



Review

Hypereosinophilic syndromes – An enigmatic group of disorders with an intriguing clinical spectrum and challenging treatment

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ABSTRACT

Hypereosinophilic syndromes (HES) comprises a group of rare disorders characterized by blood hyper-eosinophilia ($>1.5 \times 10^9/l$) accompanied by eosinophil-associated organ damage. The 2016 World Health Organization classification recognizes a category of myeloid/lymphoid neoplasms with prominent eosinophilia (M/L_{eo}) and well-characterized gene rearrangements of *PDGFRA/B*, *FGFR1* or *JAK2*. *PDGFRA/B*-rearranged patients usually manifest as imatinib-sensitive myeloproliferative neoplasms (MPNs). *FGFR1*- and *JAK2*-rearranged cases may manifest as MPNs or aggressive lymphomas/leukemias and historically have had a dismal prognosis, although clinical trials with targeted treatment are promising. A negative screen for M/L_{eo} in a patient with myeloid features should prompt consideration of a diagnosis of chronic eosinophilic leukemia-not otherwise specified. If these are excluded and a secondary cause is not identified, a diagnosis of idiopathic HES and/or other rare variants of HES should be considered. This review, through an illustrative case, summarizes current knowledge on HES pointing at new directions in diagnosis and treatment.

1. Introduction

Hypereosinophilic syndromes (HES) encompass a group of rare disorders defined by persistent blood hypereosinophilia (HE) $>1.5 \times 10^9/l$ and eosinophil-associated organ damage. A diagnostic “step by step” algorithm for patients with HE begins with screening for the many secondary causes of (reactive) eosinophilia (secondary HES), after which a detailed evaluation for primary, clonal subtypes (primary or myeloid HES) should be initiated in patients with suggestive features. The latter work-up is mainly based on a wide range of molecular and cytogenetic studies. If all of the above are excluded, a diagnosis of idiopathic HES and/or other rare variants of HES should be considered. Disease prognosis is variable and depends on HES variant and availability of targeted treatment [1]. Herein, we summarize our approach to HES through an illustrative case.

1.1. Illustrative case

A 58-year-old previously healthy woman presented to the Dermatology Unit with a 2-week history of blistering skin changes after a

manicure. Fig. 2 (February 2016). Bloodwork revealed a slightly increased leukocyte count ($11.7 \times 10^9/l$). Blood film was normal except for hypereosinophilia ($3.79 \times 10^9/l$). Hemoglobin (13.3 g/dl) and platelet count ($323 \times 10^9/l$) were within normal ranges. Routine chemistries were normal. Chest X-ray and abdominal ultrasound were unremarkable. The evaluation initially focused on a hypersensitivity reaction to cosmetic ingredients. Antihistamines and prednisone (1 mg/kg orally) therapy resulted in only mild improvement of the skin lesions.

2. Classification

The normal eosinophil count in peripheral blood (AEC) ranges from 0.05 to $0.5 \times 10^9/l$, and normal values for bone marrow aspirates are between 1% and 6%. Blood HE is defined by $AEC \geq 1.5 \times 10^9/l$, recorded at least twice with a minimum time interval of 4 weeks (this time limit is not required for cases with rapid onset eosinophil-related organ dysfunction). Tissue HE is diagnosed when one or more of the following criteria are met: 1) eosinophils constitute more than 20% of all nucleated cells in bone marrow and/or 2) there is an extensive tissue infiltration as determined by pathologist and/or 3) marked extra-cellular

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Fig. 1. Ring-shaped skin target lesions.



Fig. 2. Blistering skin changes at diagnosis.

deposition of eosinophil-derived proteins is present using specific staining. Of note, immunostaining for eosinophil granule proteins is available only in specialized centers. Interestingly, tissue HE is usually, but not always, accompanied by blood HE. HE with eosinophil-associated organ damage/dysfunction is termed hypereosinophilic syndromes (HES).

HE and HES can be classified into several clinical subtypes, including 1) familial or hereditary HE/HES, 2) secondary (associated) HE/HES with known underlying cause, such as helminth infection or drug hypersensitivity, 3) secondary (lymphocytic variant) HE/HES driven by cytokine production from clonal and/or phenotypically aberrant T-cells, 4) primary (myeloid) HE/HES, 5) overlap HES and 6) idiopathic HE (or HE of undetermined significance (HEUS)/HES [1]. Details are presented in Table 1.

3. Clinical manifestations

Organ damage/dysfunction in HES results from eosinophilic tissue infiltration and/or deposition of eosinophil granules and granule-derived proteins released during cytolysis or by piecemeal degranulation. Clinical presentations of HES are variable and can involve any organ [2–4]. Regardless of the HES variant, dermatologic manifestations are most commonly observed with an estimated prevalence of 69% in a multicenter series of 188 consecutive patients with HES [4], 57% in a series of 44 patients with *PDGFRA*-positive MHES [5] and up to 80% in 21 patients with CD3-CD4+ lymphocytic variant HES (LHES) [6]. In the same multicenter series, pulmonary and gastrointestinal manifestations were next most frequently observed (in 44% and 38% of patients,

Table 1
Clinical characteristics of HE/HES variants.

