Case-Based Review

# Hypereosinophilic Syndrome with Endomyocarditis: Identification by Next-Generation Sequencing of the JAK2-V617F Mutation

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## Abstract

Hypereosinophilic syndrome requires a peripheral absolute eosinophil count of $\geq 1.5 \times 10^9$/L with clinical manifestations attributable to peripheral or tissue hypereosinophilia. Clinical manifestations can vary greatly, with the majority of patients relatively asymptomatic and the eosinophilia detected incidentally. However, in a minority of hypereosinophilia cases, they may present with severe life-threatening organ dysfunction affecting skin, lung, heart, gastrointestinal tract, and nervous system. A case of hypereosinophilia with potentially life-threatening cardiovascular involvement is discussed. Initial laboratory investigations showed an elevated white blood cell count with 60% eosinophils. An endomyocardial biopsy revealed eosinophilic endomyocarditis with granuloma, rare giant cells, and no vasculitis, microorganisms, or malignancy. Her presentation met the criteria for either hypereosinophilic syndrome or eosinophilic granulomatosis with polyangiitis. Molecular genetic analysis was negative for myelodysplastic syndrome panel/ Platelet Derived Growth Factor Receptor Beta (PDGFRB) (5q32)/Fibroblast Growth Factor Receptor 1 (FGFR1) Fluorescence In Situ Hybridization (FISH), Feline McDonough Sarcoma-related Tyrosine Kinase 3 (FLT3) Internal Tandem Duplication (ITD) mutation, Calregulin (CALR) exon 9 mutation, and T-cell gene rearrangement/polymerase chain reaction. Bone marrow biopsy revealed a mildly hypocellular marrow with multilineage hematopoiesis,+ megakaryocyte dysplasia, and focal eosinophilia. No excess blasts, no monotypic B-cell population, and no discrete pan T-cell aberrancies were found. Bone marrow cytogenetic studies showed a normal signal pattern for myeloproliferative neoplasms panel/Sec1 Family Domain Containing 2 (SCFD2)-Ligand of Numb Protein-X (LNX)-Platelet-derived Growth Factor Receptor Alpha (PDGFRA) fluorescence in situ hybridization with a normal karyotype of 46 XX. Next-generation sequencing, however, was positive for the *JAK2-V617F* mutation, a rare molecular abnormality in hypereosinophilic syndrome. The prevalence ranges from approximately 0% to 4%. The JAK2 point mutation leads to aberrant tyrosine phosphorylation and increased cytokine activation. The case demonstrates the complexity and challenging nature of advanced diagnostic opportunities in hypereosinophilia and the potential use, in select subsets, of targeted treatments such as tyrosine kinase inhibitors.

**Keywords:** Hypereosinophilic syndrome, eosinophilic granulomatosis with polyangiitis, endomyocarditis, JAK2-V617F mutation, next-generation sequencing, reverse transcription polymerase chain reaction

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## Introduction

Hypereosinophilic syndrome is defined as a peripheral absolute eosinophil count (AEC) $\geq 1.5 \times 10^9$/L (or >1500 cells/microL) with clinical manifestations attributable to the eosinophilia or tissue hypereosinophilia. Clinical manifestations can vary greatly, with the majority of patients relatively asymptomatic and the eosinophilia detected incidentally. However, in a minority of cases, hypereosinophilia may present with severe life-threatening organ dysfunction affecting skin, lungs, heart, gastrointestinal tract, and nervous system. The effect of eosinophils on these organs depends not only on the number of eosinophils but also on their level of activation. The etiology of eosinophilia plays a role but can often be difficult to identify based on clinical presentation alone.[1] We report the case of a 61-year-old female who presented with severe decompensated heart failure due to eosinophilic infiltration of endomyocardium. Her clinical presentation met criteria for both eosinophilic granulomatosis with polyangitis (EGPA) and hypereosinophilic syndrome (HES). By next-generation sequencing, she was found to have the rare JAK2 mutation associated with some variants of HES.

