

# Hypereosinophilia: a diagnostic challenge

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## ABSTRACT

Hypereosinophilia encompasses a broad differential diagnosis of atopy/allergic reactions, drug reactions, parasitic infections and paraneoplastic syndromes. Although mostly of limited clinical significance, hypereosinophilia can also be related to hematological malignancies. One has to be aware of the potential for secondary organ damage for example, in the case of hypereosinophilic syndrome. We present three cases with different underlying mechanisms of hypereosinophilia with a brief overview of causes, diagnostic work-up and treatment options.

## KEY WORDS

Hypereosinophilia, parasitic infections, strongyloidiasis, allergy, hypereosinophilic syndrome, hypereosinophilia of unknown significance, hematological malignancy, chronic eosinophilic leukemia, imatinib, mepolizumab, corticosteroids, ivermectin

## CASE HISTORIES

### Patient A

A 29-year-old man with an unremarkable past medical history was clinically observed with fever (40°C) and myalgia two weeks after his return from Thailand. He suffered from nausea and mild abdominal pain. During his stay he had a short-lived episode of diarrhea. On physical examination, he had a temperature of 38.6°C and an erythematous maculopapular rash on his right flank and buttocks. Laboratory examination was unremarkable apart from an increased C-reactive protein (CRP) level (223 mg/l). Differential diagnosis

included *Rickettsiosis* (scrub typhus), *Salmonella typhi* and Melioidosis (*Burkholderia pseudomallei*). Malaria was excluded. Dengue, Chikungunya and Leptospirosis were less likely based on their shorter incubation periods. During his admission, he was treated with doxycycline and discharged after four days. On follow-up three weeks later, CRP-level had normalized, but a significant leucocytosis of  $24 \times 10^9/l$  had developed with 71% eosinophilia; his absolute eosinophil count was  $17 \times 10^9/l$ . Serological examination and a Triple Faeces Test (TFT) confirmed an infestation with *Strongyloides stercoralis*. The patient was treated with ivermectin (200 µg/kg) and made a full recovery. His absolute eosinophil count dropped to  $0.78 \times 10^9/l$ . Most likely, the patient was infected while walking barefoot along the shores of the River Kwai. These dermatological phenomena due to *strongyloides* is known as *larva currens*.

### Patient B

A previously healthy 62-year-old female presented with diplopia, progressive gait problems and numbness and tingling of hands and feet. She reported a recent flu-like episode with persistent complaints of weight loss and discomfort between the shoulder blades. Physical examination was unremarkable apart from multiple small cervical lymph nodes. Laboratory examinations showed an erythrocyte sedimentation rate (ESR) of 72 mm/hour, leukocytosis of  $14 \times 10^9/l$  and CRP of 71 mg/l. Leukocyte differentiation showed 21% eosinophils, with no increase in progenitor cells or basophils. The absolute eosinophil count was  $4.4 \times 10^9/l$ . Differential diagnosis included paraneoplastic syndrome associated with underlying malignancy or vasculitis. Guillain-Barre syndrome was found to be unlikely. Full body computerized tomography (CT) scan showed no primary tumor or distant metastasis and magnetic resonance imaging (MRI) showed no intracranial abnormalities or signs of vasculitis. Spinal

fluid was normal. Immunological assays to autoantibodies antinuclear antibody and antineutrophil cytoplasmic antibody (ANA/ANCA) were negative and therefore, autoimmune disease was unlikely. Mastocytosis was also unlikely due to normal tryptase levels. During admission, a progressive neurologic condition evolved, which was characterized by neuropathy, gait function disorders, facial paralysis and ptosis. Based on the progressive course of the disease, in combination with hypereosinophilia, a hypereosinophilic syndrome (HES) was suspected. Bone marrow examination revealed an eosinophil count of 20% with no increase in blasts. Bone marrow biopsy showed neither morphological aberrations, nor increase of mast cells. Molecular tests were unremarkable (no *C-KIT*, *BCR-ABL*, *JAK2* or *CALr* mutations) and fluorescence in situ hybridization (FISH) did not detect the *FIP1L1-PDGFR* fusion gene. Additional cytogenetic tests ultimately revealed a 20q-deletion, as observed in patients with chronic eosinophilic leukaemia (CEL). The patient was treated with high-dose intravenous prednisolone of 60 mg, once daily. Because of the severity of symptoms, she was concomitantly treated with interferon-alpha. She slowly recovered and during several outpatient visits, her eosinophil count eventually normalized.

