

Diagnostic and therapeutic management in patients with hypereosinophilic syndromes

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KEY WORDS

chronic eosinophilic leukemia, eosinophilia, FIP1L1-PDGFR α , hypereosinophilic syndrome, imatinib

ABSTRACT

The hypereosinophilic syndromes (HES) are rare disorders characterized by sustained, nonreactive hypereosinophilia with eosinophilia-associated organ damage/dysfunction. The most frequent clinical manifestations include skin abnormalities, cardiac failure, and neurological deficits, but disease presentations differ between patients and every organ may be affected. HES patients are currently categorized according to 2 classifications: World Health Organization 2008 and Working Classification 2006, but both have several limitations in daily practice. Despite advances in our understanding of HES pathogenesis, more than 50% of patients are still diagnosed with idiopathic disease, while the remaining subset has myeloproliferative (M-HES) or lymphocytic (L-HES) variants. In 10% to 20% of patients with M-HES, a unique genetic marker, fip1-like1/platelet-derived growth factor receptor α (FIP1L1-PDGFR α), was identified. It has dramatically changed disease management since imatinib, a tyrosine kinase inhibitor, appeared to be highly effective in these patients with up to 100% of long-term hematological response. L-HES is associated with abnormal T-cell populations secreting excessive amounts of eosinophilopoietic cytokines, mainly interleukin 5 (IL-5). Recently, encouraging results of treatment with monoclonal antibody neutralizing IL-5, mepolizumab, have been published. Corticosteroids remain the first-line therapeutic option for patients who do not have FIP1L1-PDGFR α fusion transcript, but treatment discontinuation leads to the recurrence of eosinophilia. This review reflects the current state of knowledge on the pathogenesis and therapy of HES. The shortcomings of current definitions and classifications are also discussed.

Introduction The hypereosinophilic syndromes (HES) are characterized by prolonged nonreactive peripheral blood hypereosinophilia and associated tissue damage/dysfunction. Since 1975, 3 diagnostic criteria have been used to define HES: 1) blood eosinophilia $\geq 1.5 \times 10^9/l$ for longer than 6 months; 2) lack of secondary causes of eosinophilia (e.g., allergy, parasites, and others); and 3) presumptive signs and symptoms of eosinophilia-associated organ involvement.¹ As new and modern diagnostic and therapeutic procedures have been introduced, these criteria should be modified. Currently, patients with markedly increased blood eosinophilia and obvious tissue dysfunction should start the appropriate treatment before irreversible damage occurs and do not have to be observed for 6 months. The previous term, namely idiopathic HES proposed by Chusid et al.,¹ is no longer so common because in many cases we know the etiology.² There are

more controversies. We still do not know how to classify cases with undeniable eosinophilia-associated organ involvement, confirmed by imaging and histological studies, and without blood eosinophilia exceeding the threshold level. In fact, these patients do not fulfill the stringent criteria for HES, but they require treatment initiation due to unavoidable organ damage.

Some patients with long-term blood eosinophilia exceeding $\geq 1.5 \times 10^9/l$ do not exhibit any eosinophil-mediated organ dysfunction. Should we initiate treatment to prevent the development of potential complications or these patients need only our special attention? This question remains open. Moreover, in a small proportion of HES patients, a novel mutation, namely fip1-like-1 (FIP1L1)/platelet-derived growth factor α (PDGFR α), has been identified. This group of patients may not fully fit into the original definition of HES as a disease of unknown etiology.³