Variant	Definition	Clinical characteristics
Familial	Hereditary HE or HES (excluding HE due to primary immunodeficiency)	Extremely rare Autosomal dominant transmission most common HE from birth with progression to HES uncommon
Associated	Secondary HE or HES with a defined underlying cause	Can mimic idiopathic HES Most common causes: drug hypersensitivity and helminth infection
Lymphocytic Variant	Secondary HE or HES driven by an aberrant or clonal T cell population secreting IL-5 or other eosinophil-promoting cytokines	No gender predominance Skin manifestations are common, although any organ can be involved Elevations in serum IgE, IL-5 and TARC are typically seen; IgG and IgM may also be elevated Progression to lymphoma in up to 25% of cases <i>FIP1L1-PDGFR</i> (FP) is the most common molecular abnormality identified followed by mutations/translocations involving <i>JAK2</i> Common features include: male predominance (most dramatic in <i>PDGFR</i> -associated), anemia (all)/erythrocytosis (<i>JAK2</i> only), thrombocytopenia, splenomegaly, elevated serum B12 levels, elevated serum tryptase levels (<i>PDGFR</i> and <i>KIT</i> only); increased bone marrow cellularity with dysplastic eosinophils (all) and atypical mast cells (<i>PDGFR</i> and <i>KIT</i> only), prominent fibrosis, increased blasts (CEL-NOS only) May progress to acute myeloid leukemia
Myeloid variant	Primary HE or HES with definitive or presumptive evidence of an eosinophilic primary myeloid neoplasm	Clinical manifestations depend on the underlying syndrome. Examples include single organ HES such as eosinophilic gastrointestinal disease and chronic eosinophilic pneumonia, as well as multisystem syndromes, such as eosinophilic granulomatosis and polyangiitis or episodic eosinophilia and angioedema (Gleich's syndrome)
Overlap	HES in the setting of a well-characterized clinical syndrome	Clinical manifestations are heterogeneous, can affect any organ and range from asymptomatic (hypereosinophilia of uncertain significance) to life-threatening
Idiopathic	HE or HES that does not fit into any of the above categories	

Legend: HE = hypereosinophilia; HES = hypereosinophilic syndrome; TARC = thymus and activation regulated chemokine.

respectively), followed by cardiac and neurologic involvement (each reported in 20% of patients) [4]. The most commonly reported symptoms of HES are fatigue, itching and shortness of breath [7]. In addition to eosinophilia and the resulting leukocytosis, hematologic findings can include anemia or erythrocytosis (in the setting of mutations in *JAK2*), thrombocytopenia or thrombocytosis, blood and marrow neutrophilia, basophilia, the presence of immature and dysplastic eosinophils and myeloid immaturity [3–6]. It should be highlighted that some hematological abnormalities, including thrombocytopenia and the presence of

blasts in the peripheral blood, are uncommon in patients with reactive or idiopathic HE/HES.

3.1. Case continued

The patient continued on prednisone with regression of skin changes which took a ring-shaped appearance. Fig. 3 (September 2016). AEC ($6.67 \times 10^9/l$) remained high and serum IgE level was elevated (682 IU/l; normal range < 100 IU/l). Serum tryptase and vitamin B12 levels were normal (7.66 ng/ml; $N < 11.4$ ng/ml and 345 ng/l; $N:165$ – 680 ng/l, respectively). Positron emission tomography (PET) scan demonstrated increased glucose uptake in the skin. Skin biopsy revealed subepidermal eosinophilic infiltrates forming micro-abscesses with numerous intra-epidermal blisters. Lymphocytic infiltrates were not seen. No features

typical of bullous pemphigoid or mastocytosis were demonstrated. A detailed work-up did not reveal a secondary cause of HE, and the patient was referred for hematologic consultation.

4. Work-up

Regardless of the HES variant, it is crucial to demonstrate that end-organ damage is caused by eosinophils. Although eosinophilic infiltration on tissue biopsy is touted as the gold standard, affected organs (other than skin) are not easily accessible and patients often present on corticosteroid treatment. Consequently, in routine practice, the typical initial approach is a detailed evaluation to exclude causes of organ dysfunction other than eosinophilia. Tests and studies should be guided by the patient's signs and symptoms and may include serum troponin T