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Eur J Rheumatol 2023;10(2):67-70

## Case Presentation

A 61-year-old woman presented with severe breathlessness, bilateral leg swelling for 2 days, intermittent fever, extreme fatigue, diffuse myalgia, and night sweat for 2 months. She denied chest pain, gastrointestinal, genitourinary, skin, or neurologic symptoms. She had no recent travel but had been previously admitted to a community hospital with acute breathlessness and peripheral eosinophilia that was treated successfully with a short course of oral steroid for a putative bronchial asthma exacerbation. Her past medical history was significant for a long-standing history of allergic rhinitis and 2-year history of bronchial asthma. She denied smoking or alcohol use. On physical examination, the patient was febrile 38.2°C (100.8°F) and appeared breathless at rest. Her pulse was 108 beats per minute, respiratory rate 29 per minute, blood pressure 98/56 mmHg, with an O2 saturation of 94% on room air. The jugular venous pressure was elevated, and there was evidence of clinically significant pedal edema. Her cardiovascular exam revealed a regular rhythm without murmurs, faint heart sounds, and bibasilar crackles.

Initial laboratory investigations showed an elevated white blood cell count (25.5 × 10$^9$/L) with 60% eosinophils, absolute eosinophil count (AEC) 15.2 × 10$^9$/L, hemoglobin 10 g/dL, hematocrit 31%, MCV 82 fl, platelet count (500 x 10$^9$/L), and normal renal/liver tests. Inflammatory markers were elevated. Chest radiograph demonstrated florid pulmonary edema, bilateral small pleural effusions, and enlarged cardiac silhouette. Sinus tachycardia without significant ST or T wave changes was noted on electrocardiogram. A computed tomography (CT) pulmonary angiogram revealed diffuse left ventricular (LV) myocardium thickness but no pulmonary embolism. A transthoracic echocardiogram revealed severe LV diastolic dysfunction, left atrial enlargement, and moderate pericardial effusion (2 cm). Computed tomography of the chest, abdomen, and pelvis showed diffuse LV myocardium thickness, mild hepatomegaly, no splenomegaly, and no lymphadenopathy. Both brain natriuretic peptide (BNP) and troponin levels were elevated.

The patient was immediately treated with aggressive diuretics for acute decompensated heart failure, and clinical improvement was achieved. A cardiac MRI demonstrated a 1.9 × 1.4 cm LV apical clot and minimal subendocardial delayed enhancement of the distal anterior wall/apex, involving approximately 10% of the myocardial thickness (suggestive of a subtle scar of ischemic etiology), mildly reduced global systolic function (ejection fraction 54%), minimal hypokinesis of the distal anterior wall and hypokinetic apex, concentric pericardial effusion measuring approximately 1.8 cm inferiorly, and modest PA systolic pressure elevation (estimated at 39 mmHg). She proceeded with cardiac catheterization, which found no coronary arterial disease.

An endomyocardial biopsy was performed to clarify the underlying etiology. It showed eosinophilic endomyocarditis (Loeffler endomyocarditis) with granuloma (Figure 1), rare giant cells, and no vasculitis, microorganisms, or malignancy. The presence of giant cells and eosinophilic granulomas raised the suspicion for EGPA. Of note, a sinus CT revealed patchy multifocal para-nasal mucosal thickening, with an air-fluid level in the right maxillary sinus, reflecting an acute sinusitis.

The working diagnosis, at that point, was EGPA based on peripheral and tissue eosinophilia, eosinophilic granulomas evident on cardiac biopsy in a patient with adult-onset asthma with sinus disease. Oral steroid (1 mg/kg of prednisone) was started with plans for immune suppressant therapy. Heparin with bridging warfarin was also initiated for the left apical mural thrombus. She responded well to steroid therapy with a dramatic drop in her peripheral eosinophil count the following day as well as improvement in her symptoms. Additional studies for hypereosinophilia, including next-generation sequencing, identified a positive *JAK2* V617F mutation. This raised the possibility of HES as opposed to EGPA. She was discharged home with high-dose steroids and follow up with rheumatology and hematology.