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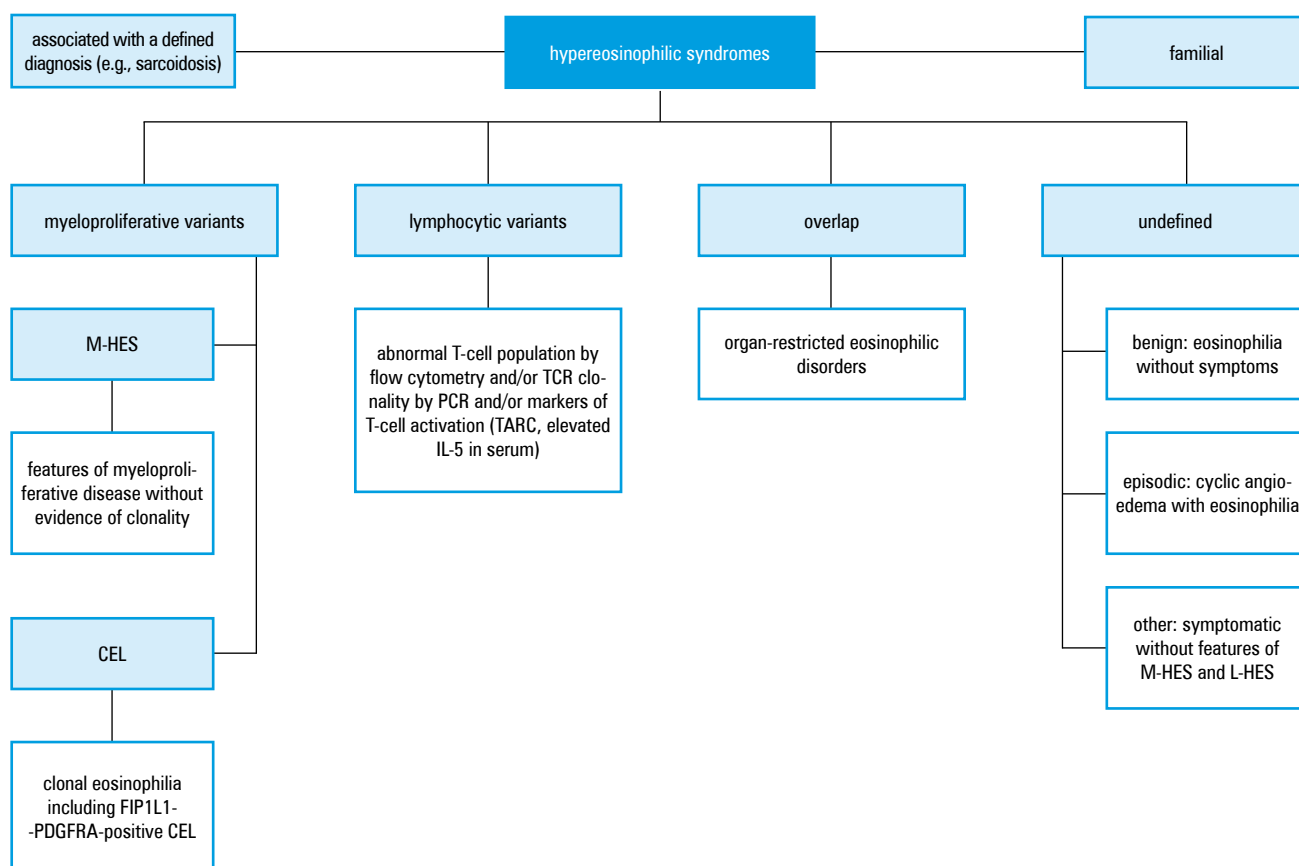


FIGURE 1 The Working Classification of hypereosinophilic syndrome, modified by authors⁴

Abbreviations: CEL – chronic eosinophilic leukemia, IL-5 – interleukin 5, L-HES – lymphocytic hypereosinophilic syndrome, M-HES – myeloproliferative hypereosinophilic syndrome, PCR – polymerase chain reaction, TARC – thymus and activation-regulated chemokine, TCR – T-cell receptor

A new clinical classification of HES was proposed in 2006, which addressed some of the controversial issues raised above.⁴ This scheme was based on clinical phenotype including also some aspects of HES pathogenesis. Unfortunately, despite the great progress in the understanding of HES pathogenesis observed in the recent years, the majority of patients fall into the category of undefined HES, which means that the mechanism of the disease remains unclear. This classification underlies the heterogeneity among the characteristics of HES (FIGURE 1).

According to the revised World Health Organization (WHO) Classification of Tumours of Hematopoietic and Lymphoid Tissues released in 2008, patients who meet HES criteria fall into 2 different categories: 1) myeloproliferative neoplasms including hypereosinophilic syndrome (M-HES) or chronic eosinophilic leukemia not otherwise specified (CEL-NOS); 2) myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, platelet-derived growth factor β (PDGFRB), and fibroblast growth factor receptor 1 (FGFR1).⁵ Unfortunately, this system has utility only in patients with proven eosinophilic clonality, and its drawback is that it is not useful in classifying idiopathic cases. Details on WHO classifications of myeloproliferative disorders were presented by Hellmann⁶ (see also TABLE 1).

To some extent, the management of HES patients appears to be standardized. Due to selection bias, there are discrepancies between the studies and therefore it seems necessary to prospectively evaluate different diagnostic procedures to better classify HES patients. The recommendations made herein are based on our long-term experience with a large patient population and the majority of conclusions are consistent with the data provided by others.

Patient 1 A 35-year-old woman suffered from progressive fatigue and pruritus. She presented erythematous papules and nodules on physical examination. Chest X-ray revealed bilateral non-specific infiltrates and echocardiography showed mitral valve regurgitation. Her white blood cell (WBC) count was $25 \times 10^9/l$ with 60% of mature eosinophils; hemoglobin concentration and platelet count were normal. Bone marrow was occupied by eosinophils in 50%; no increased number of blast cells was observed. Reactive causes of eosinophilia were excluded. Cytogenetics was normal. Molecular studies did not detect BCR-ABL, PDGFRA, PDGFRB, and FGFR1 rearrangements. No aberrant T cells in peripheral blood were seen on flow cytometry (FC); T-cell receptor (TCR) clonal rearrangements by polymerase chain reaction (PCR) were not found either.