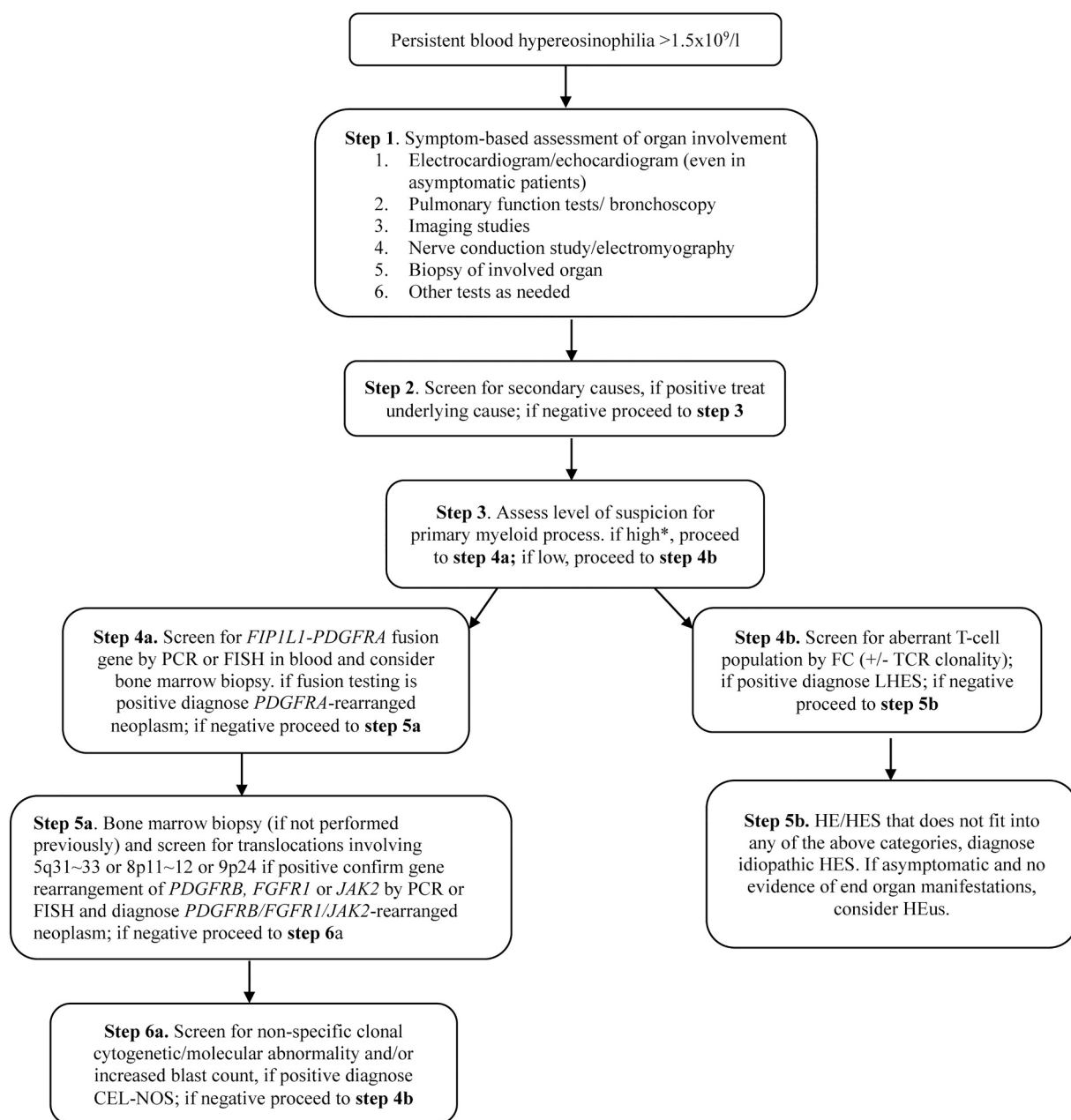


Fig. 3. Diagnostic step by step algorithm for hypereosinophilia. * including elevated serum B12 or tryptase, splenomegaly, dysplastic eosinophils or blasts in peripheral blood, unexplained anemia/thrombocytopenia, or known steroid-refractory eosinophilia. Abbreviations: CEL-NOS = chronic eosinophilic leukemia-not otherwise specified; FISH = fluorescence in situ hybridization; FC = flow cytometry; HE = hypereosinophilia; HES = hypereosinophilic syndromes; HEus = hypereosinophilia of undetermined significance; LHES = lymphocytic hypereosinophilic syndromes; PCR = polymerase chain reaction; TCR = T-cell receptor.

or I, electrocardiogram, echocardiogram, spirometry/bronchoscopy, nerve conduction study/electromyography and ultrasound/computed tomography/PET. Endoscopic examination and biopsy should be considered in patients with gastrointestinal symptoms [2].

The diagnostic process for patients with unexplained HE/HES should begin with the exclusion of the most common causes, which often requires the cooperation of many specialists. In this regard, the patient's history is crucial. Parasitic infections are among the most common causes of HE/HES worldwide. Consequently, a detailed travel and exposure history should be obtained in all patients with unexplained eosinophilia [8]. Although stool examination for ova and parasites will detect some helminth species, it is relatively insensitive and cannot detect parasites that do not have an intestinal phase (e.g., filarial species). Moreover, in many species (e.g., schistosomiasis and hookworm), eosinophilia is often most marked during early tissue before eggs or larvae are detectable in the stool. Due to the wide array of potential parasitic causes and the specialized serologic and other diagnostic testing required, consultation with an infectious disease expert is recommended if a parasitic cause is suspected. Recent initiation of a medication or dietary supplement may suggest drug hypersensitivity, and recurrent or unusual infections may point to an underlying primary immunodeficiency. Allergic and connective tissue disorders and metabolic conditions should be taken under consideration in the appropriate clinical situation. Several non-myeloid neoplasms, including Hodgkin lymphoma, T cell neoplasms, and some solid tumors, may be associated with HE/HES and should be excluded [1,2]. A list of common secondary causes of HE/HES is shown in Table 2.

