Szymczyk Agnieszka, Szydełko Magdalena, Szydełko Joanna, Jaworski Jakub, Onyshchuk Yuliya, Dziedzic Rafał, Hus Marek, Podhorecka Monika. The diagnostic difficulties of eosinophilia in clinical practice - case series. Journal of Education, Health and Sport. 2019;9(3):385-397. eISNN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.2598929
http://ojs.ukw.edu.pl/index.php/johs/article/view/6718
https://pbn.nauka.gov.pl/sedno-webapp/works/908359

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part B item 1223 (26/01/2017).
1223 Journal of Education, Health and Sport eISSN 2391-8306 7

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 15.02.2019. Revised: 15.02.2019. Accepted: 20.03.2019.

The diagnostic difficulties of eosinophilia in clinical practice - case series

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Key words: eosinophilia, differential diagnosis, hematological and non-hematological causes

Abstract

Introduction: Eosinophilia, defined as elevated level of eosinophils in peripheral blood above 5 x 10^9/L, is the hematological disorder, which may occur in multiple conditions, such as allergies, gastrointestinal, autoimmune diseases, parasite, fungal infections as well as drug related eosinophilia. Although hematological causes of eosinophilia (idiopathic, myeloproliferative and lymphocytic variant) should be taken into consideration.

Aim of the study: The aim of our study was to performed the difficulties related to the differential diagnosis of eosinophilia, especially associated with the diverse symptoms.

Materials and methods: The study included 5 patients hospitalized in the Department of Hematooncology and Bone Marrow Transplantation, due to eosinophilia associated with diverse symptoms. Medical history, physical examination, the peripheral blood as well as bone marrow samples analysis and the genetic tests for the presence of mutations or rearrangements that detect leukemia or lymphoma were analyzed. Moreover, patients were evaluated due to the presence of parasites.

Results: The case series revealed that eosinophilia may have a various etiological background. Three patient demonstrated the reactive eosinophilia, caused by bacterial, parasite infections and eosinophilic granulomatosis with polyangitis, however in two other cases the chronic eosinophilic leukemia with abnormalities of PDGFRA were diagnosed.

Conclusions: Eosinophilia is an important diagnostic and prognostic feature in a varied range of pathological conditions from infections, allergies to malignancies. For this reason, it is an enormous diagnostic as well as therapeutic challenge and requires an interdisciplinary clinical approach, especially in cases with unclear manifestations.

Introduction

Eosinophils are highly specialized cells that belong to the group of white blood cells derived from the myeloid line. They were discovered in peripheral blood in 1879 by Paul Ehrlich, however, the details of their structure, function and clinical significance were gradually known only from the mid-1970s [1]. Their effector functions are possible by the ability of these cells torelease cationic proteins stored in cytoplasmic granules by degranulation such as major basic protein 1 (MBP1; known as MBP and PRG2), eosinophil cationic protein (ECP; known as RNase3), eosinophil-derived neurotoxin (EDN; known as RNase2) and eosinophil peroxidase (EPX; known as EPO) as well as leukotrienes, prostaglandins and cytokines. As a result, these cells play an important role in mediating inflammatory processes underlying in the pathogenesis of multiple diseases [2].

The normal level of eosinophils account for about 3 to 5 percent of all peripheral blood leukocytes in healthy individuals and an absolute eosinophil count (AEC) range from 350 to 500/mm^3 (0,35 x 10^9/L to 0,5 x 10^9/L) [3,4]. Depending on the AEC, the severity of eosinophilia was divided into 3 stages: mild (higher than the upper limit of normal to 1500/mm^3), moderate (from 1500 to 5000/mm^3) and severe (above 5000/mm^3) [4]. Moreover, it is worth noting that in the case of particularly elevated (AEC > 150/mm^3) and persistent eosinophilia and/or the presence of eosinophilic infiltrates intissues, the hypereosinophilia (HE) is applied, while in the situation where multiple organ damage is also observed, the hypereosinophilic syndrome (HES) can be recognized [5].