TABLE 1 The World Health Organization classification of myeloid malignancies (abridged version which includes eosinophilia-related categories only)⁵

myeloproliferative neoplasms
chronic myelogenous leukemia, BCR-ABL1-positive
chronic neutrophilic leukemia
polycythemia vera
primary myelofibrosis
essential thrombocythemia
chronic eosinophilic leukemia not otherwise specified/hypereosinophilic syndrome
mastocytosis
myeloproliferative neoplasms, unclassifiable
myeloid and lymphoid neoplasms associated with eosinophilia and genetic abnormalities
myeloid and lymphoid neoplasms associated with PDGFRA rearrangement
myeloid neoplasms associated with PDGFRB rearrangement
myeloid and lymphoid neoplasms associated with FGFR1 abnormalities

Question: What is the diagnosis in the light of the above classifications? What are the first and subsequent lines of treatment in this case? This is an example of idiopathic HES. Due to the lack of proven clonality and myeloproliferative features, we cannot classify this patient according to the revised WHO classification.⁵ Clinically, it is an undefined category of HES. Patients belonging to this subgroup are symptomatic with evidence of organ involvement. Men are affected by HES more often than women, but this is true only for M-HES. In idiopathic HES both sexes are equally affected. Clinical manifestations of HES typically include blood (100%), heart (58%), skin (56%), nervous system (54%), and lungs (49%); however, almost every organ may be involved.² Initial evaluation of the patient with hypereosinophilia includes complete blood cell count, biochemistry, serum vitamin B₁₂, immunoglobulin (Ig)-E, and tryptase levels. The minimum imaging work-up should contain chest radiography, abdomen ultrasound, and echocardiography. Histological examination is necessary to confirm eosinophil-associated tissue involvement.

Patients with undefined HES do not meet the criteria for myeloproliferative and lymphocytic HES variants. They should have normal vitamin B₁₂ and serum tryptase levels. They usually show no anemia and thrombocytopenia and have no hepatosplenomegaly, myelofibrosis or abnormal mast cells. Marrow cellularity is not increased.⁴ There is no evidence of clonality on cytogenetic and molecular levels. We should keep in mind that this subgroup may develop T-cell clone after several years from the diagnosis, and therefore the repeated analysis towards abnormal T cells is recommended. Some authors suggest that an undefined HES may actually represent T-cell-driven disease (lymphocytic HES).⁷ On the other hand, there have been no reports on the possibility to acquire the FIP1L1-PDGFR (F/P) mutation during the disease course, which

briefly means that this fusion is either detectable or not at the initial diagnosis.

Eosinophilia-associated organ dysfunction in HES results from the detrimental effect of toxic substances released from eosinophilic granules. They include major basic protein, eosinophilic cationic protein, and eosinophil-derived neurotoxin.⁸ The major goal of HES treatment is to decrease blood and tissue eosinophilia. The first and the most important question is whether a patient needs urgent therapy. In the case of life-threatening complications including cardiac failure, respiratory insufficiency, or progressive paresis, the treatment with methylprednisolone at a dose of 1 mg/kg/d should be initiated as soon as possible. In the remaining ones, oral prednisone is started at 1 mg/kg/d for 1 to 2 weeks and then the dose is de-escalated over the next 2 to 3 months.^{9,10} After steroid initiation, we usually observe prompt decrease of blood eosinophilia with resolution of symptoms within 1 to 2 weeks. The functions of the affected organs return to normal within 2 to 3 months. Our own experience indicates that in the majority of HES patients, the minimum effective steroid dose varies between 10 and 20 mg daily, and steroid discontinuation leads to rapid eosinophilia recurrence associated with disease symptoms. We can summarize that the majority of HES patients are steroid-dependent, and in daily practice we did not observe symptom-free patients after steroid cessation. If so, the diagnosis of HES should be re-evaluated. If patient requires prednisone at a dose of 10 to 20 mg daily to maintain the response, low doses of hydroxyurea or interferon should be considered as steroid-sparing agents.^{11,12} In a small subset of steroid-resistant patients or in the case of steroid intolerance, we should start other therapies including hydroxyurea and interferon in higher doses, cladribine, or ciclosporin.¹³

Patient 2 A 55-year-old asymptomatic man was admitted to the hospital because of a markedly elevated WBC count ($55 \times 10^9/l$) observed during routine work-up. His hemoglobin concentration was slightly decreased, while the platelet count was normal. On admission, he revealed moderate splenomegaly. No other abnormalities were detected in imaging tests. There was 40% of dysplastic eosinophils in the bone marrow. Molecular tests were normal except for the presence of F/P by PCR.