#### Patient C

A man, aged 23, known with type I diabetes mellitus presented to the emergency department with acute diarrhea and vomiting. Apart from mild discomfort in the right lower quadrant of his abdomen, physical examination on admission was unremarkable. Laboratory examination showed a leucocytosis of  $14 \times 10^9/l$ . Ultrasound and subsequent CT scan showed ascites with diffuse bowel thickening of his ascending and transverse colon. Follow-up laboratory tests showed the development of a significant eosinophilia with an eosinophil percentage of 48% and an absolute eosinophil count of  $7.2 \times 10^9$ . Detailed history regarding allergies, medication and travel history was inconclusive. Stool sample cultures for pathogens remained negative, as well as serological testing and TFT for parasites. Autoimmune disorders and systemic mastocytosis were disproved by normal immunoglobulins, ANA/ANCA and tryptase. With the working diagnosis of eosinophilic gastroenteritis, a colonoscopy was performed, however this appeared normal and histological biopsy showed no significant eosinophilia or granulomas. Bone marrow examination was performed, but showed no clues of an underlying hematological malignancy (negative tests for *FIP1L1-PDGFR* fusion or t(5q32)/ *PDGFRB*). There were no signs of end-organ damage. Therefore, the patient was diagnosed with 'hypereosinophilia of unknown significance'. A wait-and-see policy was followed and after two months, he made a full clinical recovery. Laboratory results showed complete normalization of eosinophil counts.

**Table 1. Criteria and definitions**

#### Hypereosinophilia (HE)

Absolute eosinophil count  $> 1.5 \times 10^9/l$  on at least two occasions with an interval of  $\geq 1$  month **and/or** histologically proven eosinophilia in tissue defined as:

1. Bone marrow aspiration with  $\geq 20\%$  eosinophils and/or
2. Histologically proven tissue infiltration and/or
3. Deposition of eosinophil-granule proteins

#### Hypereosinophilic syndrome (HES)

Hypereosinophilic syndrome is defined as:

1. Existence of hypereosinophilia as defined above and
2. Eosinophil-mediated organ dysfunction and/or damage and
3. No other identifiable etiology for eosinophilia

*Note:* Adapted from Valent P, Klion AD, Horny HP, et al. Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. *J. Allergy Clin Immunol.* 2012;130:607-12.

#### Background

Normal peripheral eosinophil counts vary between  $0.04-0.60 \times 10^9/l$ . Peripheral blood eosinophilia can be divided into mild ( $0.5-1.5 \times 10^9/l$ ), moderate ( $1.5-5 \times 10^9/l$ ), and severe ( $> 5 \times 10^9/l$ ).<sup>1</sup> The term hypereosinophilia (HE), as used in this manuscript, is defined as an absolute eosinophil count of  $> 1.5 \times 10^9/l$  measured on at least two occasions with an interval of  $\geq$  one month and/or histologically proven tissue infiltration by eosinophils (table 1)<sup>1</sup> Milder eosinophilia can be caused by countless conditions, infectious, autoimmune or cryptogenic notably, HIV infection, granulomatous disorders, polyarthritis nodosa and primary biliary cirrhosis. Furthermore, the term hypereosinophilic syndrome (HES) is defined as the existence of HE in combination with eosinophil-mediated organ damage. The term HES cannot be used if the clinical symptoms and organ involvement have a clear identifiable etiology. The exact incidence and prevalence of HE and HES remain uncertain. The age-adjusted incidence rate is estimated 0.036 per 100,000 individuals per year.<sup>2,3</sup>

#### Pathophysiology

Eosinophils are leucocytes originating from CD34+ hematopoietic precursor cells in the bone marrow.<sup>1</sup> The most important growth factors for eosinophils are interleukin 3 (IL-3), IL-5 and granulocyte-macrophage colony-stimulating factor. They not only trigger growth but also activate normal and neoplastic eosinophils.<sup>1,4,5</sup> There are two pathophysiological mechanisms that can contribute to the development of HE. First, overproduction of eosinophilopoietic cytokines can cause an increase in differentiation and massive proliferation. Subsequently, there is an increase in migration, adhesion, activation and survival of the eosinophils.<sup>1,4,6</sup> The second mechanism includes rapid monoclonal proliferation