The prevalence of this hematological disorder is difficult to estimate, but the latest researches demonstrated an incidence of eosinophiliaof 4% [6]. The causes of elevated eosinophils' level above the upper limit of normal in the peripheral blood are routinely divided into three categories: secondary (reactive), which is the most common, primary and idiopathic [3]. Secondary eosinophilia may encompass a broad range of non-hematologic disorders such as allergic, dermatological, gastrointestinal conditions, parasite and fungal infections or autoimmune diseases (connective tissue diseases, vasculitis). Furthermore, malignancy, immunodeficiency as well as drug related eosinophilia should be taken into consideration in the differential diagnosis[7]. Although hematological causes of eosinophilia (idiopathic, myeloproliferative variant and lymphocytic variant) occur relatively rarely, after exclusion of secondary causes of elevated eosinophilia in peripheral blood, precise and sophisticated laboratory analyses should be performed [8,9].

Considering, the abundant and diverse symptomatology and causes of eosinophilia the diagnostic process should be insightful and comprehensive. All of eosinophilia cases require the accurate medical history especially involving allergy status, detailed travel history, particularly for tropical travel ormedications and the physical examination. The laboratory tests should include the analysis of peripheral blood, bone marrow smear, parasite tests, alkaline phosphatase activity, cytogenetics and fluorescent-in situ-hybridization analyses to detect the presence of acute or chronic hemato-oncological disorders (PDGFRA/PDGFRB/FGFR1, PCM1-JAK2 mutations) [10].

Aim of the work

The aim of our study was to performed the difficulties related to the differential diagnosis of eosinophilia, especially associated with the complex and diverse symptoms. Furthermore, on the example of our clinical case reports, we discussed the most common hematological as well as non-hematological disorders lying at the base of the increased number of eosinophils in the blood, which can be extremely useful in clinical practice.

Material and methods

The study included 5 patients (female n=2; male n=3) hospitalized in the Department of Hematooncology and Bone Marrow Transplantation of the Medical University of Lublin, due to eosinophilia associated with diverse symptoms. The average age of the patients was52,6 ±21,7 years. All of patients were diagnosed by the medical history, physical examination, the complete peripheral blood as well as bone marrow samples analysis and the genetic tests for the presence of mutations or rearrangements that detect leukemia or lymphoma. Moreover, patients were evaluated due to the presence of parasites. The additional tests were performed according to the symptoms presented by the patient.

Case reports

Patient 1

Female patient, age 69, suffering from hyperleukocytosis with eosinophilia, was admitted to the neurology department because of muscle weakness of the lower limbs, numbness and paresthesias of the fingers and toes. Neurological examination revealed paresis of the flexors and extensors of the foot, chiefly on the right side, with proprioceptive and superficial sensory deficits. Achilles tendon reflexes were absent. Normal protein levels in the cerebrospinal fluid suggested that acute inflammatory polyneuropathy could be excluded. Electromyography revealed conduction disturbances of both tibial nerves and the right fibular nerve, which suggested a conduction block in axonal polyneuropathy. A complete blood cell count showed hyperleukocytosis (WBC 25.3 × 10^9/L) with eosinophilia (AEC 20.88 × 10^9/L). Parasitic etiology of eosinophilia was excluded and the patient was referred to the Department of Hematooncology in order to perform further diagnostics. Bone marrow smear showed 50% eosinophils. The karyotype was normal. *JAK-2* gene mutation, *BCR/ABL* fusion gene, and *FIP1L1-PDGFRA* fusion were not detected. Laboratory tests revealed raised levels of inflammatory markers (CRP 21.88 mg/L, ESR 62 mm/h). The patient was finally diagnosed with Lyme borreliosis (ELISA test and IgM Western Blot test were positive). Treatment with ceftriaxone (2 g/day) was initiated and it resulted in the reduction of leukocytosis to 5.46 × 10^9/L and eosinophilia to 3.18 × 10^9/L. Due to the improvement of the patient's clinical condition and laboratory tests, the decision to continue the therapy with antibiotics was made and the patient was followed-up in the infectious diseases outpatient clinic.

Patient 2

Male patient, age 53, was admitted to the Department of Hematooncology because of hypereosinophilia. He had a history of low-grade fever and myalgia. Blood tests revealed WBC 9.83 × 10^9/L, RBC 4.3 × 10^{12}/L, Hgb 11.8 g/dL, MCV 85.1 fL, PLT 216 × 10^9/L, EO 5.63 × 10^9/L. Bone marrow smear showed increased percentage of eosinophils (28%). The *FIP1L1-PDGFRA* rearrangement was not detected. Eggs of *Ascaris lumbricoides* were found in the feces. Therapy with albendazole was initiated at a dose of 400 mg/day. After one month of initial treatment, the laboratory tests revealed reduction of eosinophilia to 2,67 × 10^9/L. The patient was administered the next dose of albendazole and followed up in the infectious diseases outpatient clinic.

