REVİEW
Systematic Reviews and Meta Analysis
DOI: 10.56016/dahudermj.1391630

DAHUDER
Medical Journal
e-ISSN: 2791-9250

Hypereosinophilic syndrome: Case series and review of the literature

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ABSTRACT

Hypereosinophilic Syndrome (HES) is caused by the uncontrolled proliferation of eosinophils generally associated with conditions such as allergic reactions or parasitic infections. This syndrome is characterized by excessive eosinophil production (>1500/mm^3) that persists for more than six months and cannot be explained by secondary causes. HES symptoms can affect different body organs, and usually, nonspecific symptoms include fever, malaise, fatigue, rash, shortness of breath, and myalgia.

HES is a rare disease with multiorgan involvement, including the skin, joints, kidneys, vascular system, gastrointestinal tract, cardiac and pulmonary systems. The main feature of this disease is that overproduced eosinophils accumulate in organs and cause organ damage. Cardiac involvement plays a critical role in determining morbidity and mortality, and cardiac and large vessel thrombosis with severe clinical manifestations can also be observed.

Treatment aims to reduce the absolute eosinophil count, improve symptoms, and prevent disease progression. Pharmacologic therapy aims to maintain targeted eosinophil levels below 1.5 x 10^9/L (1500 cells/µL) to reduce the symptoms of eosinophilic disease and prevent organ damage. Furthermore, indications for emergency treatment should be rapidly assessed and initiated promptly in appropriate patients.

This paper will discuss the diagnosis, clinical manifestations, treatment modalities, and management challenges of HES in detail through two rare case examples.

Keywords: Hypereosinophilia, eosinophil, hypereosinophilic syndrome

Eosinophils typically increase in conditions such as allergic reactions or parasitic infections, but in some cases, they can multiply uncontrollably and accumulate in tissues with damaging effects. Hypereosinophilic syndrome (HES) is a disease characterized by excessive eosinophil production (>1500/mm^3) that persists for more than six months and cannot be explained by secondary causes.[1,2] Symptoms may vary depending on which organs of the body it affects. It can often be challenging to identify the underlying causes of this disease. A multidisciplinary approach is required in the diagnosis and treatment process.

The main clinical manifestations include nonspecific findings such as fever, malaise, fatigue, rash, dyspnea, and myalgia.[2] HES is a rare disease with multiorgan involvement, including skin, joints, kidney, vascular, gastrointestinal, cardiac, and pulmonary systems. The main feature of the disease is that overproduced eosinophils accumulate in organs and cause organ damage. Cardiac involvement is the most crit-

Received: *November 16, 2023;* ***Accepted:*** *anuary 8, 2024;* ***Published Online:*** *January 29, 2024*

How to cite this article: *N Yalçın, Ertınmaz Özkan A, Koca N. Hypereosinophilic syndrome: case series and review of the literature. DAHUDER MJ 2024,4(1):1-6. DOI: 10.56016/dahudermj.1391630*

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ical organ involvement, determining morbidity and mortality.[3,4] In addition, severe clinical pictures characterized by cardiac and large vessel thrombosis may also be observed.[5]

In this article, we will discuss the diagnosis, clinical manifestations, treatment methods, and complexity of HES with two accurate case reports. This article, discussed in the light of current literature, will guide healthcare professionals who recognize and treat this rare disease and raise awareness.