**Table 2. Abbreviations**

|                     |   |
|---------------------|---|
| ABPA                | Allergic bronchopulmonary aspergillosis                           |
| AEP                 | Acute eosinophilic pneumonia                                      |
| ALL                 | Acute lymphatic leukemia  |
| ANA                 | Antinuclear antibodies  |
| ANCA                | Antineutrophil cytoplasmic antibodies                             |
| <i>BCR-ABL</i>      | Breakpoint cluster region - Abelson                               |
| CBFb                | Core binding factor complex                                       |
| CEP                 | Chronic eosinophilic pneumonias                                   |
| CML                 | Chronic myeloid leukemia  |
| CRP                 | C-reactive protein  |
| CSF                 | Cerebrospinal fluid   |
| CSS                 | Churg-Strauss syndrome  |
| CT                  | Computer tomography   |
| EMS                 | Eosinophilia-myalgia syndrome                                     |
| <i>FGFR1</i>        | Fibroblast growth factor receptor-1                               |
| <i>FIP1L1-PDGFR</i> | <i>FIP1</i> -like-1-platelet-derived growth factor receptor-alpha |
| FISH                | Fluorescent in situ hybridization                                 |
| GM-CSF              | Granulocyte-macrophage colony-stimulating factor                  |
| HE                  | Hypereosinophilia   |
| HES                 | Hypereosinophilic syndrome  |
| HE <sub>US</sub>    | HE of unknown significance  |
| NHL                 | Non-hodgkin lymphoma  |
| <i>PCM1-JAK2</i>    | Pericentriolar material 1-Janus kinase2                           |
| PCR                 | Polymerase chain reaction   |
| <i>PDGFRA</i>       | Platelet-derived growth factor receptor alpha                     |
| <i>PDGFRB</i>       | Platelet-derived growth factor receptor beta                      |
| PMN                 | Polymorphonuclear neutrophils                                     |
| SM                  | Systemic mastocytosis   |
| TFT                 | Triple faeces test  |

of eosinophils from myeloid progenitor cells caused by gene rearrangements of oncogenic tyrosine kinase receptors, such as *PDGFRA*, *PDGFRB* or *FGFR1* (table 2).<sup>3,6</sup> Fusion of the *PCM1-JAK2* gene was added as a provisional entity in 2016.<sup>3</sup> These mutated receptors induce constitutive tyrosine kinase activation, resulting in uncontrolled stimulation of eosinophilic progenitor cells.<sup>1</sup> CEL is often caused by deletion of 4q12, resulting in the *FIP1L1/PDGFR* fusion gene. Reactive hypereosinophilia can thus develop due to overproduction of cytokines and growth factors, or be the result of clonal eosinophilia caused by myeloproliferative disorders.

In the setting of persistent and massive activation, eosinophils can invade target organs and release their toxic mediators.<sup>15</sup> These eosinophil-derived substances may cause profound changes in the microenvironment and can lead to resultant endomyocardial fibrosis, thrombosis, cutaneous symptoms, peripheral or central neuropathy (with chronic or recurrent neurologic deficit) and other less common organ manifestations.<sup>1</sup>

### Etiology

Many conditions are associated with HE and HES, and can be divided into several subgroups in which reactive

HE and HES occurs most frequently (table 3).<sup>6</sup> Worldwide, parasitic infections are the major cause of HE (table 4), with the most prevalent being hookworms, ascariasis and filariasis infections, followed by schistosomiasis and strongyloidiasis.<sup>7</sup> In areas where there is little exposure to parasites, allergies and medication-induced HE are the leading cause.<sup>8,9</sup> Solid tumors and autoimmune disorders occur less frequently. Finally, only a small proportion is caused by the remaining other syndromes shown in table 3;<sup>5,6</sup> unfortunately, the exact relation between these syndromes and the development of HE is often obscure.

**Table 3. Subgroups**

#### Reactive/secondary HE and HES

Parasitic infections

Allergies/atopy, ABPA

Medication-induced

Auto-immune disorders

Malignant lymphomas: Hodgkin, T-ALL, T-NHL

Mastocytosis

Solid tumors (GE-tumors, lung cancer)

Graft vs Host disease

#### Neoplastic/clonal HE and HES

WHO-defined myeloid malignancies with HE

- Chronic myeloid leukemia (CML-eo)
- Myeloproliferative disorders (PMN-eo)
- Systemic mastocytosis (SM-eo)
- Myelodysplastic syndromes with HE (MDS-eo)
- CBFb-fusion gene-related AML (AML-eo)

Myeloid and hematopoietic stem cell malignancies

- *PDGFRA* rearrangement
- *PDGFRB* rearrangement
- *FGFR1* rearrangement
- Other defects: *PCM1-JAK2* fusion gene, *FIP1L1* fusion gene
- Eosinophilic leukemia e.c.i.