Patient 3

Female patient, age 26, was transferred from the Department of Neurology, where she was hospitalized because of idiopathic motor axonal polyneuropathy, to the Department of Hematooncology. She also had a history of asthma, chronic sinusitis, and meningitis in 2008. Physical examination revealed livedo reticularis, inflammation in the small joints of the hands, and nasal discharge. A peripheral blood smear showed that segmented neutrophils of normal alkaline phosphatase (ALP) activity were 21% of all cells and eosinophils were 72%. Levels of IgE were significantly raised (1994 IU/mL). During her hospitalization, a bone marrow trepanobiopsy was performed that showed an increased percentage of eosinophilic

myeloblasts and segmented eosinophils. Due to increase in eosinophilis to 18.5 × 10^9/L and an exclusion of infectious etiology of eosinophilia, steroid therapy was initiated. After 3 days of treatment the number of eosinophils returned to normal. *PDGFRA* and *PDGFRB* fusion genes were evaluated using FISH assay and no abnormalities were found. A rheumatologic consultation was conducted, but levels of antibodies against Chlamydia trachomatis, Yersinia sp., CCP (cyclic citrulianated peptide), cANCA (cytoplasmic antineutrophil cytoplasmic antibodies), and pANCA (perinuclear antineutrophil cytoplasmic antibodies) were not elevated. The patient was transferred to the rheumatology department, where on the basis of clinical picture and additional tests, she was diagnosed with eosinophilic granulomatosis with polyangiitis.

Patient 4

Male patient, age 55, who had not been previously treated, was admitted to the Department of Hematooncology because of eosinophilia (WBC 25.12 × 10^9/L, AEC 20.98 × 10^9/L) and splenomegaly. He had a history of losing about 5 kg in weight over two months and suffered from fatigue, epigastric fullness and chest discomfort. Chest X-ray did not show any abnormalities. ECG was normal and ejection fraction at echocardiography was within normal limits (60%). In abdominal ultrasonography, the long axis of the spleen was 174 mm. Bone marrow smear showed the dominance of granulocytes and significantly increased percentage of eosinophils (about 50%). The rearrangement of *FIP1L1-PDGFRA* gene was detected. Mutations in the *JAK-2* gene and *BCR/ABL* fusion gene were not identified. Infectious etiology of eosinophilia was excluded. Clinical picture and additional tests showed that patient had chronic eosinophilic leukemia with abnormalities of platelet-derived growth factor receptor alpha (*PDGFRA*). The therapy with imatinib was initiated at a dose of 100 mg/day for the first three days. Then followed at a dose of 100 mg/week. Symptoms of the disease resolved after 2 weeks of the treatment, while complete remission was achieved in the third month of the therapy. Follow-up examination performed 6 months after the initiation of the treatment did not show *FIP1L1-PDGFRA* expression. The patient continues the therapy with imatinib at a dose of 100 mg/week.

Patient 5

Male patient, age 60, with hypereosinophilia, splenomegaly, Parkinson's disease, and chronic heart failure was admitted to the Department of Hematooncologyin order to conduct additional blood tests. ECG showed flat T waves in leads II and aVF, revealed increased size of all heart cavities, left ventricular diastolic dysfunction, and mild aortic, tricuspid, mitral and pulmonic valve regurgitation. Chest X-ray showed heart enlargement and small opacities of inflammatory origin in the lower zones of both lungs, which were not in correspondence with the clinical picture. Peripheral blood cell count showed 31.3% eosinophils (AEC 7.62 × 10^9/L, WBC 24.4 × 10^9/L). A meylogram showed significantly increased percentage of eosinophils (about 40%). *PDGFRA* fusion gene was evaluated using FISH assay and the rearrangement of *FIP1L1-PDGFRA* gene was found. Therapy with prednisone at a dose of 60 mg/day was initiated once parasitic etiology of hypereosinophilia was excluded. As a result, the number of eosinophils decreased to 0.142 × 10^9/L. Due to the positive therapeutic effect, the doses of glucocorticoids were reduced. Therapy with imatinib was commenced at an initial dose of 100 mg/day for 7 days, and then at a dose of 100 mg/week to follow. The result of the treatment was hematologic and molecular remission. No adverse side effects from the treatment were observed.

