Hypereosinophilic syndromes (HES) – different possible faces – a challenge for doctors of various specialisations. Case-based review

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Abstract

For practical purposes, acquired eosinophilia can be divided into secondary, clonal, and idiopathic eosinophilia. The causes of secondary eosinophilia may be parasitic infections, allergic diseases, vasculitis, drug reactions, and lymphomas. Hypereosinophilic syndrome (HES) is a subcategory of essential eosinophilia. The diagnosis of idiopathic eosinophilia means that secondary and clonal eosinophilia have been excluded. The aim of this study was to present cases of patients with HES, showing the possible differentiation of organ involvement, which translates into various possible courses of HES. After analysing data from the literature on the clinical course of HES in our patients, we concluded that hypereosinophilic HES syndromes constitute a challenge for physicians of various specialisations. The common denominator connecting all cases will always be an increased number of eosinophilia and a good clinical response to anti-IL-5 antibody treatment.

Introduction

For practical purposes, acquired eosinophilia can be divided into secondary, clonal, and idiopathic eosinophilia. The causes of secondary eosinophilia may be parasitic infections, allergic diseases, vasculitis, drug reactions, and lymphomas [1–4]. Clonal eosinophilia is characterised by the presence of histological, cytogenetic, or molecular features of a primary bone marrow tumour. However, the diagnostic criteria for essential eosinophilia – including hypereosinophilic syndrome (HES) – are eosinophilia in peripheral blood of 1.5×10^3/µl or more persisting for at least 6 months (or shorter if there are symptoms requiring the use of drugs that reduce the number of eosinophils), with the exclusion of secondary eosinophilia and clonal signs of involvement of internal organs (various organs may be involved) and failure to detect T lymphocytes with abnormal phenotypes or clonal lymphocyte hyperplasia [5–8].

The diagnosis of idiopathic eosinophilia means that secondary and clonal eosinophilia have been excluded; the time criterion for the duration of hypereosinophilia is currently not necessary for the diagnosis of HES [9–13]. In children, rare congenital eosinophilia should be taken into account. HES is a subcategory of essential eosinophilia. HES are rare diseases, especially in children [14], with unclear aetiopathogenesis, chronic and progressive course, and varied clinical picture and prognosis, the common feature of which is high eosinophilia with the presence of eosinophilic infiltrates in tissues. An increase in the number of eosinophils is relatively common in tropical and subtropical areas, where it is mainly caused by helminthiasis affecting various organs.

In Western countries, the main causes of secondary eosinophilia are allergic diseases, drug reactions, cancer, or vasculitis, although the possibility of parasitic infection should always be taken into account [1].

To sum up, the diagnosis of HES is based on the criteria proposed in 1975 by Chusida *et al.* [5]. They include the following: hypereosinophilia > 1500 cells/µl, persisting for more than 6 months (or the patient's death within 6 months of the diagnosis of hypereosinophilia and related to hypereosinophilic disease), and exclusion of secondary eosinophilia and detection of organ complications, especially the cardiovascular system, lungs, skin, and nervous system [5]; however, according to current opinion, the criterion of duration of hypereosinophilia > 6 months is not necessary for the diagnosis of HES [12, 13].

The detection of hypereosinophilia and organ complications, especially cardiovascular ones, after excluding secondary eosinophilia, justify the diagnosis of HES and immediate initiation of treatment aimed at preventing further and irreversible organ damage. The diagnosis of HES should be considered in patients with an absolute eosinophil count > 1500 cells/µl doc-

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umented on 2 occasions at least 1 month apart and/or in patients with pathologically confirmed tissue hypereosinophilia. It should be noted that this entity has been known for decades, and early studies identify distinct groups of patients with different symptoms, test results, laboratory abnormalities, and prognoses.