CASE PRESENTATION

Case 1

A 67-year-old male patient presented to our clinic with complaints of malaise and rash on the legs. The patient had a known diagnosis of hypertension and had not changed his medication recently; his complaints had been present for about one year, and no significant response was obtained in the treatments performed by dermatology and cardiovascular surgery. Further investigations were planned after an elevated eosinophil count (1940/mm^3 (24.7%)) was noted. It was observed that eosinophil levels had been at 1700/mm^3 for about eight months, and previous eosinophil levels were within the normal range. Parasitic examination and tests for brucellosis were negative. No significant laboratory results were found in the evaluation regarding vasculitis, and no monoclonal band increase was observed in electrophoresis. FIP1L1-PDGFRA gene fusion screening, lymphocyte phenotyping, and peripheral smear were performed. No pathologic findings other than eosinophilia were found in the peripheral smear, while gene fusion screening results and lymphocyte phenotyping were negative. Computed tomography (CT) of the lung showed no involvement, and echocardiography showed no evidence of cardiac involvement or thrombus. Magnetic resonance angiography revealed a thrombus in the lower extremity, and anticoagulant therapy was initiated. As a result of the evaluations, the patient was diagnosed with idiopathic HES, and corticosteroid treatment was started. The patient received 1 mg/kg methylprednisolone treatment, and as a result of improvement in laboratory and clinical findings, the patient was discharged and taken to an outpatient clinic follow-up.

Case 2

A 34-year-old male patient presented to our outpatient clinic with complaints of early fatigue, weakness, intermittent leg rash, and shortness of breath. He had no known comorbidities and did not describe any medication use. Electrocardiography and chest radiography revealed no significant pathology in the outpatient evaluation. Laboratory results showed normal thyroid, renal, and liver function tests and no anemia. The eosinophil count was 2445/mm^3 (28.6%), and the patient was admitted to our clinic for further evaluation. In the evaluation of the patient, it was observed that eosinophil levels had been high for the last year. Parasite examination and tests for brucellosis were negative. No additional pathology was detected in the peripheral smear. The bcr-abl and myeloproliferative tests ordered because of chronic eosinophilia were negative. FIP1L1-PDGFRA gene fusion screening and lymphocyte phenotyping were performed. No gene fusion clonal T lymphocyte was detected due to the screening. The d-dimer result of the patient who described shortness of breath was within normal range, and no pulmonary involvement was found on lung computed tomography. In the cardiologic evaluation of the patient, echocardiography revealed a moderate decrease in ejection fraction and suspicious thrombus appearance, and warfarin treatment was initiated. The patient was considered to have idiopathic HES, and 60 mg/day methylprednisolone treatment was initiated. After the treatment, the patient's complaints improved significantly, and eosinophil counts returned to normal. The patient, whose eosinophil count was normalized and clinical symptoms improved with treatment, was discharged with the recommendation of cardiology and internal medicine outpatient clinic follow-up.

DISCUSSION

The percentage of eosinophils in peripheral blood is 3-5%, and the absolute count is between 350-500/µL (1). Eosinophilia, which refers to an increase in eosinophils in peripheral blood, is classified as mild (upper limit 1500/µL), moderate (1500-5000/µL), and severe (>5000/µL).[6,7] Hypereosinophilia is generally used for values above 1500/µL.[8]

Hypereosinophilic syndrome is a multisystemic disease and may present with simple clinical symptoms or severe clinical outcomes. It occurs as a result of eosinophil infiltration in the affected organ. Although it is mainly observed in the age group of 20-50 years, it can occur at any age.[9] Male predominance is remarkable, as in our cases.10 Although the actual prevalence of the disease is not known precisely, it

Table 1. Hypereosinophilic syndrome diagnostic criteria

1. Eosinophil count of 1,500/μL or higher for at least 6 months (this does not apply in the presence of symptoms requiring eosinophil-lowering therapy)
2. Exclusion of secondary and clonal eosinophilia
3. Presence of evidence of organ involvement
4. Absence of phenotypically abnormal and/or clonal T lymphocytes

was found to be between 0.36 and 6.3 per 100,000 in a data-based study.[11]

Secondary causes include parasitic infections, allergic diseases, drug side effects, T-cell lymphomas, and various carcinomas that should be excluded for diagnosing HES. Recently, eosinophilic syndromes that cannot be categorized as secondary have been divided into clonal and idiopathic categories. HES is primarily evaluated in the idiopathic eosinophilia category. In the absence of organ damage, the definition of idiopathic eosinophilia should be preferred instead of HES.[8] The World Health Organization (WHO) has classified clonal eosinophilia into two subcategories.12 Current diagnostic criteria for HES are given in Table 1.[13]