The most important data on the described cases was presented in Table 1.

Discussion

Eosinophils are bone marrow-derived cells originating from CD_{34+} hematopoetic precursor cells. The average half-time survival in peripheral blood is about 8 to 18 hours, and

then they reside in tissues for at least a few weeks [7].The main role of eosinophils is to maintain homeostasis and integrity in many conditions. These blood cells by influence on the microenvironment of tissues can lead to endomyocardial fibrosis, peripheral and central neuropathy, thrombosis, cutaneous disorders and other organ damages [11].According to the above case reports, eosinophilia is an important hematological disorder indicating the need for detailed diagnostic evaluation for a number of various diseases from infections to even malignancy.The various causes of eosinophilia was summarized in Table 2.

One of the most common causes of secondary eosinophilia are infections caused by parasites,bacteria or fungi [10,12].It is well known that eosinophils migrate to the site of inflammation and produce α-defensin, the substance which is an antibacterial peptide, however in the case of these etiologic factors the level of eosinophils is not significantly increased. It have been previously reported only the single case reports of eosinophilia in the course of infection caused by *Mycobacterium* and *Borrelia burgdorferi* [13,14]. Lyme borreliosis is a multi-organ disease caused by *Borrelia burgdorferi*, whose vector is ticks of the genus Ixodes. The clinical picture is associated with the involvement of the skin, joints, nervous system and heart [14]. The first manifestation of this disease are commonly flu-like symptoms, erythema migrans, while in the disseminated stage,the development of arthritis (swollen, knee, elbow) or less frequently myocarditis can be observed [15].Neurological symptoms occur in early disseminated Lyme Borreliosis and in the chronic late stage. The Lyme boreliosis may be responsible for a large variety of peripheral neurologic manifestations such as axonal polyneuropathy, radiculopathy, or facial nerve palsy [16]. The peripheral nervous system is usually occupied only at the late stage of the development of that disease and manifests as sensorimotor neuropathy usually involving cranial nerves [17]. However, as we demonstrate in ourcase report peripheralnerves supplying the upper and lower limbswere affected, which evidence as paresthesia and abnormal superficial andproprioceptive sensation. Furthermore, the cerebrospinal fluid examination did not show significant deviations that could be indicative of an infectious etiology. It is worth noting that the neuroborreliosis usually leads to the development of lymphocytic meningitis or spinal cord inflammation [17]. Interestingly, the peripheral hypereosinophilia in the case of our patient was observed. This hematological disorders is an unique clinical manifestation of Lyme boreliosis and is an enormous diagnostic challenge, especially when the parasite as well as clonal etiology of eosinophilia were excluded. It is noteworthy that during the successful treatment of borreliosis with ceftriaxone, a reduction in the number of eosinophils in peripheral blood was achieved, which is likely to indicate the contribution of eosinophilia to the *Borrelia burgdorferi* infection.To date, only isolated cases, showing the relationship between eosinophils and Lyme disease have been described, where eosinophilia d in the cerebrospinal fluid as well as coexistence of eosinophilia in the peripheral blood with borrelial fasciitis and lymphadenitis or eosinophilia in synovial fluid in the course of boreliosis-related arthritis were detected [18,19,20,21].Taking into account the above data, serological diagnostics (determination of specific IgM and IgG by ELISA, confirmed by Western blotting) should be performed in patients with unclear clinical picture, with hyperleukocytosis, eosinophilia and after excluding other most common primary or secondary causes (parasitosis, allergic diseases) of eosinophilia.

Epidemiological data show that parasitic infections are one of the pivotal causes of reactive eosinophilia [12].For this reason, parasite-related eosinophilia should be taken into account especially in patients with travels to tropical, developing countries and immigrant or refugee mentions in medical history.The statistics analyses revealed that about 2 billion of people is currently infected by at least one parasite, and the total number of cases of parasitosis reaches 3 billion [22]. Data from sanitary institutes suggest that in Europe, every third person is infected with a parasite, however Poland is one of the few European countries

where indicators of the prevalence of parasitic infections of the gastrointestinal tract have not been estimated yet [22,23]. In Poland, the most frequent infections are caused by such parasites as *Enterobius vermicularis*, *Trichocephalus trichiurus, Ascaris lumbricoides*and *Giardia lamblia* [23].In Europe and North America, often the infections are caused by *Echinococcus granulosus, Fasciola spp*., and *Trichinella spp*., in turn. It is worth noting, that the chronic peripheral eosinophilia usually is associated with the presence of such helmint's infections as strongyloidiasis, opistchoriasis and paragonimiasis [12]. Ascariasis is the most

Table 1. Data regarding the presented patient cases.