In the past, such patients were treated with non-targeted immunosuppressive drugs, often with limited effectiveness. The development of science has allowed for a more detailed definition of many subgroups of diseases characterising HES [15–19]. As a cell, a mature eosinophil produces various mediators, i.e. substances responsible for causing and maintaining inflammation. Mediators secreted by eosinophils participate in the process of killing viruses, bacteria, cancer cells, and parasites and influence the functioning of other cells of the immune system. In addition to these beneficial functions for the body, eosinophils are involved in the development of various diseases, mainly allergic but not limited to them; therefore, in the course of hypereosinophilic syndromes, various organs and systems may be affected and, therefore, very diverse clinical symptoms may occur, which significantly delays both the diagnosis as well as the implementation of appropriate therapeutic procedures [20]. Advances in the study of polymorphonuclear eosinophils have led to new approaches in HES, contributing to the development of new and effective therapies. Recently, advances in knowledge of eosinophil biology and molecular diagnostics have allowed for a more detailed definition of many subgroups of diseases that characterise hypereosinophilic syndrome. The identification of these groups has led to a personalised approach to treatment [17]. The decision to treat HES should be guided by both the clinical picture and the results of laboratory and mutational analyses [15]. HES is defined as persistent and marked eosinophilia and eosinophil-related organ damage in the absence of any obvious cause of hypereosinophilia. Two variants of HES have been characterised, differing in prognosis and possible associations with cancer diseases, such as myeloid leukaemia or T-cell lymphomas. The lymphocytic variant of HES (L-HES) is characterised by the presence of T-cell clones, IL-5 expression, and possible progression to T-cell lymphoma. In addition to steroid therapy, the anti-IL-5 monoclonal antibody mepolizumab is considered a targeted therapy for L-HES.

Currently, clinical trials are being conducted on the effectiveness of the anti-IL-5r monoclonal antibody benralizumab in the treatment of HES, which appears to be at least equally effective alternative to mepolizumab.

The myeloproliferative variant of HES (M-HES) is associated with an increased risk of myeloid leukaemia and good response to anti-tyrosine kinase therapy. The target of imatinib is a kinase resulting from an 800-kb deletion on chromosome 4. The Fip1-like fusion gene for platelet-derived growth factor 1a (FIP1L1-PDGFRA) has been recognised as a marker of response to anti-tyrosine – this is the so-called kinase therapy. Due to this, early identification of HES variants seems to be crucial for the rapid implementation of early and appropriately adapted therapy [16].

Aim of the research

The aim of this study was to present cases of patients with HES, showing possible differences in organ involvement, which translates into various possible courses of HES. The paper describes the case of 18- and 42-year-old patients with HES, whose first clinical manifestation was involvement of the respiratory system, and a 56-year-old patient whose first clinical manifestation was skin involvement.

Case reports

Case 1

An 18-year-old patient with diagnosed bronchial asthma and chronic rhinitis accompanied by sinusitis and high eosinophilia was admitted to expand the allergological diagnosis and possibly verify the therapy. In the interview, the patient was diagnosed with juvenile idiopathic arthritis – monoarticular form in the first year of life (she was treated with sulfasalazine and prednisone from the beginning – the treatment was discontinued in 2007 due to achieving remission) and later with skin psoriasis. Upon admission to the ward, physical examination revealed single scaly patches on the scalp and trunk. Visible features of hirsutism were seen, as well as features of nasal blockage and auscultation of single wheezes over the lung fields. Specific IgE was taken – in class 2 for beef and pork, other results were in class 0. In spirometry, obstruction was reversible, the improvement was insignificant. Echocardiography showed that the left ventricle (LV) muscle was not enlarged, there were no specific contractility disorders, and the heart valves were without any significant changes. In colonoscopy there were no changes. In gastroscopy, gastritis, gastroesophageal reflux disease (GERD), and urease test were negative. The patient remains under gastrointestinal observation. Taking into account the course of the disease and the results of additional tests, the diagnosis of bronchial asthma and chronic rhinitis with sinusitis was maintained, and HES was diagnosed. After analysing the medical history, the respiratory system was considered to be the first location of the disease.

Case 2

A 56-year-old woman, after thyroidectomy in 1998 due to papillary carcinoma, with eosinophilia and leukocytoclastic vasculitis diagnosed for many years, was referred to the department to extend the diagnos-

