CASE REPORT

Eosinophilia caused by *Toxocara canis* infection

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Abstract

Eosinophilia is defined as an absolute peripheral blood eosinophil count > 0.5 GL. Most often, its intensity is mild. Eosinophilia usually accompanies other diseases such as allergic, rheumatological, infectious, or oncological. The signs depend on the underlying diseases. After starting treatment of the underlying disease, the eosinophil count returns to the reference range. The diagnosis of eosinophilia starts by excluding the secondary causes. Clonal eosinophilia is a rare disease in which eosinophils are part of a tumor clone. The clonality is confirmed by molecular biology methods. The most common eosinophilic infiltration includes skin, lungs, and heart. The symptoms are not connected with a count of eosinophils in blood or bone marrow. The manifestation can be mild but also severe, life-threatening like venous thromboembolism.

This article presents a case of 36-year-old man with eosinophilia caused by Toxocara canis infection manifested by systemic symptoms, erythroderma, and liver failure.

Key words: eosinophilia, hypereosinophilia, *Toxocara canis*, toxocariasis

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Introduction

Eosinophils are a subpopulation of leukocytes, which are formed from the myeloid stem cells in the bone marrow where they stay for 5–6 days until they reach maturity. The maturation process is regulated by interleukin 1 (IL-1), interleukin 5 (IL-5) and the granulocyte-macrophage colony-stimulating factor (GM-CSF) [1–5]. Interleukin 5 is of particular importance for their development and functions, as well as for the duration of their survival [1–5]. Mature eosinophils are released from the bone marrow and circulate in the blood for 8–18 hours, then they penetrate the tissues, where, after activation, they release active mediators from their granules, such as pro-inflammatory cytokines, free radicals, and enzymes which damage the surrounding tissues, e.g. acid phosphatase, major basic protein, and eosinophil cationic protein [3, 4]. Eosinophils are responsible for the defence response against para-sites, antibody-dependent cellular toxicity and allergic reactions. They are also likely to play a role in the development of post-vaccination immunity, the modulation of T-lymphocyte function, and glucose and lipid metabolism [6]. Under normal conditions, the number of eosinophils in the peripheral blood is 0–500/μL, which is 1–3% of all leukocytes (there are even several hundred times more in tissues). Their maximum survival time is several days [4].

Eosinophilia is defined as an absolute peripheral blood eosinophil count greater than 500/μL. Most often it is secondary to another disease (reactive eosinophilia). Primary eosinophilia is associated with the presence of the neoplastic clone of eosinophils [7, 8].

Hypereosinophilia is defined as a persistently elevated peripheral blood eosinophil count of 1500/μL or higher on two occasions at least one month apart and/or the presence of eosinophilic organ infiltration [7, 8]. The spectrum of symp-

toms of hypereosinophilia depends on the organs and systems involved; however, the severity of symptoms and the degree of end-organ damage are not related to eosinophil counts. The most common symptoms are fatigue, fever, cough, rash, erythroderma, thromboembolic events (including retinal vascular thrombosis causing visual disturbances), fibrosis of the affected organ, and behavioural changes and memory impairment [8, 9]. Particular attention should be paid to symptoms related to cardiac involvement, as progressive myocardial fibrosis may lead to heart failure, arrhythmias and, not infrequently, death. Thromboembolic events also pose a threat to the patient's life, as they may result in myocardial infarction or stroke [10, 11].

Eosinophilia is most often of a secondary nature and may result from many conditions, including allergic, rheumatic, infectious or cancerous diseases. Clonal eosinophilias are rare diseases in which eosinophils are part of the neoplastic clone.

Toxocariasis is one of the most common human zoonoses caused by *Toxocara spp.* — mainly *Toxocara canis* (dog roundworm) and *Toxocara cati* (cat roundworm). The infection occurs as a result of accidental consumption of food, water or soil contaminated with invasive eggs (e.g. in sandboxes) [12].