#### Syndromes associated with HE and HES

Gleich syndrome

Churg-Strauss syndrome

Omenn syndrome

Eosinophilic-myalgia syndrome

Hyper IgE syndrome

Hereditary HE (not otherwise specified)

#### HE of unknown significance (HE<sub>US</sub>)

Idiopathic HE

Note: Adapted from Valent P et al. J. Allergy Clin Immunol. 2012<sup>1</sup> and Valent P et al. World Allergy Organ J. 2012<sup>6</sup>

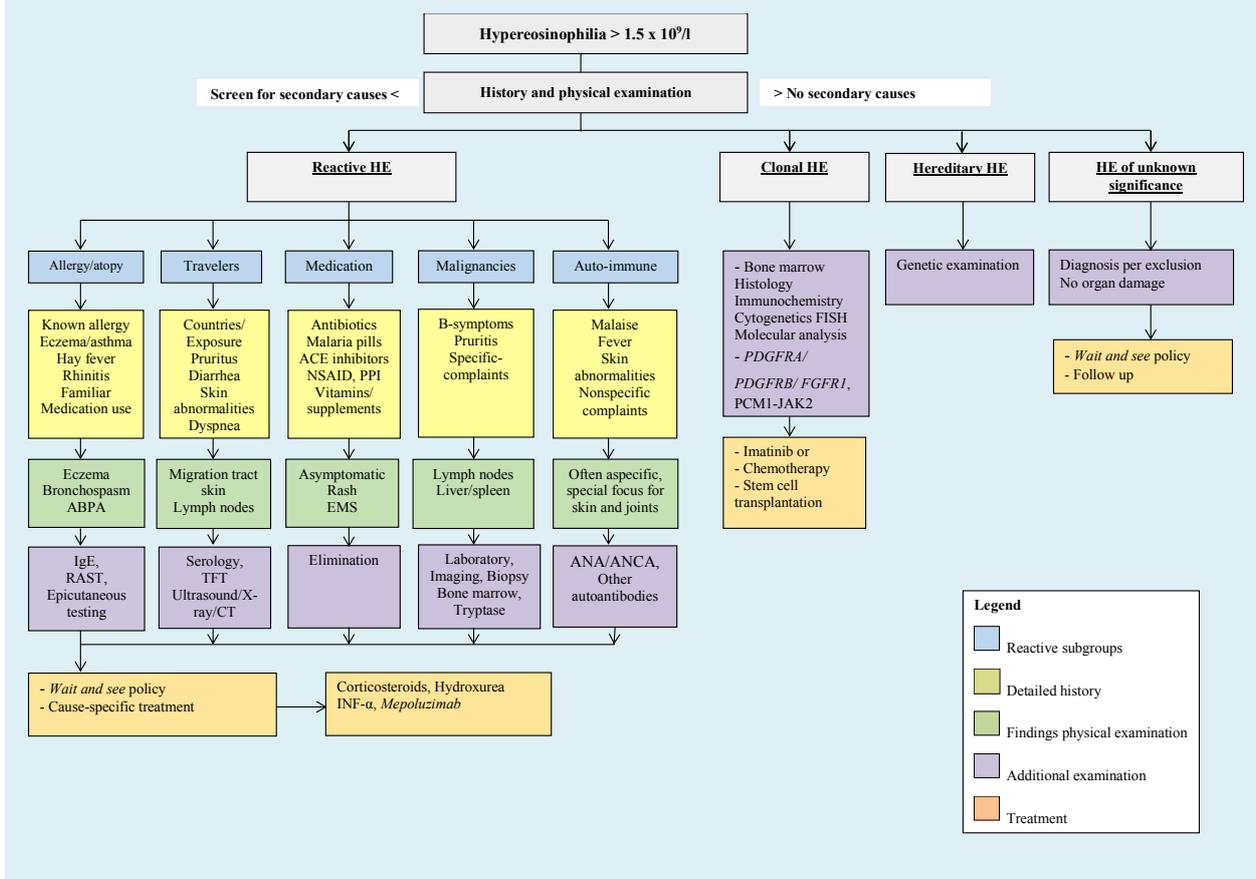
**Table 4.** Most common parasitic infections associated with HE

