrointestinal symptoms present in the infant and the considerable variation in the mechanisms of food hypersensitivity, it is difficult to determine the cause of eosinophilia in this case. It is worth emphasising the presence of a potential relationship between the onset of giardiasis and the development of food hypersensitivity reactions in the infant.

CONCLUSIONS

The diagnosis of a disease with accompanying eosinophilia is a big challenge for the paediatrician. Eosinophilia in an infant requires careful and detailed diagnosis. Parasitic infections and allergic diseases are important elements of differentiation among many causes of eosinophilia.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Wang SA. The Diagnostic Work-Up of Hypereosinophilia. *Pathobiol* 2019; 86: 39-52.
2. Schwartz JT, Fulkerson PC. An Approach to the Evaluation of Persistent Hypereosinophilia in Pediatric Patients. *Front Immunol* 2018; 9: 1944.
3. Gotlib J. World Health Organization-defined eosinophilic disorders: 2017 update on diagnosis, risk stratification and management. *Am J Hematol* 2017; 92: 1243-1259.
4. Montgomery ND, Dunphy CH, Mooberry M, et al. Diagnostic Complexities of Eosinophilia. *Arch Pathol Lab Med* 2013; 137: 259-269.
5. Williams KW, Ware JA, Abiodun A, et al. Hypereosinophilia in children and adults: a retrospective comparison. *J Allergy Clin Immunol Pr* 2016; 4: 941-947.
6. Navabi B, Upton JE. Primary immunodeficiencies associated with eosinophilia. *Allergy Asthma Clin Immunol* 2016; 12: 27.
7. Williams KW, Milner JD, Freeman AF. Eosinophilia Associated with Disorders of Immune Deficiency or Immune Dysregulation. *Immunol Allergy Clin North Am* 2015; 35: 523-544.
8. Mukherjee M, Lacy P, Ueki S. Eosinophil Extracellular Traps and Inflammatory Pathologies – Untangling the Web! *Front Immunol* 2018; 9: 2763.

9. Matoszka N, Działo J, Tokarz-Deptuła B, Deptuła W. NET and NE-Tosis – new phenomenon in immunology. *Postep Hig Med Dosw* 2012; 66: 437-445.
10. Akuthota P, Weller PF. Eosinophils and Disease Pathogenesis. *Semin Hematol* 2013; 49: 113-119.
11. Bałajewicz-Nowak M, Glanowska I, Hosiawa W, et al. Wodobrzusze w przebiegu hipereozynofilii – opis przypadku i przegląd piśmiennictwa. *Curr Gynecol Oncol* 2018; 16: 57-63.
12. Cotton JA, Beatty JK, Buret AG. Host parasite interactions and pathophysiology in *Giardia* infections. *Int J Parasitol* 2011; 41: 925-933.
13. Ahmad RN, Sherjil A, Mahmood A, et al. Severe eosinophilia in a case of giardiasis. *Mediterr J Hematol Infect Dis* 2011; 3: e2011009.
14. Suzuki Y, Nakamura T, Tokoro M, et al. A case of giardiasis expressing severe systemic symptoms and marked hypereosinophilia. *Parasitol Int* 2010; 59: 487-489.
15. Lakshman A, Nampoothiri RV, Law AD, et al. Hypereosinophilia in a Young Patient: Occam's Razor or Hickam's Dictum? *Indian J Hematol Blood Transfus* 2016; 32 (Suppl 1): 340-343.
16. Rogawski ET, Bartelt LA, Platts-Mills JA, et al. Determinants and Impact of *Giardia* Infection in the First 2 Years of Life in the MAL-ED Birth Cohort. *J Pediatric Infect Dis Soc* 2017; 6: 153-160.
17. Kubiak K, Dzika E, Dobrzańska M, et al. Giardiasis in the Warmia and Mazury province (north-eastern Poland) – an epidemiological analysis. *Polish Ann Med* 2017; 24: 5-8.
18. Halliez MCM, Buret AG. Extra-intestinal and long term consequences of *Giardia duodenalis* infections. *World J Gastroenterol* 2013; 19: 8974-8985.
19. Minetti C, Chalmers RM, Beeching NJ, et al. Giardiasis. *BMJ* 2016; 355:i5369.
20. Czarkowski MP, Cielebąk E, Staszewska-Jakubik E, Kondej B. Choroby zakaźne i zatrucia w Polsce w 2017 roku. Narodowy Instytut Zdrowia Publicznego – Państwowy Zakład Higieny Zakład Epidemiologii Chorób Zakaźnych i Nadzoru, Warszawa 2018.
21. Cernikova L, Faso C, Hehl AB. Five facts about *Giardia lamblia*. *PLoS Pathog* 2018; 14: e1007250.
22. Gardner TB, Hill DR. Treatment of Giardiasis. *Clin Microbiol Rev* 2001; 14: 114-128.
23. Guarino A, Ashkenazi S, Gendrel D, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition/European Society for Pediatric Infectious Diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe: update 2014. *J Pediatr Gastroenterol Nutr* 2014; 59: 132-152
24. Soares R, Tasca T. Giardiasis: an update review on sensitivity and specificity of methods for laboratorial diagnosis. *J Microbiol Methods* 2016; 129: 98-102.
25. Adeyemo FE, Singh G, Reddy P, Stenström TA. Methods for the detection of *Cryptosporidium* and *Giardia*: From microscopy to nucleic acid based tools in clinical and environmental regimes. *Acta Trop* 2018; 184: 15-28.
26. Charakterystyka produktu leczniczego Metronidazol. 07.06.2018 r.
27. Jeske J, Malinowska B, Kamerys J, et al. Effectiveness of azithromycin in the treatment of giardiasis. *Med Sci Monit* 1998; 4: 547-550.
28. Beer KD, Collier SA, Du F, Gargano JW. Giardiasis Diagnosis and Treatment Practices Among Commercially Insured Persons in the United States. *Clin Infect Dis* 2017; 64: 1244-1250.
29. Ho MH, Wong WH, Chang C. Clinical spectrum of food allergies: a comprehensive review. *Clin Rev Allergy Immunol* 2014; 46: 225-240.
30. Yamada Y, Nishi A, Ebara Y, et al. Eosinophilic Gastrointestinal Disorders in Infants: A Japanese Case Series. *Int Arch Allergy Immunol* 2011; 155 (Suppl 1): 40-45.
31. Rogowska A. [Eosinophilic gastrointestinal disorders]. *Gastroenterol Klin* 2012; 4: 105-116.