Toxocariasis has several clinical forms:
- larva migrans syndrome — most often manifested by fever, chills, lack of appetite, abdominal pain, cough, enlargement of the liver, spleen and lymph nodes, pain in muscles and joints, and leukocytosis accompanied by eosinophilia ($> 2000/\mu$L) and hypergammaglobulinemia;
- ocular toxocariasis — visual impairment, endophthalmitis, retinitis;
- neurotoxicariasis — causing meningitis, encephalitis, vasculitis, inflammation of the spinal cord with usually non-specific symptoms such as fever, headache, seizures;
- latent toxocariasis — asymptomatic, most often diagnosed by chance or after Toxocara infection is detected in other family members [12–14].

In the life cycle of *Toxocara spp.*, humans are only accidental hosts – the parasite does not complete its development in the human body. For this reason, its eggs are absent in the stool and the diagnosis is based on the detection of specific antibodies [13].

The article presents a case of a 36-year-old man with eosinophilia with severe systemic symptoms, generalized erythroderma and liver damage.

Case report

A 36-year-old man with a history of hypertension, obesity, low-risk pulmonary embolism in 2012, atopic dermatitis (AD) and bronchial asthma diagnosed in childhood was referred to a haematology clinic due to eosinophilia. Atopic dermatitis and bronchial asthma were in remission and did not require treatment. A few years earlier, the patient had an episode of foot arthritis, which was successfully treated with non-steroidal anti-inflammatory drugs (NSAIDs) for about a month. At that time, rheumatological diagnostics were performed and rheumatic diseases were excluded. Since 2012, the patient has been taking rivaroxaban, and for about a month he has been taking antihistamines due to itchy skin.

About six months before the diagnosis of eosinophilia, the patient had an episode of severe joint pain (the pain was generalized, with no predominant location, without oedema). After a consultation with a rheumatologist, sulfasalazine and celecoxib were introduced. After about 4 weeks of treatment, the patient noticed a fine blotchy skin rash. The treatment was continued for approximately 3 months; then, it was stopped due to persistent rash approximately 3 weeks before the onset of fever and erythroderma.

On admission to the haematology clinic, the patient reported a fever of up to 39°C lasting about 3 weeks. The fever was accompanied by a rash, initially mainly on the lower limbs, then on the skin of the whole body, with severe itching and erythroderma. The lesions were most severe on the skin of the neck and face, with slight erosions present. On the lower limbs and the hands, around the nails, there were numerous confluent ecchymoses based on erythema. Physical examination also revealed bilateral axillary lymphadenopathy (approx. 2 cm) and splenomegaly (the spleen was palpable 3 cm under the costal arch). Peripheral blood counts were: white blood cells (WBC) 20 G/L, including eosinophils 3.49 G/L, haemoglobin (Hb) 12.6 g/dL, platelet count (PLT) of 86 G/L. The blood smear test showed slight hypochromia and anisocytosis. The result of blood differential test was as follows: segmented granulocytes 9% (normal range 40–70%), basophils 2% (normal range 0–1%), eosinophils 15% (normal range 1–6%), lymphocytes 59% (normal range 20–40%), monocytes 15% (normal range 5–12%). Biochemical tests revealed signs of liver damage: alanine aminotransferase (ALT) 157 U/L, aspartate aminotransferase (AST) 161 U/L, gamma-glutamyl transpeptidase

(GGTP) 1996 U/L, alkaline phosphatase (ALP) 711 U/L. Total bilirubin remained within the reference limits, while direct bilirubin was slightly elevated (0.55 mg/dL). In addition, significantly increased levels of lactate dehydrogenase (LDH) (940 U/L; normal range 135–225 U/L), beta$_2$-microglobulin (6.41 mg/L; normal range 0.8–2,4 mg/L), carbohydrate antigen (CA) 19-9 protein (102 U/mL; normal range < 39 U/mL) and increased erythrocyte sedimentation rate (ESR) (116 mm after 1 hour) were found. Blood levels of C-reactive protein (CRP) and procalcitonin remained within the reference range. Total immunoglobulin E (IgE) in serum was 1789 IU/mL (normal range < 100 IU/mL), and IgG4 was 1121.1 mg/L (normal range 864 mg/L). Serum tryptase level was normal (6.4 μg/L; normal range < 11.4 μg/L). The following infections were excluded: hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), Epstein-Bárr virus (EBV), cytomegalovirus (CMV) and *Toxoplasma gondii*. No parasite eggs were present in the stool. The results of serological tests to detect IgG antibodies against Toxocara canis (11.11 NTU [nephelometric turbidity unit]) and human roundworm (9.1 NTU) were inconclusive.