tics towards hypereosinophilic syndrome. For many years, she had been reporting purpura-like lesions that persisted on the skin of the lower legs and periodically appeared on the skin of the forearms. For this reason, the patient was diagnosed for many years and hospitalised several times in dermatology clinics. The patient has also been under observation for HES for many years. In September 2022, the patient was hospitalised in the Department of Internal Diseases – the tests performed there revealed eosinophilia, high D-dimer concentration, high γ-glutamyl transferase (GGTP) activity, and increased lgA and lgG concentrations; no cryoglobulins, antinuclear antibodies, or p- and c-ANCA were detected, the concentration of complement component C3 was normal, and increased concentration of complement component C4 was found. Computed tomography (CT) of the abdominal and pelvis described enlargement of the liver (190 mm) and spleen (136 × 88 × 163 mm), and dilatation (up to 18 mm) of the portal vein and splenic vein and the distal section of the superior mesenteric vein. During the diagnosis, a trephine biopsy was performed – no signs of primary bone marrow disease were found. In May 2023, she was hospitalised in the Rheumatology Department – tests performed in the department revealed anaemia with moderate eosinophilia, slightly elevated inflammatory parameters, uric acid, TSH, alkaline phosphatase and GGTP levels, and hypertriglyceridaemia. No parasite eggs were found in the stool. Sterile leukocyturia and erythrocyturia were observed. Infection with hepatotropic viruses was excluded. Upon admission, the patient reported pain in the knee joints and persistent purpuric lesions on the skin of the lower legs. There was no fever, Raynaud's phenomenon, or symptoms of dryness during the course of the disease. Upon admission to the department, physical examination revealed purpuric-type lesions on the skin of the lower limbs, and no other significant deviations from the normal condition were found. Abdominal ultrasound revealed right kidney stones and enlargement of the liver and spleen. The echocardiogram was normal. The patient underwent bronchofiberoscopy, which did not reveal any changes. Non-contrast CT scan of the chest revealed discrete fibrotic changes in the apexes. Segmental pleural thickening and small subpleural linear lesions in the dorsal-basal segments of the lungs were seen. A subpleural nodule with diameter of 3 mm was revealed in right segment 2. Discreet small nodular lesions were seen at the top of right segment 6 with a slight thickening of the oblique fissure at their level. Apart from that, the lungs had no focal changes or parenchymal densities. The width of the bronchial tree was normal. Subcarinal and periesophageal lymph nodes had a diameter of up to 12 mm in the short axis. Moreover, the mediastinum did not have significantly enlarged lymph nodes. In ECHO of the heart, trace of fluid was seen in the pericardial sac. The liver had dimensions AP – 162 mm, and spleen with dimensions 135 × 79 mm. In the upper abdomen, the lymph nodes are larger than 15 mm in the short axis. This was accompanied by high eosinophilia of 32.30%. Taking into account the course of the disease and the results of additional tests, the diagnosis of leukocytoclastic vasculitis was maintained, and HES was diagnosed. After analysing the medical history, the skin was considered to be the first location of the disease.

Case 3

A 42-year-old woman with bronchial asthma and a family history of rheumatoid arthritis (mother) and psoriasis (father) was admitted to the department due to persistent hypereosinophilia and chronic sinusitis with polyps, for diagnosis and possible modification of treatment. In the interview, the patient reported the occurrence of psoriatic lesions on the skin approximately 7 years ago – at that time she was consulted by a dermatologist and topical preparations were used in the treatment, with improvement being achieved.

The first joint symptoms in the form of peripheral joint pain with variable localisation and swelling of the left ankle and wrist joints occurred in April 2023. Non-steroidal anti-inflammatory drugs were used in the treatment, with partial improvement. The tests performed did not reveal the presence of rheumatoid factor or anti-citrulline antibodies. No inflammatory changes were observed in the radiographs of the hands and feet. The patient was diagnosed with seronegative arthritis; since June 2023 she has been treated with methotrexate and is also taking aceclofenac. Abdominal imaging studies (December 2022 – ultrasound, February 2023 – MRI) described a cyst in the appendix uncinate pancreas, cyst and hepatic vascular malformation. The current symptoms include chronic nasal blockage, cough, periodic shortness of breath, pain in the knee joints, mainly the right and left wrist, with periodic swelling. The patient also reports episodic and local itching of the skin with the formation of linear lesions after scratching. The symptoms are accompanied by morning stiffness for about an hour. No significant abnormalities were described in the chest X-ray performed in October 2022. During the current stay in the department, a specific IgE food panel was collected, milk plus gluten – positive for egg yolk, peanut, sesame, pork, chicken in class 2 and beef in class 3, and inhalation high level of antibodies in class 5 to *Candida albicans*, house dust mites *Dermatophagoides pter.* and *Blomia tropicalis* in class 2 and farinae, flour mite, Timothy grass in class 1, and other results in class 0. In the echocardiographic examination, results were negative. The spirometry test revealed mild obstructive ventilation disorders. Abdominal ultrasound revealed liver and pancreas cysts. The blood count showed eosinophils at 24.90%. Due to the above test