| Parasites   | Eosinophilia  | Diagnosis   |
|---|---|---|
| <b>Nematodes (roundworms)</b>   |   |   |
| <i>Ascaris lumbricoides</i>   | Moderate/high at migration, low afterwards  | Eggs in stool, serology   |
| Hookworms   | High at migration, low/moderate afterwards  | Eggs in stool   |
| <i>Strongyloides stercoralis</i> *  | Persistently high   | Larvae in stool**, serology   |
| <i>Filaria</i> species ****<br><i>Trichinella</i> species<br><i>Angiostrongylus</i> species<br><i>Anisakis</i> species<br><i>Capillaria</i> species   | Variable<br>Moderate/high<br>Moderate/high<br>Moderate/high<br>Variable   | Microfilariae***, serology<br>Serology, muscle biopsy<br>Larvae CSF, PCR of CSF<br>Serology<br>Serology, liver biopsy         |
| <i>Toxocara</i> species   | Moderate/high   | Serology  |
| <b>Cestodes (tapeworms)</b>   |   |   |
| <i>Taenia solium</i> (cysticercosis)  | Moderate/high at infection, low afterwards  | Eggs/proglottids in stool, serology, ultrasound, CT   |
| <i>Echinococcus</i> species   | Moderate/high at infection, often absent afterwards   | Serology, ultrasound, CT  |
| <b>Trematodes</b>   |   |   |
| <i>Schistosoma</i> species<br><i>Fasciola hepatica</i><br><i>Clonorchis sinensis</i><br><i>Opisthorchis</i> species<br><i>Paragonimus westermani</i>  | High at invasion, moderate/low afterwards<br>High at invasion, moderate/low afterwards<br>High at invasion, moderate/low afterwards<br>High at invasion, moderate/low afterwards<br>High at invasion, moderate/low afterwards | Eggs in stool, serology<br>Eggs in stool, serology<br>Eggs in stool or bile<br>Eggs in stool or bile<br>Eggs in stool, sputum |
| <b>Protozoa</b>   |   |   |
| <i>Cystoisospora belli</i><br><i>Sarcocystis</i> species  | Questionable<br>Variable  | Cysts in stool<br>Cysts in stool, biopsy  |
| <b>Ectoparasites</b>  |   |   |
| <i>Scabies</i> *****  | Questionable  | Microscopic identification  |
| <p>* In the case of <i>Strongyloides</i> hyperinfection, hypereosinophilia can be absent.<br/> ** <i>Strongyloides stercoralis</i> larvae can be detected by the Baermann method (based on migration of larvae) or PCR.<br/> *** Microfilariae can be detected in blood or skin, depending on the species.<br/> **** <i>Filaria</i> species include among others, <i>Brugia</i> species, <i>Wucheria bancrofti</i>, <i>Loa loa</i>, <i>Mansonella ozzardi</i>, <i>Mansonella perstans</i> and <i>Mansonella streptocerca</i>.<br/> ***** Eosinophilia is uncommon in classic scabies, and in approximately 50% of patients with crusted scabies, a marked eosinophilia may develop.<br/> Note: Adapted from 'Evaluation and differential diagnosis of marked, persistent eosinophilia' by Nutman TB<sup>8</sup> and 'Eosinophilia in Infectious Diseases' by O'Connell EM and Nutman TB<sup>9</sup></p> |   |   |

If no obvious 'reactive' mechanism is identified, further exploration for a possible hematological malignancy is indicated. Malignancies associated with hypereosinophilia include chronic eosinophilic leukaemia, myeloproliferative disorders (chronic myeloid leukaemia or polycythaemia vera), variants of acute myeloid leukaemia (AML) and some lymphoproliferative disorders (Hodgkin lymphoma and T-cell lymphomas) and systemic mastocytosis.<sup>3,6</sup> In the case of myeloid

disorders, eosinophilia is clonal and part of the myeloid malignancy. On the other hand, when there is an underlying lymphoproliferative disorder, eosinophilia is polyclonal and frequently due to overproduction of IL-5. Sometimes, the underlying pathology of HE remains unclear even after extensive examination. In this case, the term 'hypereosinophilia of unknown significance' (HE<sub>US</sub>) is used.<sup>1</sup> The main characteristic of HE<sub>US</sub> is the absence of eosinophil-related organ damage.

Figure 1. Diagnostic algorithm



### Clinical manifestations

Depending on the underlying mechanism of HE or HES, a variety of clinical symptoms can occur. Essentially all organ systems can be affected, primarily skin, lungs, the digestive tract and heart.<sup>6</sup> Most common presenting symptoms are fatigue (26%), coughing (24%), dyspnea (16%), myalgias and angioedema (14%), rash or fever (12%) and rhinitis (10%).<sup>3</sup> Neurological deficits are also described, including muscle weakness and polyneuropathy. Special care should focus on the development of endomyocardial fibrosis (which is associated with risk of progressive heart failure) and thrombosis.