Question: Should we start any treatment in this asymptomatic HES patient expressing the FIP1L1-PDGFR fusion? How should we treat the FIP1L1-PDGFR mutant cases? A small proportion of patients fulfilling the stringent Chusid's criteria have an interstitial deletion in chromosome 4q12 that generates the F/P fusion protein.³ These cases are currently classified as CEL F/P-positive (Working Classification) or myeloid neoplasms with PDGFRA mutation (WHO Classification). F/P

TABLE 2 Characteristic clinical features of the myeloproliferative hypereosinophilic syndrome¹⁵

male sex in a majority of patients
FIP1L1-PDGfra fusion positive in about 10%–20%
dysplastic eosinophils in differential
elevated serum vitamin B ₁₂ level
elevated serum tryptase level
anemia or thrombocytopenia
hepatosplenomegaly
increased bone marrow cellularity
atypical mast cells in marrow
myelofibrosis
response to imatinib
cardiac involvement

fusion has been detected in a variable proportion of patients and the estimated frequency of this mutation varies between 10% and 20%.^{13–15} This discrepancy may result from referral bias of patients who present various clinical manifestations and therefore consult doctors of different subspecialties. Moreover, we have observed the difference in the inclusion criteria between the published reports. Clinical presentation of CEL F/P-positive patients include splenomegaly, skin changes, neurological and cardiac involvements.^{15–18} Details of clinical features of M-HES are presented in **TABLE 2**.

Nowadays, it is crucial to detect the F/P mutation early in the disease course. Delay in molecular testing may lead to misdiagnosis and progression to an accelerated phase of the disease.¹⁹ The exquisite response to tyrosine kinase inhibitor (TKI), imatinib mesylate (IM), in HES patients expressing F/P fusion has been well documented in several clinical trials.^{3,15,17,18} This fusion gene is detected using PCR or fluorescence in situ hybridization (FISH) for CHIC2 deletion.³ IM at 100 mg daily is sufficient to induce clinical and hematological remission with a response rate close to 100%.^{15,17,18} A dose needed to maintain remission has not been established yet. In 2 large studies, the maintained IM dose was 100 mg daily.^{17,18} Our study showed that a single weekly dose of IM was effective for remission maintenance even at a molecular level.²⁰ These encouraging results were then confirmed in our follow-up study.²¹ On the other hand, it was proved that IM dose reduction or discontinuation may lead to a clinically occult relapse.²² Our long-term analysis (maximum follow-up at maintained dose of 61 months) denies this statement. In clinical practice, we recommend to start IM therapy at 100 mg daily and then continue at 100 mg weekly as a remission maintenance with molecular check-up every 3 to 6 months.

Given the poor prognosis of F/P-associated CEL,²³ treatment with IM is recommended even in asymptomatic patients to prevent the development of organ irreversible damage. It is noteworthy that IM resistant, mutant F/P-positive cases have been reported. It was documented that

TABLE 3 Characteristic clinical features of the lymphocytic hypereosinophilic syndrome

both sexes affected
FIP1L1-PDGfra fusion negative
elevated serum immunoglobulin E levels
elevated serum interleukin (IL)-5 and/or IL-4 levels
elevated serum thymus and activation-regulated chemokine
abnormal or clonal T-cell population in blood
frequent cutaneous manifestation
history of atopy
good response to corticosteroids

T674I mutation was sensitive to second generation TKI, nilotinib.²⁴ In TKI-resistant cases, allogeneic hematopoietic stem cell transplantation (AH SCT) needs to be considered.^{9,10} It should be kept in mind that IM treatment may induce cardiac failure, which is reversible with corticosteroids (CS). It is recommended to measure serum troponin levels and perform echocardiography before IM institution; if the heart is involved, we continue concomitantly IM with CS for the first 2 weeks of therapy.²⁵

Patient 3 A 42-year-old men presented with eczema and congestive heart failure. His blood eosinophil count was $5 \times 10^9/l$, he was also slightly anemic (hemoglobin, 10.8 g/dl). Bone marrow has shown 80% of eosinophils. The following mutations were undetectable: BCR-ABL, PDGFRA, PDGFRB, and FGFR1, while TCR clonal rearrangements were found by PCR. FC revealed the aberrant subset of CD2+CD3–CD4+CD5+CD7–CD8–T cells. Serum IgE and interleukin (IL)-5 levels were elevated.