No.	Diagnosis	WBC (K/µL)	Eosinophilia (K/ µL)	ALP	% of eosinophils in the myelogram	FIP1-L1/ PGFRAmutation	Size of the spleen	Results of parasite tests	History of allergies	Symptoms
Patient 1	Lyme borreliosis	25.3	20.88	2	50.00%	not found	normal	negative	negative	muscle weakness of the lower limbs, numbness and paresthesias of the fingers and toes, proprioceptive and superficial sensory deficits
Patient 2	Ascariasis	9.83	5.63	none	28.00%	not found	normal	ascariasis	negative	low-grade temperature, myalgia
Patient 3	Eosinophilic granulomatosis with polyangiitis	26.6	18.6	86	27.80%	not found	normal	negative	asthma, chronic sinusitis	motor axonal polyneuropathy livedo reticularis, inflammation in the small joints of the hands, nasal discharge
Patient 4	Chronic eosinophilic leukemia with abnormalities of PDGFRA	25.12	20.98	6	60.00%	present	174 mm long axis	negative	negative	weight loss, fatigue, epigastric fullness, chest discomfort
Patient 5	Chronic eosinophilic leukemia with abnormalities of PDGFRA	24.4	7.62	3	40.00%	present	150 mm long axis	negative	negative	Symptoms Parkinson's disease and chronic heart failure

widespread parasitosis in the worldwide. Although, it primarily occurs in tropical and subtropical countries with low hygienic status and high population density, due to large population migrations, it is increasingly isolated [24].Most cases of ascariosis are asymptomatic. However, if it moderate to heavy infestations, it may cause various symptoms, depending on which part of your body is affected such as skin rash, tender hepatosplenomegaly, acute abdominal pain, pancreatitis, cholecystitis, fever, myalgia or cough and dyspnea as a result of larval migration through the pulmonary tissue. This eosinophilic pneumonitis, called as Löffler syndrome occurs as the result of hypersensitivity reaction to *Ascaris lumbricoides*[25]. The laboratory tests typically reveal the eosinophilia, and the chest X-ray may show pulmonary infiltrates. The parasitic infection must be sought by examination of stool for the presence of Ascaris' eggs and eventually serological analysis [23,25]. As the second Patient's case report revealed the parasite infection may lead to moderate eosinophilia. However, making the diagnose sometimes it may require additional tests (bone marrow smear, molecular test for the presence of FIP1L1-PDGFRA rearrangement) due to the fact that the symptoms presented by the patient are non-specific and may be associated with other causes: the treatment used, the process of proliferation.Nevertheless, the parasite infection may not manifest by eosinophilia, so the absence of that disorder does not exclude the helminths invasion.