The patient underwent an outpatient bone marrow biopsy. Molecular genetics analysis was negative for myelodysplastic syndrome (MDS) panel/PDGFRB(5q32)/FGFR1 FISG, FLT3 ITD mutation, CALR exon 9 mutation, and T-cell gene rearrangement/polymerase chain reaction (PCR). Bone marrow biopsy revealed a mildly hypocellular marrow with multilineage hematopoiesis, megakaryocyte dysplasia, and focal eosinophilia. No excess blasts, no monotypic B-cell population, and no discrete pan
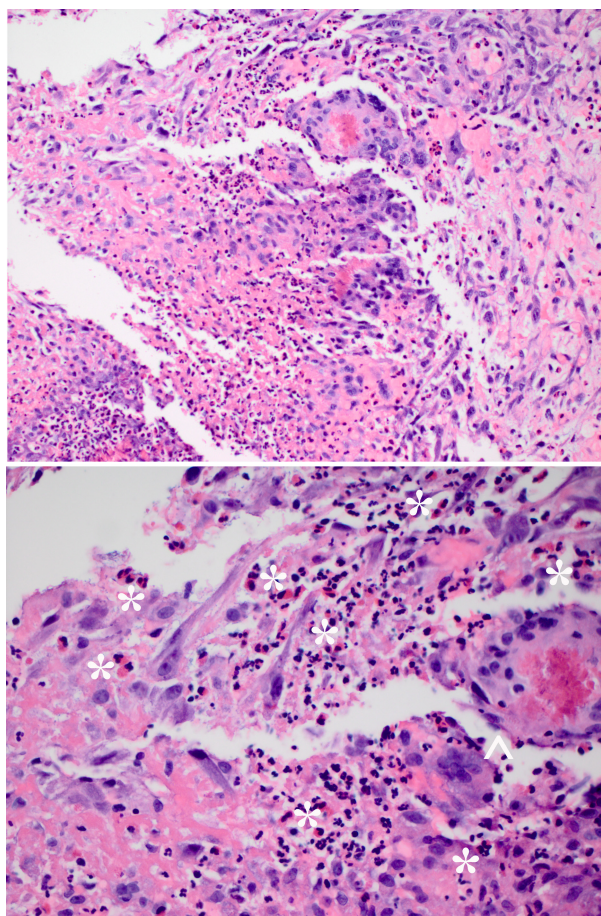


**Figure 1.** (A) Biopsy of the right ventricular septum showing eosinophilic endomyocarditis, rare giant cells, and eosinophilic granulomas/microabscesses. Hematoxylin and Eosin stain, original magnification 320×. (B) Enlarged view with annotated eosinophils (*) and granuloma (^).

T-cell aberrancies were found. Bone marrow cytogenetic studies showed a normal signal pattern for myeloproliferative neoplasms (MPN) Panel/SCFD2-LNX-PDGFRA fluorescence in situ hybridization (FISH) with a normal karyotype of 46 XX.

Her final diagnosis was HES associated with JAK2 V617F mutation. She continues to remain well without recurrence of symptoms after a slow taper of steroid without further immune suppressant therapy.

All patients agree to a HIPAA compliant statement, prior to being seen at the Medical Center, explaining that it is an educational instituition. Redacted data, examinations, laboratoy tests, and histologic images may be used for lectures and publications.

## Discussion

Hypereosinophilic disorders are a heterogenous group of diseases, with a broad differential including allergic disorders, drug reactions with eosinophilia and systemic symptoms (DRESS) neoplasms, infections (e.g., *Strongyloides stercoralis*, *Ascaris lumbricoides*), and gastrointestinal (GI) specific eosinophilic disorders (i.e., esophagitis, gastritis, and colitis). Initially, stratifying based on the level of eosinophils can help guide diagnostic work-up. Eosinophilia (defined as counts 500-1500/mm$^3$) can be found in allergic asthma, urticarial, and many connective tissue disorders, including dermatomyositis, severe rheumatoid arthritis, severe systemic sclerosis, IgG4-related diseases, and some eosinophilic fasciitis. Fewer disorders are associated with hypereosinophilia (defined as counts >1500/ mm$^3$), including EGPA and HES, diagnostic criteria for which includes clinical manifestation attributable to the eosinophilia.[2] Though skin and pulmonary manifestations are more common in HES, isolated cardiac involvement has been rarely reported.[3] Given that both EGPA and HES can manifest with eosinophilic infiltration of the heart, diagnosis between the 2 can be challenging. This discussion will focus on the differentiation between HES iterations and the implications for management.

*JAK2* mutation in HES is a rare diagnosis with a prevalence ranging from approximately 0% to 4%.[4-8] Like other myeloproliferative disorders, these can be associated with a high thromboembolic risk. Dasari et al[8] and Mishchenko et al[9] report cases with Budd–Chiari syndrome, subsequently diagnosed with *JAK2* mutation-associated HES. This mutation is one of a few

molecular abnormalities associated with HES. Based on the 2012 international consensus for classification of HES, there are 6 variants of HES, including myeloproliferative HES, lymphocytic variant HES, overlap HES, associated HES, familial HES, and idiopathic HES.[10]