1. Myeloid/lymphoid neoplasms with eosinophilia and mutations (PDGFR α/β or FGFR1).

2. Chronic eosinophilic leukemia, not otherwise specified

Generally, symptoms have a slow onset and may not always be specific. While malaise, fatigue, chronic cough, rash, and myalgias may be observed, they may also present with a clinical picture with a high risk of mortality with severe thrombosis and cardiac and neurologic involvement.[14] In both of our cases, complaints of weakness and fatigue were at the forefront, and our second patient described dyspnea. Table 2 shows the HES variants and their characteristics.[15] The occurrence rate of HES-related complications such as dermatologic (rash), pulmonary (cough and dyspnea), gastrointestinal, cardiac, neurologic, and others are 37%, 25%, 14%, 5%, and 4%, respectively.[16]

Cardiac involvement

Cardiac involvement usually occurs in three stages. The early necrotic stage is usually asymptomatic and may involve the endocardium and myocardium. Rarely, it may cause acute heart failure. It is followed by a stage in which thrombi develop in the damaged endocardium and may cause peripheral embolism. The final stage is the fibrotic stage, which results in restrictive cardiomyopathy. Advanced heart failure and valvular pathologies may accompany.[17,18]

Echocardiography may appear normal in the acute necrotic stage. There may be a chance of diagnosis in the early stage with magnetic resonance. Endomyocardial biopsy is helpful in definitive diagnosis in the ear-

Table 2. The HES variants and their characteristics

HES variant	Defined abnormalities	Clinical and laboratory features
Myeloid variant	PDGFRB and FGFR1 rearrangements JAK2 point mutation and translocation	↑ Serum B12 Anemia and/or thrombocytopenia Hepatomegaly and/or splenomegaly Circulating leukocyte precursors
T-cell lymphocytic HES	Abnormal IL-5 producing T cells	Prominent skin manifestations (including plaques, erythroderma, urticaria) Polyclonal hypergammaglobulinemia
Familial HES	5q 31-33 mutation	Congenital asymptomatic eosinophilia, autosomal dominant
Idiopathic HES		Multi-system involvement
Specific/defined syndromes associated with Hypereosinophilia	Examples include episodic angioedema with eosinophilia, eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss), other disorders associated with immune dysregulation.	Marked eosinophilia in the setting of an underlying disorder associated with eosinophilia; the exact role of eosinophils in disease manifestations remains unclear

HES: Hypereosinophilic syndrome

ly stage.19 The second stage of heart disease involves thrombus formation along areas of damaged endocardium. The tissue factor, believed to be very important in thrombus formation, is directly expressed by eosinophils. The main complication of intracardiac thrombus formation is that it leads to embolic strokes, ischemia of the extremities, and other embolic events.[20] In the fibrotic stage, echocardiography may show mitral or tricuspid regurgitation, cardiomegaly, restrictive cardiomyopathy, or T-wave inversions. Echocardiography may show intracardiac thrombus.

Neurologic involvement

Neurological involvement may include peripheral polyneuropathy and encephalopathy with central infiltration, depending on the location of eosinophil infiltration. Cerebral thromboembolism may result from intracardiac thrombi and may present as embolic strokes or transient ischemic episodes. Magnetic resonance imaging may reveal multiple infarcts. Encephalopathy may manifest as behavioral changes, confusion, ataxia, and memory loss. Affected patients may also have upper motor neuron damage signs, such as increased muscle tone, deep tendon reflexes, and positive Babinski response.[21]

Cutaneous involvement

Cutaneous manifestations are usually nonspecific, resemble urticarial and dermatitis-like lesions, and are frequently seen in patients with HES. Common cutaneous manifestations of HES include eczema (involving the hands, flexural areas, or scattered plaques), erythroderma, generalized thickening of the skin (lichenification), dermographism, recurrent urticaria and angioedema.[22]