4.1. Case continued

Bone marrow biopsy showed normal cellularity without fibrosis. Hematopoiesis was normal without features of dysplasia in any lineage. Mature eosinophils occupied approximately 60% of the bone marrow. There was no increase in blast cells. Cytogenetics revealed a normal diploid karyotype. The presence of clonal T lymphocytes in the blood was excluded using multiparameter flow cytometry. Molecular studies were negative for the following rearrangements: *BCR-ABL1*, *FIP1L1-PDGFR*, *ETV6-PDGFRB*, *JAK2V617F* and *FGFR1*. The patient was referred back to the dermatologist.

5. Workup (continued)

Once potentially treatable secondary causes of HES have been excluded, primary myeloid disorders should be considered. The blood smear should be carefully examined for the presence of blast cells, left-shifted leukocytosis, monocytosis and dysplastic features. Measurement of serum vitamin B12 and/or tryptase levels is useful, as elevations can be a clue to the presence of an eosinophilic myeloid neoplasm, especially those involving molecular abnormalities in *PDGFR* or *KIT*. Bone marrow aspiration and/or biopsy should be performed in all patients with

suspected primary myeloid HES. In-depth assessment should focus on the presence of dysplastic or immature eosinophils as well as on other abnormalities within myeloid or lymphoid cell lines. Standard karyotyping on marrow cells is mandatory. Immunohistochemistry and molecular analysis for *KIT* mutations should be done to exclude mast cell disease, especially when serum tryptase is elevated. Blood or marrow cells can be used for additional immunophenotyping and molecular assays [2].

The recognition of a growing number of eosinophil-associated molecular abnormalities prompted the creation of a new category in the World Health Organization (WHO) Classification including "Myeloid and lymphoid neoplasms with eosinophilia and recurrent abnormalities of platelet-derived growth factor receptor alpha/beta (*PDGFR*), fibroblast growth factor receptor 1 (*FGFR1*) or with *PCM1-JAK2*" [9] (Table 3). Recurrent cytogenetic abnormalities and point mutations have also been described. The initial evaluation of suspected myeloid HE/HES should be directed at the detection of a molecular or cytogenetic abnormality. Testing should begin with the screening of the peripheral blood for the presence of *FIP1L1-PDGFR* (F/P) rearrangement [10], the most common molecular abnormality associated with primary myeloid HES, accounting for approximately 10%–20% of patients with unexplained HE/HES [2,4,11]. F/P-associated myeloid neoplasms occur predominantly in males with peak incidence between 30 and 50 years of age, although rare cases have been described in children [12] and women [5,13,14]. Skin changes and splenomegaly are the most common clinical manifestations, although patients may present with a variety of symptoms and significant respiratory and cardiac involvement are relatively frequent. Some patients are asymptomatic with HE detected incidentally on routine blood examination [13].

Typically caused by a cytogenetically occult interstitial deletion on chromosome 4, del (4)(q12q12), the F/P fusion gene can be detected

Table 3
The 2016 WHO classification of eosinophil-related disorders [9].

Category	Criteria
<i>PDGFR</i> -rearranged neoplasm	1. Myeloid/lymphoid neoplasms with eosinophilia and 2. the presence of <i>FIP1L1/PDGFR</i> fusion gene or with other fusions of <i>PDGFR</i> gene
<i>PDGFRB</i> -rearranged neoplasm	1. Myeloid/lymphoid neoplasms with eosinophilia, sometimes with neutrophilia or monocytosis and 2. the presence of t(5;12) or a variant translocation or demonstration of an <i>ETV6-PDGFRB</i> fusion gene or other fusions of <i>PDGFRB</i> gene
<i>FGFR1</i> -rearranged neoplasm	1. MPN, MDS/MPN, AML or T-/B-cell lymphoblastic lymphoma/leukemia with eosinophilia and/or neutrophilia and/or monocytosis and 2. the presence of t(8;13) or a variant translocation leading to <i>FGFR1</i> rearrangement
<i>JAK2</i> -rearranged neoplasm	1. Myeloid/lymphoid neoplasms with eosinophilia and 2. the presence of t(8;9) or a variant translocation leading to <i>JAK2</i> rearrangement
Chronic eosinophilic leukemia-not otherwise specified	1. Blood hypereosinophilia 2. Exclusion of <i>BCR-ABL1</i> positive and negative MPN 3. Exclusion of <i>PDGFR</i> , <i>FGFR1</i> and <i>JAK2</i> -rearranged neoplasms 4. Exclusion of AML with inv.(16) or t(16;16) 5. The presence of clonal cytogenetic and molecular abnormalities (e.g. trisomy 8 or <i>ASXL1</i>) or blast cells >2% in blood or > 5% in marrow
Idiopathic hypereosinophilic syndrome	1. Exclusion of all above 2. Exclusion of secondary causes 3. The presence of eosinophil-associated end organ damage

Table 2
Common secondary causes of hypereosinophilia.