Occasionally, diagnosis of eosinophilia may require enhanced laboratory tests, especially when the most common causes of eosinophilia (allergies, infections) have been excluded.As shown by the third patient's case report, eosinophilia can be observed in the course of autoimmune diseasesboth vasculitis and connective tissue diseases (CTD).Among the second group of diseases, eosinophilia is relatively frequently observed in the course of systemic lupus erythematosus, rheumatoid arthritis (usually mild and transient) as well as in the course of eosinophilic fascitis (Shulman disease), where eosinophilia was recently included in the minordiagnostic criteria [3,26,27].The eosinophilic granulomatosis with polyangiitis (EGPA), formerlyknown as Churg-Strauss syndrome, is a rare disease with an incidence of 0,5-4,2 cases per million inhabitants and generally affects people aged 40-60 years [28]. EGPA is a systematic necrotizing vasculitis of small- and medium- vessels associated with preexisting asthma and eosinophilia [29]. Interestingly, the Churg-Strauss syndrome is a disease that lies on the borderline of two categories of disorders: the small vessel vasculitides with coexistence of antineutrophil cytoplasmic antibodies (ANCAs) such as: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and the hypereosinophilic syndrome, where the serology status is usually negative, but the myeloid, lymphoid neoplasms with associated abnormalities of PDGFRA, PDGFRB, FGFR1 rearrangements or idiopathic form should be taken into consideration [28,30]. The EGPA may have a different clinical manifestations with the severe neurologic and cardiac involvements, however, commonly preexisting asthma associated with upper airway respiratory disorders (allergic rhinitis, chronic sinusitis, nasal polyps), arthralgia, myalgia, persistent low-grade fever or weight loss should raise a suspicion of that disease [31]. According to the Lanham criteria the EGPA may be diagnosed, when asthma, eosinophilia (>10% or >1,5x10^9/L) and the systematic vasculitis involving two or more extra-pulmonary organs are presence [32]. It is worth noting that, the ANCA antibodies are positive only in less than 50% ((30-40%) of EGPA cases and the pANCA (perinuclear immunofluorescence pattern) incidence range from 74 to 90% in that group of patients [33]. In case of our patient, the levels of antibodies against Chlamydia trachomatis, Yersinia, CCP, cANCA as well as pANCA were not elevated, nevertheless the clinical manifestations may strongly recognize the EGPA diagnosis.Furthermore, the IgE levels were significantly raised, which is also a common finding in the course of Churg-Strauss syndrome. Considering, the coexistence of asthma, eosinophilia, above 1.5x10^9/L and systemic symptoms, but lack of vasculitis and positive

ANCA antibodies, differential diagnosis towards the hypereosinophilic syndrome has been carried out [30]. After exclusion of rearrangement of PDGFRA and PDGFRB genes and low ALP activity, steroid therapy was included.This case highlights the importance of primary care physicians understanding the importance of differential diagnosis in the cases of patient presenting heterogeneous clinical manifestations related to persistent peripheral blood eosinophilia.

Despite the leading causes of hypereosinophilia are non-hematological diseases with the most common reactive pathogenesis, hematological (clonal) disorders must also be taken into consideration and oncological vigilance should always be maintained. In the course of various bone marrow neoplasms, such as myeloid and lymphoid neoplasms with eosinophilia and abnormalities of platelet derived growth factor receptor alpha (PDGFRA), platelet-derived growth factor receptor beta (PDGFRB), or fibroblast growth factor receptor 1 (FGFR1), as well as acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), systemic mastocytosis (SM),myelodysplatic syndrome (MDS), the classic myeloproliferative neoplasms (MPN), and MDS/MPN overlap disorders, peripheral eosinophilia mayrepresent one ofan early paraclinical sign [4,6]. That is why the comprehensive diagnostic methods should be performed.

Chronic eosinophilic leukemia (CEL) with FIP1L1-PDGFRA rearrangement (F/P+), which was diagnosed in our fourth and fifth male patients' case reports, is myeloproliferative neoplasm and a subset of hypereosinophilic syndrome (HES) with its incidence varies from 3–56% (approximately 23%) among HES patient population according to different authors [34-36]. What is more, it usually affects people between 20 to 50 years old with a median age of onset late in fifth decadeof life and has an overwhelming predilection in males (male to female ratio of 9:1 to 17:1) as in case of our patients [37, 38].

The initial clinical manifestations of CEL includes vide range of symptoms from asymptomatic presentations or non-specific complaints, such as fatigue, weight loss as in the case of our fourth patient, to dermatological, pulmonary, and gastrointestinal signs. However, it occurs, especially in case of disease progression or delayed diagnosis, that the first symptoms involve cardiac (generally chronic heart failure, mitral and tricuspid valve regurgitation, restrictive cardiomyopathy) and neurologic problems which were noted in fifth case report's patient [35, 38]. Besides, according to the literature splenomegaly, revealed in both our cases, is the most common eosinophilic organ damage/dysfunction in patients with CEL F/P+ mutation, therefore detailed physical examination and abdominal ultrasound examination should be performed [39].

The pivotal role in the diagnostic process of eosinophilia plays conventional cytogenetics method detecting the majority of abnormalities involving PDGFRB and FGFR1, as well as fluorescence in situ hybridization (FISH) molecular analysis which, as the only one, enables to find cryptic interstitial deletion 4q12 characteristic for PDGFRA [34]. Nevertheless, detecting the molecular rearrangement is important due to its prognostic and predictive value and is also clue for implementation an adequate treatment.