Table 1. Summary of research results

Result	56-year-old patient	42-year-old patient	18 -year-old patient	Scope of standards
WBC	9.25 G/l	9.42 G/l	5.69 G/l	[4.00–10.00]
NEUT#	1.34 G/l	4.55 G/l	1.58 G/l	[2.80–6.80]
LYMPH#	3.42 G/l	1.93 G/l	1.47 G/l	[0.80–4.30]
MONO#	0.32 G/l	0.56 G/l	0.71 G/l	[0.20–0.80]
EOZ#	3.96 G/l	2.35 G/l	1.84 G/l	[0.00–0.50]
BASO#	0.05 G/l	0.03 G/l	0.09 G/l	[0.00–0.10]
NEUT%	14.50%	48.40%	27.80%	[48.70–70.10]
LYMPH%	37.00%	20.50%	25.80%	[17.40–44.30]
MONO%	3.50%	5.90%	12.50%	[3.10–12.00]
EOZ%	42.80%	24.90%	32.30%	[0.30–5.40]
BASO%	0.50%	0.30%	1.60%	[0.20–1.20]
RBC	3.16 T/l	4.26 T/l	4.62 T/l	[4.20–5.40]
HGB	8.5 g/dl	10.8 g/dl	13.3 g/dl	[12.0-16.0]
HCT	26.0%	33.2%	38.9%	[37.0–50.0]
PLT	164 G/l	320 G/l	282 G/l	[150–400]
IgE	44,600 IU/ml		67,100 IU/ml	[< 160]

results, the patient was also diagnosed with hypereosinophilic syndrome. After analysing the medical history, respiratory symptoms were considered to be the first manifestation of the disease (Table 1).

Discussion

Due to the fact that HES are a heterogeneous group of rare disorders characterised by peripheral eosinophilia and eosinophilic organ complications in various organs, diagnosis, as shown in the examples of the above patients, can be difficult and may be faced by physicians of various specialisations, for example, among the eosinophilic diseases treated by rheumatologists. Apart from eosinophilic granulomatosis with polyangiitis, there are also other organ and systemic diseases with hypereosinophilia, such as rare eosinophilic fasciitis. Only accurate differential diagnosis separating the diseases allows pathogenesis-oriented treatment [21, 22]. It should always be remembered that the most common causes of eosinophilia in the world are not HES but parasitic diseases, and in developed countries allergic diseases [23].

An additional difficulty is the fact that these diseases may coexist, as in our patients, which further complicates the diagnosis, and the fact that conventional therapies, including glucocorticoids and cytotoxic and immunomodulatory agents, have variable effectiveness and significant toxicity.

Although the recent development of eosinophil-targeted therapies, including tyrosine kinase inhibitors and monoclonal antibodies, provides the possibility of a more effective, less toxic approach to the treatment of HES, there are few data available on treatment effectiveness [18].

After excluding other causes of hypereosinophilia, all our patients were diagnosed with HES. All patients were qualified for a clinical trial assessing the effectiveness and safety of a monoclonal antibody directed against the interleukin-5 receptor. The monoclonal antibody directed against interleukin-5 is already used to treat HES – it limits the production of eosinophils in the bone marrow and reduces their number in the blood and lungs. Adult patients with inadequately controlled HES without an identifiable secondary non-haematological cause may be eligible for treatment with the preparation.

Based on the results of our patients, it is also worth noting that eosinophilia increases with age and decreases in morphotic parameters – it is difficult to say whether this is related to the duration of eosinophilic inflammation or whether it is a coincidence. To answer this question, a larger number of patients should be examined. A characteristic feature of all our patients was, apart from high eosinophilia, the presence of various rheumatic diseases, which may translate into a different course of the disease in each of them.

The basis for such different courses is the diverse and multipotential role of the eosinophil as a cell, which translates into the possible involvement of various organs. This large clinical diversity makes early diagnosis and, consequently, appropriate targeted treatment difficult – this is also shown by data from

the available literature [5, 7, 23]. Based on the cases considered, it seems that the duration of the disease is also important, which is related to the duration of eosinophilic inflammation, but this requires further observation. The authors treat the cases analysed above as an introduction to further considerations on hypereosinophilic syndrome, which can take many forms.

Conclusions

Although hypereosinophilic syndromes (HES) are rare HES disorders [14], they should be considered in patients with an absolute eosinophil count > 1500 cells/μl documented twice with an interval of at least 1 month and/or in patients with pathologically confirmed by tissue hypereosinophilia [17–19]. It is worth noting that in the course of HES, various organs and systems may be affected, including various first manifestations of the disease – the cardiovascular system, respiratory system, or skin [21, 22]. Therefore, HES hypereosinophilic syndromes constitute a challenge for physicians of various specialisations. The common denominator connecting all cases will always be an increased number of eosinophilia and a good clinical response to anti-IL-5 antibody treatment.

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Ethical approval

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Conflict of interest

The authors declare no conflict of interest.

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