Echocardiography showed no abnormalities. Due to axillary lymphadenopathy, computed tomography (CT) of the whole body was performed with contrast medium showing numerous enlarged cervical lymph nodes in the area of the mandibular angles (16 × 16 mm), submandibular lymph nodes (13 × 10 mm) and axillary lymph nodes (up to 27 × × 19 mm on the right and 24 × 12 mm on the left) as well as an enlarged spleen (longitudinal dimension 175 mm). The material was collected from the axillary lymph node for histopathological examination.

A myelogram was performed showing a hypercellular bone marrow with numerous eosinophils (14%) and plasmocytes. Additionally, about 5% were undifferentiated cells with various degrees of maturity — half of them were blasts with irregular nuclei and azurophilic granules. The percentage of myeloblasts was 0.5%. Bone marrow immunophenotyping showed approximately 23% lymphocytes, 5% monocytes and 14.6% eosinophils.

The consulting dermatologist did not find any changes characteristic of specific skin disease. They suggested that drug reactions or lymphoma should be considered in the differential diagnosis. A neck-skin sample was collected. The histopathological examination showed a slightly spongy epidermis and a subepidermal, perivascular chronic inflammatory infiltrate. In the hair follicles, acidophilic masses of an ambiguous appearance were

present, which did not allow the exclusion of parasitic infection. The picture most closely corresponded to the lesions observed in AD.

Diagnostic rheumatological tests did not reveal the presence of anti-citrulline antibodies; the titer of the rheumatoid factor was normal. The presence of ANA3 antinuclear antibodies was excluded by immunoblot analysis. The consulting rheumatologist ruled out inflammatory systemic connective tissue disease.

The histopathological examination of the axillary lymph node showed a preserved histoarchitecture with the presence of reactive follicles [the expression pattern of follicular dendritic cell (FDC) was as follows: CD20 +, BCL6 +, CD10 +, LMO2 +, BCL2–, CD5–, cyclin D1–, CD23 +]. Interfollicular areas were expanded, occupied by T-cells (CD3 +, CD5 +; Ki-67 proliferation index within 30–35%; CD38–, MUM1 +, SOX – 11–, TdT–).

Based on the overall clinical picture and the available results of laboratory tests, including the inconclusive IgG antibody test result, *Toxocara canis* infection was suspected. While waiting for histopathological and cytogenetic examinations of the bone marrow, the patient was referred to the infectious disease ward where the infection was confirmed by detecting specific antibodies to *Toxocara canis* and treatment with albendazole at a dose of 800 mg/day was started. During the follow-up visit, after a few days of treatment, erythroderma was no longer observed. Peripheral lymphadenopathy was also absent. Laboratory tests showed that the eosinophil count was 0.74 G/L; Hb and blood PLT levels were normal. A significant reduction in the activity of liver enzymes was observed: ALT 77 U/L, AST 42 U/L, ALP 69 U/L, GGTP 71 U/L, LDH 183 U/L. Due to the presence of lymphadenopathy at the baseline CT, the examination was repeated and no abnormalities were found. In subsequent follow-up blood count tests, the eosinophil count was normal.

Cytogenetic examination of the bone marrow revealed a normal male karyotype. The presence of *PDGFRα, PDGFRβ, FGFR1* and *JAK2* gene rearrangements were excluded through fluorescence *in situ* hybridization (FISH). The image of the bone marrow on trephine biopsy was abnormal; abnormalities of the granulocytic and platelet lines with an increased percentage of plasmocytes (approx. 10%), without light chain restrictions, and granulomas were described. These findings suggested reactive changes (infection?), followed by a myeloproliferative tumour. Due to a history of unprovoked pulmonary embolism years ago,

the diagnostics were extended to include tests for congenital and acquired thrombophilia, which were excluded. Chronic anticoagulation was not indicated and rivaroxaban was discontinued. Due to the increased serum level of Ca 19-9, an endoscopic examination of the gastrointestinal tract was performed. The images of organs in gastroscopy and colonoscopy were normal.