The first-line recommended treatment for patients with CEL F/P+ fusion gene is imatinib (tyrosine kinase inhibitor) in the initial dose of 100 mg per os daily as in both our males. However, it should be remembered that in patients with heart involvement, glucocorticoids application is required for first 7-10 days of treatment [38, 40]. As the literature reports and our two CEL F/P+ analyzed cases show, the rearrangement of PDGFRA and similar PDGFRB have a relatively good prognosis whereas FGRFR1 is associated with poor prognosis.

Table 2. Various causes of eosinophilia.

Reactive/secondary eosinophilia	
Subgroups of diseases	**Examples of diseases**
Allergic sensitization	asthma, atopic dermatitis, eczema, seasonal allergic disorders (rhinitis syndrome, hay fever)
Parasite- and infection-related eosinophilia	**Nematodes:**Angiostrongyliasis costaricensis, Ascariasis, Hookworm infection, Strongyloidiasis, Trichinellosis, Visceral larva migrans, Gnathostomiasis, Cysticercosis, Echinococcosis; **Filariases:** Tropical pulmonary eosinophilia, Loiasis**,** Onchocerciasis; **Flukes:** Schistosomiasis**,** Fascioliasis**,** Clonorchiasis Paragonimiasis**,** Fasciolopsiasis; **Protozoan infections:** Isospora belli**,** Dientamoeba fragilis; **Bacteria:** Mycoplasma, Borrelia burgdorferi; **Viruses:** Huma Immunodeficiency Virus
Vasculities	microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, Werner syndrome), polyarteritis nodosa (PAN), osinophilic granulomatosis with polyangiitis (Churg-Strauss vasculitis)
Connective tissue diseases	systemic lupus erythermatosus (SLE), eosinophilic fasciitis (Shulman disease), severe rheumatoid arthritis (RA), progressive systemic sclerosis, Sjoegren syndrome, dermatomyositis
Gastrointestinal disorders	primary gastrointestinal eosinophilic disorders (oesophagitis, gastritis, colitis), chronic pancreatitis, inflammatory bowel disease, coeliac disease
Eosinophilia associated with drugs	**Antibiotics:** Penicillins, cephalosporins, dapsone, sulfa-based antibiotics; **Xanthine oxidase inhibitor:** Allopurinol; **Antiepileptics:** Carbamazepine, phenytoin, lamotrigine, valproic acid; **Antiretrovirals:** Nevirapine, efavirenz; **Nonsteroidal antiinflammatory drugs:** Ibuprofen
Malignant lymphomas and solid tumors	**Blood-related neoplasms**: acute or chronic eosinophilic leukemia, lymphoma (T cell and Hodgkin), chronic myelomonocytic leukemia **Solid organ–associated malignancies**: adenocarcinomas of the gastrointestinal tract (gastric, colorectal), lung cancer, squamous epithelium related cancers (cervix, vagina, penis, skin, nasopharynx, bladder), thyroid cancer
Graft vs Host disease	**Rejection of solid organs including:** liver, pancreas, kidney, heart; **Chronic Graft vs Host dsease** after hematopoetic stem cell transplantation
Primary (clonal) eosinophilia	
Subgroups of diseases	**Examples of diseases**
Hematological neoplasms clonal eosinophilia	Myeloid and lymphoid neoplasms
	Chronic eosinophilic leukemia
	Atypical chronic myeloid leukemia with eosinophilia
	Chronic myelomonocytic leukemia with eosinophilia
	Chronic myeloid leukemia in accelerated phase or transformation
	Acute myeloid leukemia with eosinophilia
	Acute lymphoblastic leukemia
	Systemic mastocytosis
Idiopathic eosinophilia	

Summary
Eosinophilia is an important diagnostic and/or prognostic feature in a varied range ofpathological conditions from infections and allergies to malignancies. For this reason, this hematological disorder is anenormous diagnostic as well as therapeutic challenge and requires an interdisciplinary clinical approach, especially in cases with unclear manifestations. The development in understanding of possible causes of eosinophilia/hypereosinophilia and introducing molecular methods to diagnostic pathways contributed to improvement in prognosis in that groups of patient. However, a thorough medical history, the knowledge of the less common causes of eosinophilia and above all an interdisciplinary approachshould be applied in cases of eosinophilia by all physicans.

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