Category	Examples*
Allergic disorders	Asthma, atopic dermatitis
Infections	fungal (coccidioidomycosis, aspergillosis, histoplasmosis), helminthic (strongyloidiasis, filariasis, hookworm), ectoparasite (scabies), HIV
Neoplasms	leukemia, B- and T-cell lymphoma, Hodgkin lymphoma, solid tumors
Inflammatory disorders	Sjogren syndrome, IgG4-related disease, inflammatory bowel disease
Drug hypersensitivity	any prescription or nonprescription drug or supplement
Primary	hyper-IgE syndrome, Omenn's syndrome
Immunodeficiency	
Miscellaneous	cholesterol emboli, radiation, chronic graft-versus-host disease

using reverse transcriptase polymerase chain reaction (RT-PCR) and/or fluorescence in situ hybridization (FISH) [10]. RT-PCR detects most of the breakpoints within *PDGFRA* (exclusively exon 12) and *FIP1L1* (variable exons) but is not widely available and misses the rare cases of *PDGFRA*-associated neoplasms with alternate fusion partners and those with breakpoints in *FIP1L1* located outside the region of primer binding. FISH analysis is more convenient, due to the rapid detection of most deletions and easy access to many commercial probes, but is less sensitive and can miss splice variants with small deletions [15]. Other techniques, including next generation sequencing and quantitative (q) RT-PCR have been used but are more expensive and/or available only in specialized centers [16]. Of note, several fusion partners of *PDGFRA* other than *FIP1L1* as well as point mutations in *PDGFRA* have been identified [17]. These may be missed by standard diagnostic assays. Although there are no consensus guidelines, most experts recommend molecular monitoring using RT-PCR or FISH (if RT-PCR is not available) every 3 months during the first 3 years and every 3–6 months thereafter. Unlike CML, qPCR is not routinely used to monitor molecular response, in part due to technical issues related to the variable sizes of the deletion in individual patients [16,18].

PDGFRA-associated myeloid neoplasms usually manifest as chronic eosinophilic leukemia but can also present as T-cell lymphoblastic lymphoma (T-LBL) or acute myeloid leukemia (AML) [19] and rarely as chronic neutrophilic leukemia [20]. Whereas increased spindle-shaped mast cells are commonly seen, the typical paratracheal tight clustering seen in D816V *KIT*-positive systemic mastocytosis is rare [21].

Absence of the F/P fusion in a patient with clinical features of a primary myeloid neoplasm should prompt consideration of a trial of imatinib (see below) and evaluation for other less frequent eosinophil-related molecular abnormalities some of which, in contrast to F/P fusion, may be evident on conventional cytogenetics. The findings on karyotyping may suggest the need for more detailed testing using PCR or FISH to detect translocations involving 4q12 (other than F/P fusion partners of *PDGFRA*), 5q31-33 (*PDGFRB*), 8p11 (*FGFR1*) or *PCM1-JAK2*.

The frequency of the *PDGFRB*-rearranged neoplasms is reported to be low (less than 2% of all MPN) affecting males more commonly than females with a peak incidence in middle-aged adults [22,23]. Most patients have splenomegaly. Dermatologic involvement is rare but has been reported [24]. To date, more than 30 gene fusion partners of *PDGFRB* have been described, however the *ETV6-PDGFRB* fusion resulting from t(5;12)(q32;p13.2) is the most frequent. *PDGFRB*-rearranged neoplasms usually manifest as chronic myeloproliferative neoplasms (MPN) or chronic myelomonocytic leukemia (CMML). Single cases of AML with detectable *PDGFRB* fusions have also been reported [22,23].

FGFR1-related neoplasms are even less common (less than 1% of all MPN) and typically present as MPN with prominent eosinophilia. Patients may also show features of AML or T- or B-cell LBL [9]. Fourteen different *FGFR1* fusion genes have been identified to date, of which *ZMYM2-FGFR1* resulting from t(8;13)(p11;q12) is the most frequent. *FGFR1*-associated myeloid neoplasms have a moderate male predominance with a median age of onset of 30 years. Historically, the clinical course has been aggressive with poor prognosis [9,25], although recent case reports of durable remission with *FGFR1* inhibitors are encouraging [26]. Similar disease phenotypes and clinical outcomes have been reported for patients with *JAK2* fusions, of which *PCM1-JAK2* as a consequence of t(8;9)(p22;p24) occurs with the highest frequency. The initial clinical presentation of *JAK2*-rearranged patients is closer to that of chronic myeloid leukemia (CML) than any other MPN, but rapid progression to blast phase is typical. Males are predominantly affected with a median age of 50 years [9,27]. Since blood eosinophilia is frequently seen in patients with CML [28], screening patients for Philadelphia chromosome and/or *BCR-ABL* is also recommended. Finally, it is important to screen for recurrent molecular abnormalities associated with eosinophilic myeloid neoplasms that are not detected by cytogenetics, including mutations in *JAK2* (V617F and a recently described

mutation in exon 13), D816V *KIT*, and *STAT5b* [29–31].

A negative screen for recurrent molecular abnormalities in a patient with a bone marrow and clinical presentation suggestive of a myeloid neoplasm may be indicative of a diagnosis of chronic eosinophilic leukemia- not otherwise specified (CEL-NOS). CEL-NOS is an extremely rare MPN characterized by the presence of an increased percentage of blast cells in peripheral blood or bone marrow (more than 5% and less than 20%) and/or evidence of eosinophil clonality by karyotyping or molecular studies. Myeloid neoplasms with eosinophilia e.g. AML with inv16 or t(16;16) should be excluded. Of note, organ damage is not required for diagnosis [9]. A recent study from Mayo Clinic reported on the frequency and clinical outcome of a series of patients meeting WHO criteria of CEL-NOS. CEL-NOS accounted for <2% of all patients presenting with HE. The median age of patients was 63 years, and there was a male predominance (88%). Cytogenetic abnormalities were identified in 88% of patients, and *ASXL1* was the most common mutation on next generation sequencing (NGS) (43%) [32]. The prognosis of CEL-NOS remains poor with a median survival of 22 months and a high rate of leukemic transformation [32,33].