Discussion

Most cases of eosinophilia are secondary to various diseases (the most important ones are listed in Table 1); therefore, diagnostics tests for a possible underlying disease should be performed first.

When diagnosing eosinophilia, drug hypersensitivity should always be considered. Both over-the-counter medications and prescribed drugs, as well as herbal preparations and dietary supplements, may trigger adverse reactions [3, 15]. The drugs that most commonly cause eosinophilia are listed in Table 2. Treatment-related eosinophilia is usually mild, often asymptomatic, but can also be life-threatening, taking the form of a drug reaction with eosinophilia and systemic symptoms (DRESS) [16]. It is characterized by fever, rash, and organ failure, sometimes with lymphadenopathy. Usually, it develops in the first 2–3 weeks of therapy but may occur even up to 3 months after its initiation [16]. The mortality rate of DRESS is 10–40% [15, 17]. DRESS most often occurs during treatment with antiepileptic drugs, sulfonamides or allopurinol [16]. The mainstay of DRESS therapy is the discontinuation of the potentially harmful drug and, in severe cases, steroid therapy. The described patient had taken sulfasalazine and celecoxib in the time preceding the onset of symptoms. The presence of DRESS could also be indicated by rash, fever, laboratory signs of liver damage, and lymphadenopathy. Whereas the rash occurred when the patient was taking both drugs and was the reason for discontinuation of therapy, the remaining symptoms appeared about 3 weeks after treatment cessation. Due to the lack of temporal relationship, DRESS was excluded as a cause of symptoms.

The differential diagnosis also included bronchial asthma and AD, and additionally, due to increased IgE and IgG4 titers, hyper-IgE syndrome (HIES) and IgG4-related diseases.

Asthma is not a homogeneous disease. Among its many phenotypes, there are two that are associated with eosinophilia:
- allergic asthma with eosinophilia — one of the most common phenotypes, responding well

Table 1. The causes of reactive eosinophilia

Allergic diseases	Asthma Atopic dermatitis Allergic rhinitis Seasonal allergies
Rheumatic diseases	Vasculitis Systemic lupus erythematosus Rheumatoid arthritis
Infectious diseases	Parasitoses HTLV-1
Gastrointestinal diseases	Eosinophilic esophagitis, gastritis, cholangitis, cholecystitis Chronic pancreatitis Inflammatory bowel diseases Celiac disease
Respiratory diseases	Asthma Löffler syndrome
Neoplasms with non-clonal eosinophilia	Gastrointestinal cancers Lung cancers Thyroid cancers Squamous cell carcinomas Lymphomas
Miscellaneous	Drugs Adrenal insufficiency Chronic GvHD

HTLV-1 — human T-cell leukaemia/lymphoma virus; GvHD — chronic graft--versus-host disease

Table 2. Drugs associated with eosinophilia

Antibiotics (including penicillins, cephalosporins)
Antiepileptic drugs (including carbamazepine, lamotrigine, phenytoin)
Antidepressants (including fluoxetine, amitriptyline)
Non-steroidal anti-inflammatory drugs (including ibuprofen, naproxen, diclofenac)
Sulfonamides (including sulfasalazine, cotrimoxazole)
Hypotensives (beta-blockers, ACEI, hydrochlorothiazide)
Antiviral drugs (including nevirapine, efavirenz)
Other: allopurinol, cyclosporine, ranitidine

ACEI — angiotensin-converting-enzyme inhibitor

to treatment, usually coexisting with AD and other allergies;
- non-allergic asthma with eosinophilia — no data on concomitant allergy; in severe cases, it is associated with nasal polyps, hypersensitivity to NSAIDs and vasculitis with eosinophilia [18].