### Diagnosis

Figure 1 presents an algorithm for the diagnostic work-up of HE which can be used in any clinical setting. Atopic constitution is often obvious from history and physical signs. An elevated serum level IgE or more specific tests such as radioallergosorbent or epicutaneous testing, further support this diagnosis. Pulmonary eosinophilia, which will not be discussed here, is a rare entity with both non-infectious (like allergic bronchopulmonary aspergillosis, acute and chronic eosinophilic pneumonias, Churg-Strauss syndrome) and infectious etiologies

(mostly parasitic).<sup>3</sup> A detailed history of used medication is important and should include the use of over-the-counter drugs, vitamins and supplements. For instance, in America, an epidemic of Eosinophilia–myalgia syndrome was linked to the use of L-tryptophan consumption.<sup>10</sup> A travel history with sufficient exposure warrants a search for parasites. Serological methods are more sensitive and practical than the demonstration of eggs/cysts in stool. Particularly, HE is the immunological response to circulating worm antigens, which is most profound during the initial phase of infestation when larvae migrate through the organs and tissues of the host.<sup>7-9</sup> Production of eggs detectable in varying quantities in stool samples is often apparent weeks later. When suspicion remains high, repeated testing is indicated.

Bone marrow examination is indicated in all patients with unexplained and persistent HE and should include cytological assessment of the aspirate, immunohistochemistry, cytogenetics, FISH and molecular analysis. Screening of rearrangements of *PDGFRA*, *PDGFRB* and *FGFR1* is essential.<sup>3</sup> The identification of the *FIP1L1-PDGFR* fusion gene has to be performed with FISH or reverse transcription polymerase chain reaction (RT-PCR).

Furthermore, it is clinically relevant for all patients with persistent HE to screen for progression to HES and secondary organ failure. This often demands a multidisciplinary approach with different specialists in a consultative role. A thorough work-up by a cardiologist (echocardiography), dermatologist (skin biopsy) and neurologist may be advised.

#### Treatment and follow up

The first step in the management of HE is to identify and stop exposure to potential triggers such as medication and allergens. Parasitic infections require specific treatment, depending on type and stage of infection. Adequate treatment of *Strongyloides* infection with ivermectin is important because of the risk of *Strongyloides* hyperinfection.<sup>7</sup> Repeated courses may be necessary to achieve full eradication. Empiric treatment with ivermectin 0.22 mg/kg in case of urgent need to initiate corticosteroid therapy, while results of serology are still pending, is justifiable. For patients with mild HE without signs of secondary organ damage, a *wait-and-see* policy can be justified.

Regular follow-up is essential to evaluate progression to HES with subsequent organ damage. If treatment is indicated, systemic corticosteroids (0.5-1 mg/kg) are highly effective in rapidly reducing the eosinophil count.<sup>3,6</sup> Concomitant use of corticosteroid-sparing agents, such as hydroxurea and interferon- $\alpha$ , is often necessary because of side-effects and/or intolerance.<sup>5</sup> Mepolizumab, an anti-IL-5 antibody, appeared to be safe and effective but is not currently approved by the Food and Drug Administration for HE(S).<sup>3,6,11</sup> However, exceptional use for individuals with life-threatening HES who failed prior therapies, is described.

Patients with underlying hematological malignancies will generally fail to respond to steroids. Detailed discussion of different therapies is out of scope here. Referral to, or consultation of, a center of expertise is then recommended. When a *PDGFRA* or *PDGFRB* fusion gene is established, treatment with imatinib can be started (tyrosine kinase inhibitor).<sup>3,11</sup> A low dose of 100 mg per day is often sufficient to achieve molecular remission. Prompt treatment is necessary to prevent irreversible complications such as endomyocardial fibrosis and thrombosis.<sup>6</sup> Patients

with a *FGRF1* mutation are often resistant to treatment with imatinib (response varies between 14-60%). Intensive chemotherapy followed by allogeneic stem cell transplantation is often recommended.<sup>3</sup>

#### CONCLUSION

Hypereosinophilia is a rather frequently identified as laboratory abnormality. In most cases, there is an obvious identifiable cause, but sometimes more extensive exploration is necessary. A detailed history is still the most important first step in diagnosis. We must be aware of hematological malignancies and not hesitate to perform a bone marrow examination when the diagnosis remains unclear. Finally, in the case of persisting HE, we must always be aware of the progression to HES.

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