Biopsies of papular or nodular lesions show perivascular infiltration with eosinophils and mild to moderate perivascular neutrophilic and mononuclear infiltrates without vasculitis. Less commonly, mucosal ulcers, which are often difficult to treat, develop in the mouth, nose, pharynx, esophagus and stomach, or penis or anus.[9]

Lung involvement

Pulmonary involvement may range from normal lung imaging to restrictive pulmonary disease. While some patients may complain of a chronic dry cough, they may also present with restrictive disease due to diffuse infiltrations.[23] Pulmonary involvement is common in HES and may result from eosinophilic infiltration of the lung followed by fibrosis, heart failure, or pulmonary embolism. In a Mayo Clinic study, respiratory symptoms were reported in 63 percent of patients. The most common presenting symptoms were shortness of breath (45%), cough (39%) and wheezing (24%). Abnormal chest radiography or computed tomography (CT) findings were seen in 43 percent of patients and included parenchymal infiltrates (37%), pleural effusion (14%), intrathoracic lymphadenopathy (12%) and pulmonary embolism (4%).24

Gastrointestinal involvement

Gastrointestinal involvement may manifest as abdominal pain, nausea, and diarrhea. Eosinophilic gastritis, enterocolitis, or colitis may be seen due to eosinophil infiltration. Hepatitis and focal hepatic lesions may be observed as hepatic involvement.9

Treatment

The main aim of treatment is to reduce the absolute eosinophil count, improve signs and symptoms, and prevent disease progression.[25]

The timing of treatment in patients depends on the severity of Hypereosinophilia (HE) and the presence of signs and symptoms.[26]

If patients have symptoms of hyperleukocytosis due to extremely high levels of eosinophils, even if rarely present, hypercellularity should be rapidly reduced. Most patients are asymptomatic and have less severe eosinophil levels. Pharmacologic therapy aims to reduce the signs and symptoms of eosinophilic disease and maintain levels below 1.5 x 10^9/L (1500 cells/µL) to help prevent the development of end-organ damage.

The choice of therapeutic agent in patients to be treated depends on the presence or absence of FIP1L1-PDGFRA fusion. The myeloid variant with a fusion defect (i.e., PDGFRA-positive HES) is initially treated with imatinib mesylate, while patients with other HES types are initially treated with glucocorticoids.

Indications for emergency treatment: There are conditions indicating emergency treatment in HES patients.[9,27,28]

1) Extremely high eosinophil levels (i.e., absolute eosinophil count [AEC] >100 x 10^9/L; >100,000 cells/µL).

2) Signs and symptoms of leukostasis (i.e., pulmonary or neurologic dysfunction with a white blood cell count >50 x 10^9/L [>50,000 cells/µL]).

3) Signs and symptoms or other evidence of potentially life-threatening complications of HES (i.e.,

acute heart failure, thromboembolic events).

4) In patients with lung involvement, urgent treatment is required in patients showing eosinophil-associated disease (i.e., extensive interstitial infiltrates, ground-glass opacities, condensation) consistent with clinical symptoms.

Corticosteroids are the treatment of choice for HES. In patients for whom emergency treatment is indicated, the most preferred agent is corticosteroids. Imatinib, rituximab, cyclophosphamide, and hydroxyurea are the other main agents tried in treatment. Although various immunosuppressive agents have been tested over time, corticosteroids have maintained their position in treatment.[29] In terms of holistic therapy, it is essential to perform additional treatments for the system involved in the disease and to treat complications.

CONCLUSION

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: NY, AEÖ, NK; Study Design: NY, AEÖ, NK; Supervision; NY, AEÖ, NK; Funding: NY, AEÖ, NK; Materials: NY, AEÖ, NK; Data Collection and/or Processing: NY, AEÖ, NK; Analysis and/or Data Interpretation: NY, AEÖ, NK; Literature Review: NY, AEÖ, NK; Critical Review: NY, AEÖ, NK; Manuscript preparing: NY, AEÖ, NK.

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