AD is a chronic disease with periods of exacerbation and remission, usually beginning in early childhood. Eosinophilia occurs in most AD patients,

mainly in a mild form, and its severity is related to the activity of the disease [19].

The aforementioned allergic diseases were diagnosed in the patient in childhood; however, they have never caused eosinophilia, have been in remission for several years and did not require pharmacological treatment. The occurrence of eosinophilia was not associated with an exacerbation of these diseases.

Hyper-IgE syndrome is a rare autosomal dominant genetic disorder that is caused by a mutation in the *STAT3* gene. The triad of symptoms includes increased IgE titer, eosinophilia and recurrent infections of the skin and respiratory system [20]. In turn, IgG4-related diseases are a new clinicopathological entity associated with increased IgG4 titer and a characteristic histopathological picture of the affected organ (lymphoplasmacytic infiltration, fibrosis, obliterative phlebitis, tissue eosinophilia). Eosinophilia is present in almost all cases and infiltrates can occur in any organ [21, 22].

The described patient reported joint pain, which could indicate a rheumatic disease. Eosinophilia is most often observed in systemic lupus erythematosus or rheumatoid arthritis. However, this symptom is not specific to any of these diseases, and eosinophilia is usually mild [23].

Due to the history of bronchial asthma, eosinophilic granulomatosis with polyangiitis (formerly called Churg-Strauss syndrome) was also considered in the differential diagnosis. It is a necrotizing inflammation of small and medium-sized vessels associated with anti-neutrophil cytoplasmic antibodies (ANCAs). It often coexists with severe bronchial asthma (> 95% of patients), eosinophilia, chronic sinusitis and nasal polyps. The main symptoms, in addition to fever and asthma symptoms, are weight loss, glomerulonephritis, and mononeuropathy. There may also be haemoptysis due to bleeding into the alveoli. The diagnosis is made based on the clinical picture (the presence of symptoms from at least two organs, including the diagnosis of bronchial asthma) and, if possible, histopathological examination. The most common treatment is glucocorticosteroids [24, 25]. In the presented patient, asthma was in remission, apart from skin involvement, no symptoms from other organs were observed, and no characteristic changes were found in the histopathological examination of the skin specimen. Moreover, no ANCA was found in the peripheral blood.

In all cases of eosinophilia, diagnostic tests for parasitic infections should also be performed. The most common causes of eosinophilia are parasitoses, such as ascariasis, bilharziasis, strongyloidiasis, trichinosis, echinococcosis, duodenal hookworm infection, toxocariasis, protozoal infections, and endemic helminthiasis. The cause of eosinophilia can also be viruses, most often human T-lymphocytic virus (HTLV-1) [26]. In the described patient, an inconclusive result was obtained for IgG antibodies against *Toxocara canis* and human roundworm. *Toxocara canis* infection was confirmed in the infectious diseases ward by detecting the presence of specific antibodies.

Eosinophilia accompanies malignant neoplasms in 0.5–7% of cases and correlates with their advancement. The most common are squamous cell carcinomas and cancers of the digestive system, lung and thyroid gland. Among haematological neoplasms, it accompanies lymphomas (especially those derived from T cells) and chronic myeloid leukaemia [27]. In the described case, an increased level of Ca 19-9 protein was found, which could indicate a tumour of the digestive system. The imaging diagnostics performed (CT of the whole body, endoscopic examinations of the gastrointestinal tract) did not reveal any concomitant neoplastic disease.

At the same time, diagnostic tests for clonal eosinophilia were performed. Clonal eosinophils may accompany other malignancies of the hematopoietic or lymphatic system. Then the eosinophils are part of the neoplastic clone or eosinophilia may be primary [7]. Primary eosinophilias arise from eosinophilic precursors in the bone marrow. Their uncontrolled proliferation results in eosinophilia in the bone marrow and peripheral blood, or tissue infiltration. Mutations leading to the formation of fusion genes with the activity of tyrosine kinases — *FIP1L1-PDGFRα, FIP1L1-PDGFRβ, FGFR1* — are the basis of primary clonal eosinophilia. As a result of the discovery of these mutations in 2008, newer World Health Organization (WHO) classifications distinguished groups of myeloid/lymphoid neoplasms with eosinophilia and gene rearrangements of platelet-derived growth factor receptors alpha and beta (*PDGFRα, PDGFRβ*) and fibroblast growth factor receptor (*FGFR1*) [7]. Eosinophilic infiltrates most often affect the skin, lungs and heart, leading to damage to these organs. Tables 3 and 4 show the causes of clonal eosinophilia and the classification of primary clonal eosinophilias.