Lymphocytic variant HES is a term used to describe patients with a form of HES characterized by the expansion of clonal T-cells with an aberrant immunophenotype that produce cytokines that drive a reactive (secondary) eosinophilia [34]. This variant should be considered in a diagnostic “step by step” algorithm as these patients tend to be more difficult to treat and have an increased risk of developing lymphoma [6,35]. LHES variant accounts for approximately 15%–20% of cases with unexplained HE, and cutaneous manifestations are common [4]. Most commonly, these abnormal lymphocytes have dim or absent expression of CD3 (CD3-CD4+) or have a double-negative expression pattern (CD3 + CD4-CD8-); however other immunophenotypic abnormalities have been described [36]. Although isolated T-cell clonality by PCR without an abnormal T-cell immunophenotype is a relatively common finding in patients with HES, this is not sufficient to diagnose LHES in the absence of documentation of abnormal cytokine production by the clone [37]. Other biomarkers suggestive, but not diagnostic, of LHES include elevated serum IgE and thymus and activation regulated chemokine (TARC) levels.

Despite the growing progress in the development of molecular techniques, identification of recurrent molecular or cytogenetic abnormalities has been largely restricted to patients with clinical features suggestive of a myeloid neoplasm. Interestingly, a gain-of-function mutation in *STAT3* has been described in a patient with CD3-CD4+ lymphocytic variant HES [38] and a wide variety of somatic mutations have been reported using next-generation sequencing (NGS) in patients with idiopathic HES [39–41]. These findings should, however, be treated with caution as it is not clear whether the identified mutations are associated with the pathogenesis of the eosinophilia. A diagnostic algorithm for hypereosinophilia is presented in Fig. 1.

Early data on the epidemiology and clinical outcome of idiopathic HES are confounded, most likely due to the difficulty in separating between different HES variants. Nonetheless, survival in patients with idiopathic HES has improved over the years from 12% in the 1970s to >80% today, largely due to the success of imatinib treatment of patients with *PDGFRA*-associated myeloid neoplasms. That said, morbidity is significant, and cardiac failure remains the main cause of death [42].

5.1. Case continued

A repeat skin biopsy was inconclusive. The patient complained of severe itching, and the skin was dry with erosions, excoriations and blisters. Melanoderma was evident. Fig. 4 (August 2018). Blood HE was still present, and prednisone at 1 mg/kg was re-initiated without effect. She subsequently received dexamethasone, hydroxyurea, imatinib and vincristine, without clinical improvement. Blood HE remained $>20 \times 10^9/L$. Mepolizumab (Nucala™, GlaxoSmithKline) was initiated at 300 mg subcutaneous monthly in August 2019 with normalization of blood

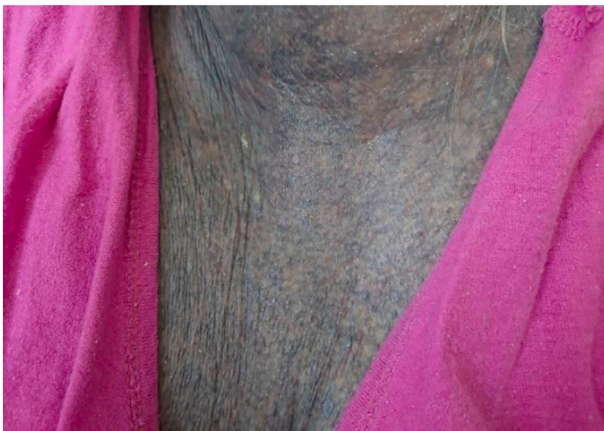


Fig. 4. Melanoderma while on steroids.

eosinophilia and significant resolution of clinical symptoms despite persistent melanoderma. She has required no further corticosteroid therapy. Fig. 5 (April 2020).

6. Treatment

The choice of therapy should be guided by acuity, clinical subtype and the nature of clinical manifestations resulting from eosinophil-attributable organ dysfunction (Table 4). Patients with imminent life-threatening complications of eosinophilia should be treated with high dose corticosteroids (at least 1 mg/kg prednisone equivalent). If there is a history of potential exposure to *Strongyloides*, this should be accompanied by a single dose of ivermectin (200 µg/kg). Conversely, treatment is generally not recommended for patients with asymptomatic HE (HEUS) [43], although some physicians (including one of the authors) prescribe a short course of prednisone when blood HE is persistently $>5 \times 10^9/l$ with the aim of reducing potential end organ complications [44]. In patients with a treatable secondary cause of HE, the treatment should be directed at the underlying disease.