The myeloproliferative HES include molecular defects which lead to constitutive activation of tyrosine kinase. The most common is a deletion in chromosome 4q12 leading to tyrosine kinase fusion gene involving PDGFRA and subsequent eosinophil expansion. They are detected via reverse transcription polymerase chain reaction (RT-PCR) or FISH of peripheral blood and/or bone marrow. These patients may also present with splenomegaly, peripheral smear with myeloid precursors, elevated serum B12, increased tryptase levels, and evidence of dysplastic eosinophils.[2] Identifying these patients has become especially important since the discovery of targeted treatment with imatinib, which is a tyrosine kinase inhibitor that can be essentially curative.[11] For this particular group of patients, glucocorticoids are not effective. Other genetic rearrangements in this variant, collectively referred to as PDGFRA-negative, include tyrosine kinase fusion proteins with PDGFRB, FGFR1, and point mutations in JAK2 V617F and KIT D816V.[4]

The JAK2 point mutation leads to aberrant tyrosine phosphorylation and increased cytokine activation. Jones et al[5] report the frequency of this mutation in their study of 480 samples with suspected diagnosis of myeloproliferative disorders. In the idiopathic HES subtype, they report a frequency of only 2% JAK2 mutations. This study confirms that while JAK2 mutation is common in polycythemia vera (81%) and essential thrombocythemia (41%), this molecular abnormality is rare in HES.[5] Diagnosis of this rare mutation also leads to questions about treatment. While imatinib is highly effective in PDGFRA-positive HES (88% respond), it is not effective for PDGFRA-negative HES (only 23% respond).[12] PDGFRA-negative patients, however, respond well to corticosteroids. Further, Helbig et al[13] report a case of JAK2 mutation-associated hypereosinophilia, which was effectively treated with interferon-alpha-2a after failing treatment with hydroxyurea and imatinib. Corticosteroids were not used for treatment in the aforementioned case, but was highly effective monotherapy in the current case. For patients refractory to imatinib, treatment options can also include alternative tyrosine kinase inhibitors, higher dose of imatinib, hydroxyurea, and vincristine.[4]

The lymphocytic HES is due to a T-cell receptor gene rearrangement pattern leading to abnormal T-cell populations. These clones drive eosinophilia by overproduction of cytokines such as IL-5. Diagnosis is via RT-PCR and flow cytometry to look for abnormal clones. These patients tend to have elevated serum IgE levels and elevated thymus-and-activation-regulated chemokine.[2] Clinically, they tend to present with more skin and soft tissue manifestations. Patients often respond to steroids; however, new studies suggest that anti-IL-5 treatment may also be of benefit.[2] Familial HES is due to a rare autosomal dominant abnormality. Idiopathic HES is of unknown etiology.

The overlap HES group includes those eosinophilic disorders that affect a single organ, for example eosinophilic GI diseases and eosinophilic dermatitis. Some may only need topical corticosteroid therapy. Eosinophilic granulomatosis with polyangitis is considered a disease of "one" organ as it is primarily a vasculitis with eosinophilic infiltration of blood vessels. However, this can be multisystem and involve lungs, heart, skin, nerves, and other organs. Thus, a patient presenting with HES and 1 organ involvement, especially in the setting of negative antineutrophil cytoplasmic antibody (ANCA), would meet diagnostic criteria for both EGPA from HES. In addition, in the early stages of EGPA, tissue biopsy may show eosinophilic infiltration without the expected vasculitis or granulomas with eosinophilic necrosis.[14] The current patient's cardiac biopsy showed eosinophilic endomyocarditis with rare giant cells and eosinophilic granuloma, which suggested possible EGPA. Corticosteroids can be effective treatment for both HES and EGPA. As such, response is not supportive of a specific diagnosis. Consequently, in addition to a variety of tests (including troponins, ANCA, transthoracic echocardiogram, pulmonary function tests, and pan-computed tomography) evaluations need to include tissue biopsy, bone marrow with cytogenetics, advanced evaluations for mutations via FISH or RT-PCR, T- and B- cell receptor rearrangement studies, next-generation sequencing, and flow cytometry.[2]

## Conclusion

There are 6 HES variants that include myeloproliferative, lymphocytic, overlap, associated, familial, and idiopathic.[10] The present case demonstrates that sophisticated molecular and genetic diagnostic opportunities are important in differential diagnosis and treatment management. Specifically, next-generation sequencing was pivotal in distinguishing

EGPA from HES, with the identification of a positive *JAK2-V617F* mutation in a patient with severe cardiac disease and systemic symptoms. Although both EGPA and JAK2-V617F-associated HES might both respond to steroids, the dose, duration and long-term treatment options may differ.

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