In the discussed case, the rearrangement of *PDGFRα, PDGFRβ, and FGFR1* genes and the presence of the *BCR-ABL* fusion gene were excluded. Neither the myelogram nor the bone marrow biopsy revealed any evidence of a myeloproliferative tumour.

Table 3. The causes of clonal eosinophilia

Myeloproliferative neoplasms associated with eosinophilia and rearrangements of *PDGFRα, PDGFRβ, FGFR1* and *PCM1-JAK2*
Chronic eosinophilic leukaemia not otherwise specified (CEL-NOS)
Acute myeloid leukaemia with eosinophilia (AML-Eo)
Chronic myelomonocytic leukaemia with eosinophilia (CMML-Eo)
Systemic mastocytosis (SM)
Acute lymphoblastic leukaemia (ALL)

FGFR1 — fibroblast growth factor receptor 1; PCM1-JAK2 — fusion gene pericentriolar material 1 and Janus kinase 2; PDGFRα — platelet-derived growth factor receptor α; PDGFRβ — platelet-derived growth factor receptor β

Table 4. 2016 World Health Organization classification of primary clonal eosinophilia according to the diagnostic criteria, based on the literature [7]

Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRα, PDGFRβ*, or *FGFR1*, or with *PCM1-JAK2*
Myeloid/lymphoid neoplasms with eosinophilia and PDGFRa rearrangement
Myeloid/lymphoid neoplasms with eosinophilia and PDGFRb rearrangement
Myeloid/lymphoid neoplasms with eosinophilia and FGFR1 rearrangement
Myeloid/lymphoid neoplasms with eosinophilia and PCM1-JAK2 rearrangement
Chronic eosinophilic leukaemia not otherwise specified (CEL-NOS)
Peripheral blood eosinophil count of > 1.500 G/L
Clonal cytogenetic abnormality and/ or blast cells > 2% in peripheral blood or > 5% in the bone marrow
Blast cell count < 20%
Exclusion of *BCR-ABL1(+)* chronic myeloid leukaemia, chronic myeloproliferative neoplasms (essential thrombocythemia, polycythaemia vera, primary myelofibrosis, myeloproliferative-myelodysplastic syndrome)
Absence of *PDGFRα, PDGFRβ*, or *FGFR1* rearrangement, or *PCM1-JAK2*
Lymphocyte variant of the hypereosinophilic syndrome (L-HES)
Polyclonal hypereosinophilia caused by overproduction of IL-5 by clonal T cells
Exclusion of other myeloid neoplasms associated with eosinophilia
Idiopathic hypereosinophilic syndrome (I-HES)
Persistent peripheral blood eosinophilia> 1.500 G/L recorded on 2 occasions with an interval of ≥ 4 weeks accompanied by organ damage
Exclusion of reactive eosinophilia, including L-HES
Exclusion of other myeloid neoplasms associated with eosinophilia
Exclusion of chronic myeloproliferative neoplasms, AML and ALL with rearrangements of *PDGFRα, PDGFRβ, FGFR1*, and *PCM1-JAK2*
Exclusion of CEL-NOS

Summary

Moderate to severe eosinophilia, whatever its cause, can lead to organ damage that may sometimes be irreversible. Eosinophilia is reactive in most cases. The key element of the diagnostic procedure is a very detailed interview including possible causes of eosinophilia. In the described case, eosinophilia was accompanied by severe general symptoms, erythroderma and liver damage. The detection of *Toxocara canis* infection and the introduction of antiparasitic treatment led to the complete resolution of clinical symptoms and normalization of laboratory test results in a short time.

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