Question: How should we manage the patient with L-HES? What is the prognosis in such cases? In L-HES, an aberrant T-cell subsets produce an excessive amount of IL-5. Concomitant production of IL-4 and IL-13 by T lymphocytes may explain the association of blood eosinophilia with elevated serum IgE levels. It was proved that HES patients with increased serum IgE levels had less likely life-threatening complications of hypereosinophilia and responded better to the treatment with steroids.²⁶ The presence of abnormal T cells in peripheral blood by FC and/or TCR clonal rearrangements are currently required to diagnose L-HES. The estimated frequency of L-HES among all HES patients is about 17%.¹³ Characteristics of clinical features of L-HES was shown in **TABLE 3**.

The pioneer investigation of T cells in a male patient with hypereosinophilia and elevated serum IgE levels led to the discovery of a phenotypically abnormal population of CD4+ cells lacking membrane expression of CD3. These CD4+CD3– cells produced IL-4 and IL-5 in vitro and they appeared to be monoclonal.²⁷ Of note, measurement of serum IL-5 levels is not indicative of T-cell-mediated

disease, and it should be measured in supernatants of ex-vivo T cells, but it is not applicable in daily practice.²⁸ The presence of purified aberrant T cells secreting excessive amounts of IL-5 was then reported by others, namely the CD4+CD3- cells were demonstrated in 26% of the patients studied by Simon et al.²⁹ Now it has become a common practice to analyze blood T-cell phenotype by FC and/or investigate TCR gene rearrangement by PCR. Although the CD4+CD3- are the most prevalent T-cell clones associated with L-HES, 2 other lymphocyte T subsets seem to be involved in this variant, namely CD3+CD4-CD8- and CD3+CD4+CD7-. It was also demonstrated that these cells were monoclonal and they secreted IL-5.³⁰ On the other hand, it was also proved that quite large HES population may have isolated TCR clonal rearrangement.^{31,32} In these particular cases without concomitant aberrant T cells in immunophenotyping, the diagnosis of L-HES cannot be established. We can only suspect T-cell-mediated HES, but the mechanism of hypereosinophilia remains unclear.²⁸ Moreover, isolated T-cell clonality was found in older patients³³ and in patients with cytomegalovirus (CMV) infection.³⁴ TCR clonal rearrangement was also detected in F/P-positive CEL^{31,32} and disappeared after imatinib treatment.³¹ In a vast majority of patients, we are not able to demonstrate the presence of T-cell clones, but the diagnosis of L-HES is likely. An indirect evidence includes an increased serum eosinophilopoietic cytokines levels or T-cell activation marker such as thymus and activation-regulated chemokine.²⁶

Another important finding regarding patients with CD4+CD3- cells is the development of T-cell lymphomas after several years of sustained hypereosinophilia.²⁹ There were single reports that partial deletion of chromosome 6q in CD4+CD3- cells was responsible for the progression to overt lymphoma.³⁵

In the light of presented data, it is crucial to eradicate the abnormal T-cell clone to prevent the development of T-cell lymphoma. CS remain the first-line option, but the results published to date are unsatisfactory. The affected patients responded well in terms of clinical symptoms and blood eosinophilia, but proportion of T-cell clones circulating in blood remained stable or only a minor decrease was noted.^{36,37} There was a single report on the high efficacy of interferon α combined with CS. The authors documented a complete disappearance of the CD4+CD3- cells in blood.²⁸ Our current attention is focused on 2 monoclonal antibodies: anti-CD52 (alemtuzumab) and anti-IL-5 (mepolizumab). In a recently published study, intravenous alemtuzumab at a dose of 5 to 30 mg 1 to 3 times a week resulted in 91% of response defining as normalization of eosinophilia count and disease symptoms alleviation. Due to increased risk of immunosuppression, the risk/benefit ratio must be taken into consideration.³⁸ Mepolizumab has been shown to reduce CS dose in a majority of HES patients, but its efficacy in L-HES requires to be evaluated separately.³⁹

Patient 4 A 29-year-old man suffered from progressive weakness and productive cough. Examination showed enlargement of cervical and supraclavicular lymph nodes and splenomegaly. Chest X-ray revealed bilateral pulmonary infiltrates. Mitral regurgitation was noted on echocardiography. His blood eosinophilia was $24 \times 10^9/l$ and 32% of marrow was occupied by eosinophils. Serum IL-5 levels were elevated, while serum IL-4, tryptase and IgE levels were within the normal range. Molecular tests and immunophenotyping were normal. He was diagnosed with idiopathic HES and remained resistant to CS, hydroxyurea, interferon α , and ciclosporin.