Patients with known imatinib-sensitive mutations, including rearrangements of *PDGFRA/B* should receive imatinib mesylate (IM) as a first-line agent. In patients with a detectable *PDGFRA* fusion gene, IM should be initiated at 100–400 mg daily. The hematologic response is expected to be achieved within the days; whereas molecular response requires several weeks to months. The efficacy of low dose IM (100 mg daily) for suppression of *PDGFRA*-positive HES has been demonstrated by numerous groups with most patients in complete hematologic and



Fig. 5. Melanoderma persists on mepolizumab.

Table 4

Therapy for eosinophil-related disorders.

Disease category	Most common therapies	Suggested doses
<i>PDGFRA</i> -rearranged neoplasm	Imatinib	100–400 mg daily
<i>PDGFRB</i> -rearranged neoplasm	Imatinib	400 mg daily
<i>FGFR1</i> -rearranged neoplasm	Chemotherapy followed by allo-SCT	varied
<i>JAK2</i> -rearranged neoplasm	Ruxolitinib followed by allo-SCT	varied
Chronic eosinophilic leukemia-not otherwise specified	Hydroxyurea Interferon- α Pegylated interferon Chemotherapy followed by allo-SCT ^a	500–1000 mg daily 3–4 mU thrice a week 90 µg weekly varied
Idiopathic hypereosinophilic syndrome	Prednisone Hydroxyurea Interferon- α Pegylated interferon- α -2b Imatinib ^a Mepolizumab ^b Chemotherapy followed by allo-SCT ^c	varied 500–2000 mg daily 1 mU daily – 3 mU thrice a week 45–90 µg weekly 400–800 mg daily 300 mg iv/sc monthly varied
Lymphocytic variant hypereosinophilic syndrome	Prednisone Interferon- α Pegylated interferon- α -2b Mepolizumab Alemtuzumab	1 mg/kg daily 3–4 mU thrice a week 45–90 µg weekly 300 mg-700 mg iv/sc monthly 5-30g iv thrice a week

Legend: allo-SCT = allogeneic stem cell transplantation; iv = intravenous; sc = subcutaneous.

^a For patients with idiopathic HES with myeloid features.

^b FDA-approved for asthma (100 mg sc monthly), eosinophilic granulomatosis with polyangiitis and hypereosinophilic syndromes (300 mg sc monthly).

^c in resistant or transformed cases.

molecular remission after long-term follow-up [5,17,45]. Lower maintenance doses of IM (from 100 mg to 400 mg weekly), have also been used effectively, albeit in small series [46].

Durable remission after IM discontinuation has been reported in some *PDGFRA*-positive patients in complete molecular remission [14,45,47–49]. In one study of 12 patients, molecular relapse-free survival was 91% at 12 months and 65% at 24 months after stopping IM [48]. In a second series of 46 patients, 57% of patients relapsed after a median of 45 months [49]. Predictors of relapse included time to IM initiation and duration of IM treatment prior to cessation. Of note, all studies have confirmed that relapsed patients retain IM sensitivity and rapidly achieve second molecular response. Whereas primary IM resistance appears to be exceedingly uncommon in *PDGFRA*-positive disease, rare cases of acquired resistance to imatinib involving the T674I mutation within the ATP-binding domain of *PDGFRA* have been reported in the literature. Although the number of treated patients is few, nilotinib and sorafenib showed limited efficacy in this setting, whereas ponatinib seems to be highly effective [50,51].

Imatinib is also first line therapy in *PDGFRB*-rearranged neoplasms; however, a dose of 400 mg daily is usually required to achieve long-term response. In a small study of 26 patients, 6-year progression-free survival was 88% and a 10-year overall survival exceeded 90% [52]. In contrast, there is no place for imatinib in the treatment of patients with *FGFR1*-rearrangements. The therapeutic role of other small molecule inhibitors appears limited, although midostaurin and ponatinib were each found to be effective in single patients [53,54], and a recent phase 2 study of pemigatinib, a selective, oral inhibitor of *FGFR1*, in 14 patients resistant to prior therapy produced exciting results with 80% of patients achieving major cytogenetic and clinical response [55]. Nevertheless, at the present time, most patients require intensive chemotherapy alone or in combination with small molecules followed by allogeneic stem cell transplantation [56]. Similarly, whereas complete hematologic and

cytogenetic response to ruxolitinib therapy has been reported in some patients with *JAK2*-rearrangements, the durability of response has been variable [57,58]. Several agents have shown some efficacy in single patients with CEL-NOS, including hydroxyurea, interferon alpha, vincristine, cyclophosphamide, etoposide and cladribine. Corticosteroids (CS) are ineffective and should not be used [2].

Most patients with newly diagnosed HES, other than those with documented myeloid neoplasms, receive CS monotherapy as first-line treatment. Although the initial response rate is high (85% after one month of therapy), many patients become refractory over time or develop significant steroid side effects [4]. Whereas the starting and maintenance doses of CS are not standardized, the therapeutic goal is to find the minimal effective dose [59,60]. This minimal effective dose varies considerably depending on the HES clinical variant [60] and, in some patients may be related to high IL-5 levels [61] or abnormal steroid receptors [62].

The approach to second-line therapy in *PDGFRA*-negative, steroid non-responders with HES is complex and depends on a variety of factors, including HES clinical variant, side effect profile, patient and provider preference and cost (reviewed in [2]). Imatinib, the FDA-approved for the treatment of HES, has been used to treat patients with idiopathic HES with response rates between 20% and 40% at doses of 400-800 mg daily [4,63]; however, recent data suggests that durable responses are limited to patients with clinical findings indicative of an occult myeloid neoplasm [14].