Question: What is the next treatment option in this patient? Should we consider allogeneic transplantation in resistant HES cases? This case presents an advanced and resistant variant of idiopathic HES. The dilemma is what kind of treatment should we offer. First, we should consider IM, but the target is not defined. In a vast majority of published reports, IM appeared to be ineffective in idiopathic HES.⁴⁰ The initial dose of IM for these patients is 400 mg a day. In the largest study in this patient subset to date, hematological remission was documented in 14% of the cases, but the duration of response was very short.¹⁷ Better results were presented by the German Eosinophilic Study Group; 15 patients were treated with IM at 400 mg daily and 4 of them achieved long-term response.¹⁸ It has been suggested that short-course of higher IM dose (800 mg daily) may overcome disease resistance and lead to clinical response.⁴¹ We have documented long-term response in 4 of 8 IM-treated patients with a maximum remission duration of 88 months (data not published). It is likely that responding patients might have had yet undefined IM-sensitive mutations. The other option for resistant patients may include monoclonal antibodies.^{38,39} There is also a single report showing the efficacy of AHSCT.⁴² Shortly, AHSCT should be reserved only for patients with resistant disease as a salvage procedure.

Patient 5 A 43-year-old woman who presented with blood eosinophilia of $3 \times 10^9/l$ was referred to a hematological outpatient clinic. No abnormalities were found on physical examination. Hemoglobin concentrations and platelet count were normal. Cytogenetic, molecular and immunophenotypic tests were normal. The repeated blood examination performed 3 months later revealed $5 \times 10^9/l$ of eosinophils.

Question: How should we manage this case? This patient shows asymptomatic, chronic idiopathic eosinophilia. It is undefined, benign HES according to the Working Classification.⁴ Currently, no evidence justifies early introduction of treatment in such cases.¹⁰ Based on our own experience with a large population of HES patients, we suggest to follow blood eosinophilia in such patients at 3-month intervals. Once a year, we should

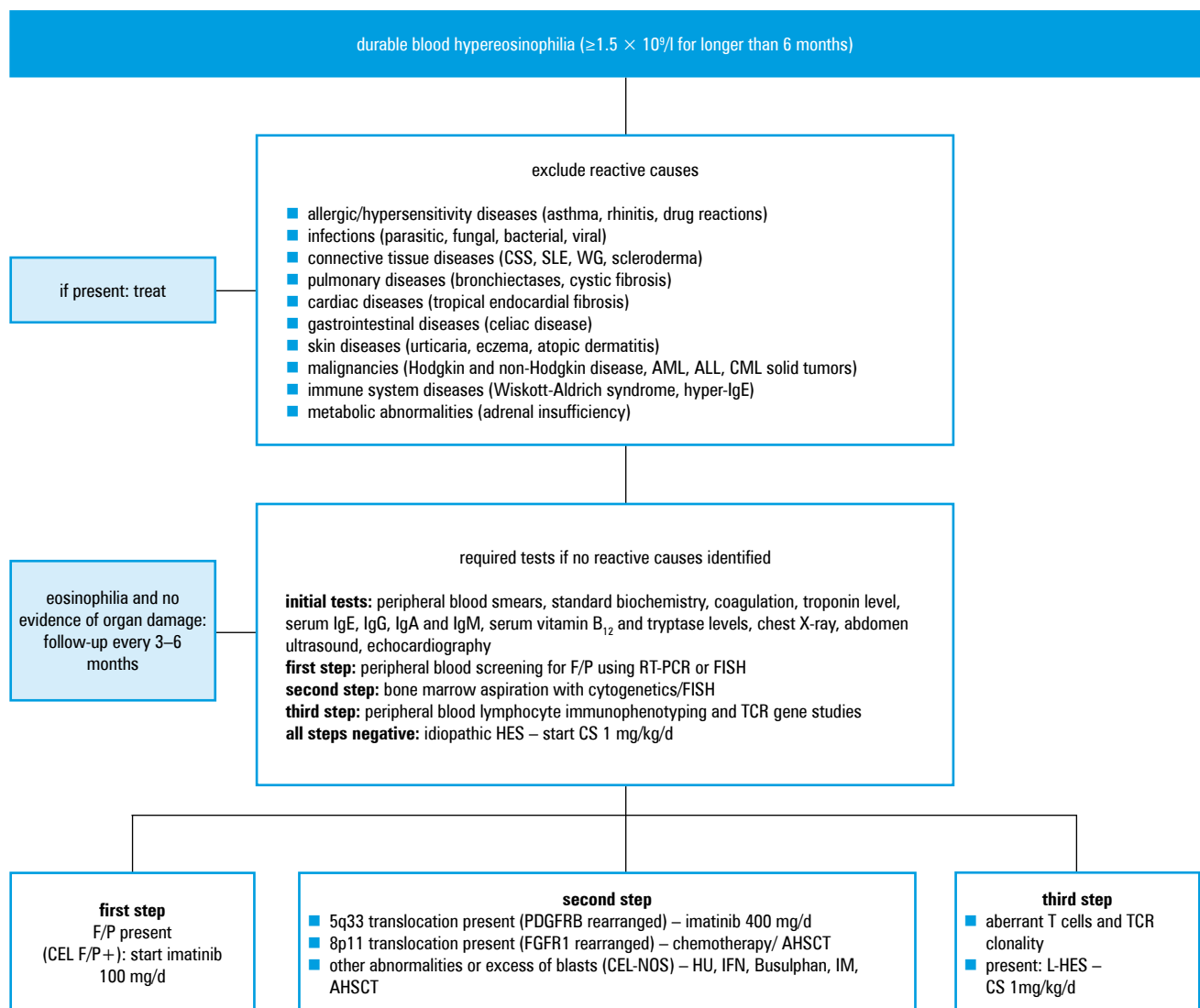


FIGURE 2 Diagnostic algorithm for patients with hypereosinophilia

Abbreviations: ALL – acute lymphoblastic leukemia, AHSCT – allogeneic hematopoietic stem cell transplantation, AML – acute myeloid leukemia, CEL-NOS – CEL not otherwise specified, CML – chronic myelogenous leukemia, CS – corticosteroids, CSS – Churg-Strauss syndrome, FGFR – fibroblast growth factor receptor, FISH – fluorescence in situ hybridization, F/P – FIP1L1-PDGFR α , HES – hypereosinophilic syndrome, HU – hydroxyurea, IFN – interferon, IM – imatinib, PDGFR β – platelet-derived growth factor receptor β , RT-PCR – reverse transcription-PCR, SLE – systemic lupus erythematosus, WG – Wegener granulomatosis, others – see **FIGURE 1**

perform abdomen ultrasound, chest X-ray, and echocardiography. Serum troponin levels should be also monitored regularly. In our practice, not supported by evidence, we initiate CS in asymptomatic HES patients only when blood eosinophilia exceeds $5.0 \times 10^9/l$ with a special attention to adverse drug effects. Our long-term experience shows that some patients without signs of disease at initial presentation may develop organ dysfunction after several years of moderate eosinophilia. As there are no standard guidelines, we recommend an individualized approach.

Patient 6 A 67-year-old man was diagnosed with acute myeloid leukemia (AML) M4 according to the French-American-British (FAB) classification. He had moderate splenomegaly at presentation. His WBC count was $22 \times 10^9/l$. Blood differential revealed 50% of eosinophils and 30% of myeloblasts. Hemoglobin concentration and

platelet count were 8.1 g/dl and $46 \times 10^9/l$, respectively. The marrow was occupied by myeloblasts in 35% and there was prominent eosinophilia (45%). Cytogenetics detected normal male karyotype. Molecular assay showed the presence of F/P rearrangement, whereas the CBF-MYH11 and RUNX1-RUNX1T1 transcripts were negative.

Question: Should this patient be treated with imatinib in monotherapy or in combination with chemotherapy? Is it reasonable to offer a prompt AHSCT? It was well documented that not only eosinophils were affected by F/P mutation. The presence of this fusion gene in multiple cell lineages was reported already in 2004.⁴³ To determine which hematopoietic cells are involved in HES pathogenesis, Robyn et al.⁴⁴ purified cells from specific lineages from a patient with M-HES variant and performed analysis towards F/P mutation using the PCR and FISH methods. It was

proved that not only eosinophils but also neutrophils, monocytes, lymphocytes T and B carried this mutation. This study provided the evidence that oncogenic hit occurs in a pluripotent stem cell, but it seems that only eosinophils and mast cells are sensitive to proliferation signal. In the light of presented data, it is not surprising that F/P mutation was found in patients with T-cell non-Hodgkin lymphoma and AML. In the largest report to date, five F/P-positive patients with AML were reported. All patients were male and AML was presented with different FAB subtypes. IM was initiated at the following doses: 100 mg daily (n = 4) and 400 mg daily (n = 1). Molecular remission was achieved in all cases after median of 6 months of therapy (range 1–14).⁴⁵ To conclude, we recommend screening all CBF-MYH11-negative patients with AML and eosinophilia towards the presence of F/P mutation. If this fusion is present, IM should be initiated concomitantly with conventional chemotherapy. Due to insufficient number of such cases, the long-term prognosis is difficult to be evaluated and AHST should be considered.

Patient 7 A 23-year-old man was diagnosed with CEL-NOS. He was treated with hydroxyurea and low dose of cytarabine. One year later, he was admitted to the hematological unit due to enlarged cervical lymph node. The histological examination of the excised lymph node revealed T-cell lymphoblastic lymphoma. His marrow aspiration performed at the same time was consistent with CEL. Conventional cytogenetic study detected translocation t(8;13) in 20 metaphases. He was re-diagnosed with the 8p11 myeloproliferative syndrome (EMS). Molecular assay confirmed the presence of FGFR1 mutation.