Given the central role played by IL-5 as a differentiation, activation and survival of eosinophils, several drugs targeting the IL-5 axis have been investigated as potential therapies for HES. The best studied to date is mepolizumab (GlaxoSmithKline), an antibody to IL-5 that is approved for the treatment of severe asthma (100 mg sc monthly) and eosinophilic granulomatosis and polyangiitis (EGPA; 300 mg sc monthly). In a double-blind, placebo-controlled phase 2 trial in 85 patients with steroid-sensitive HES, mepolizumab (750 mg iv monthly) was significantly more effective than placebo as a steroid-sparing agent [64]. Subsequent studies demonstrated the durability of the response to mepolizumab [65] and the utility of mepolizumab in the treatment of steroid-refractory HES (as in the case of the patient described) albeit with lower response rates [66]. Based on the results of a phase 3 trial of mepolizumab (300 mg sc monthly) in reducing flares in adolescent and adult patients with steroid-responsive HES mepolizumab was approved by the FDA for the treatment of HES in November 2020. Whereas reslizumab (Teva Pharmaceuticals), a second monoclonal antibody to IL-5, is likely to be effective in HES, data is limited to a single small phase 2 trial [67] and isolated case reports. Finally, benralizumab, an afucosylated antibody to IL-5 receptor, that depletes eosinophils and their precursors by enhanced antibody-dependent cytotoxicity, was recently shown to be effective in a randomized, double-blind, placebo-controlled, phase 2 trial, in *PDGFRA*-negative treatment-refractory HES patients [68]. A phase 3 trial of benralizumab for HES is ongoing (NCT04191304). Other promising agents currently under study include monoclonal antibodies to the eosinophil inhibitory receptor, Siglec-8 (AK002), small molecule inhibitors of the eotaxin receptor and the oral dexamipexole (reviewed in [69]). Finally, allogeneic stem cell transplantation has been used successfully in treatment-refractory patients with aggressive disease, although its role in the routine treatment of HES has yet to be established [70].

7. Conclusions and future directions

Growing progress in the molecular understanding of unexplained HE has diminished the number of cases labelled as “idiopathic” HES and has translated into more precise therapy. In patients with *PDGFRA/B*-rearrangement, the tyrosine kinase inhibitor, imatinib mesylate, has assumed an unquestionable position in targeted treatment. In contrast, novel effective compounds are strongly needed for patients with other rearrangements that carry poor prognosis, including those involving

FGFR1 and *JAK2*, and for CEL-NOS. Multicenter studies are needed to evaluate the long-term outcome of HEUS and its risk of transformation into overt HES. Novel and more reliable methods to assess the clonality of eosinophils, especially in patients with normal cytogenetics and without well-known mutations, are also crucial. Broader use of NGS allowing better assessment of cases with unknown and persistent HE should be introduced into clinical practice.

7.1. Practice points

- ✓ In-depth exclusion of known secondary causes of hypereosinophilia should be the initial step in a diagnostic algorithm for HE/HES.
- ✓ Molecular studies for the presence of *PDGFRA/B*, *FGFR1* and *JAK2* rearrangements are recommended in every patient with unexplained non-reactive hypereosinophilia and myeloproliferative features.
- ✓ A wide panel of laboratory and imaging methods should be implemented for the assessment of end-organ damage, however biopsy of accessible tissue/organ remains optimal.
- ✓ The tyrosine-kinase inhibitor, imatinib mesylate, is the first-line therapeutic option for *PDGFRA/B*-rearranged neoplasms.
- ✓ Discontinuation of imatinib for *PDGFRA/B*-rearranged neoplasms may be possible in some patients with sustained molecular remission.
- ✓ Intensive chemotherapy followed by allogeneic stem cell transplantation should be considered for treatment-refractory, aggressive HES, including eosinophilic myeloid neoplasms with poor prognosis such as those with rearrangements involving *FGFR1* and *JAK2* and CEL-NOS.
- ✓ Although corticosteroids remain a mainstay of treatment for idiopathic and lymphocytic variant hypereosinophilic syndromes, novel targeted biologics are on the horizon.

7.2. Research agenda

- ✓ A standardized myeloid mutation panel should be established to identify novel molecular abnormalities associated with idiopathic HES and potential new therapeutic targets.
- ✓ A multicenter cooperation should be initiated to characterize predictive factors for discontinuation of imatinib in patients with *PDGFRA/B* rearrangements.
- ✓ Clinical trials with novel more potent and selective compounds are needed for patients with *FGFR1/JAK2*-rearranged neoplasms.
- ✓ Patients with LHES should be better defined and the factors responsible for transformation to lymphoma transformation established.

Authorship

GH and ADK equally contributed in this manuscript. GH, ADK-conception, design, drafting, reviewing, approval.

Statement of informed consent

Informed consent was obtained from the patient described in this manuscript.

Declaration of Competing Interest

GH received honoraria for lectures and board membership from Novartis. ADK declares no conflict of interest. This study was funded in part by the Division of Intramural Research, NIAID, NIH.

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