Question: How do we manage patients with EMS?

EMS is a rare disorder characterized by simultaneously or sequentially occurring BCR-ABL-negative myeloproliferative disorder and T-cell lymphoma. It terminates as AML, which remains resistant to conventional chemotherapy. The most frequent cytogenetic abnormality includes translocation at the 8p11 locus involving FGFR1 with the zinc finger gene-ZNF198 located at 13q11, but other partners for 8p11 were reported.⁴⁶ Typically, EMS affects men at different ages. It presents as generalized lymphadenopathy and hepatosplenomegaly.⁴⁷ This diagnosis of lymphoma may be preceded by several years of relatively stable course of myeloproliferative disorder. At the lymphoma presentation, disease is progressing aggressively, usually with high leukocyte count, but almost normal hemoglobin concentration and platelet count. The bone marrow shows features typical for chronic phase of myeloproliferative disorder with prominent eosinophilia except cases with AML transformation, in which blast predominance occurs.⁴⁸ Patients with EMS require aggressive combined chemotherapy followed by AHST.⁴⁹

Conclusions This review reflects the current knowledge on HES, based on which we propose a diagnostic algorithm for patients with hypereosinophilia (FIGURE 2).

Great progress in the recent years in the understanding of pathogenic pathways in HES has modified our diagnostic and therapeutic approach. The discovery of FIPL1-PDGFR fusion in a proportion of patients has changed our view on the disease mechanism and dramatically improved the prognosis in patients with this mutation. It should stimulate us to perform further molecular investigations, especially that more than 50% of HES cases are still idiopathic. The current definition of HES and the available classifications have many limitations and some adjustments should be introduced. The promising results of treatment with TKI and monoclonal antibodies not only point to novel therapeutic options, but also have a crucial role in the understanding of new pathogenic pathways. Prospective studies on large patient populations are needed to better characterize and classify this heterogeneous disease.

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Postępowanie diagnostyczne i terapeutyczne u pacjentów z zespołami hipereozynofilowymi

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SŁOWA KLUCZOWE

eozynofilia,
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imatinib, przewlekła
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hipereozynofilowy

STRESZCZENIE

Zespoły hipereozynofilowe (*hypereosinophilic syndromes* – HES) stanowią grupę rzadkich jednostek chorobowych charakteryzujących się długotrwałą, niereaktywną hipereozynofilią oraz uszkodzeniem eozynofilowym różnych narządów czy tkanek. Najczęstsza manifestacja kliniczna obejmuje zmiany skórne, niewydolność mięśnia sercowego oraz uszkodzenia nerwów, ale obraz kliniczny jest różny u poszczególnych chorych i każdy narząd może być objęty procesem chorobowym. Pacjenci z HES są obecnie klasyfikowani według klasyfikacji Światowej Organizacji Zdrowia z 2008 roku oraz Klasyfikacji Roboczej z 2006 roku, jednak praktyczne zastosowanie tych klasyfikacji ma wiele ograniczeń. Pomimo istotnego postępu w zrozumieniu patogenezy HES, u ponad 50% chorych przyczyna choroby nadal pozostaje nieznana, podczas gdy u pozostałych pacjentów wyróżniamy wariant mieloproliferacyjny i limfocytowy. U około 10–20% chorych z postacią mieloproliferacyjną zidentyfikowano rzadki marker genetyczny – onkogen FIP1L1-PDGFR. Jego odkrycie całkowicie zmieniło nasze postępowanie terapeutyczne, odkąd wykazano, że imatinib – inhibitor kinazy tyrozynowej – wykazuje dużą skuteczność w tej grupie chorych ze wskaźnikiem długotrwałych odpowiedzi hematologicznych sięgającym blisko 100%. Limfocytowy wariant HES jest wynikiem nadprodukcji cytokin eozynopoetycznych, zwłaszcza interleukiny 5 (IL-5) przez nieprawidłowe populacje komórek T. Ostatnio opublikowano obiecujące wyniki leczenia z zastosowaniem przeciwciała monoklonalnego skierowanego przeciwko IL-5 – mepolizumabu. Stosowanie kortykosteroidów pozostaje nadal leczeniem z wyboru u chorych z HES bez obecności genu FIP1L1-PDGFR, jednak zaprzestanie podawania tych leków wiąże się z nawrotem eozynofilii. Przedstawiona praca poglądowa odzwierciedla aktualny stan wiedzy na temat patogenezy i leczenia HES. Ponadto w pracy przedyskutowano niedoskonałości aktualnej definicji choroby oraz dostępnych klasyfikacji.

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