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CARDIO-ONCOLOGY

CASE REPORT: CLINICAL CASE

Incessant Ventricular Tachycardia

An Atypical Presentation of Chronic Eosinophilic Leukemia

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ABSTRACT

Hypereosinophilic syndrome comprises a diverse and intricate array of rare disorders, exhibiting clinical manifestations that extend across various medical subspecialties. Within its myeloid form, chronic eosinophilic leukemia represents a rare myeloid malignancy characterized by severe hematological complications and distinctive organ dysfunction, notably affecting the cardiovascular system. This report presents a rare case of chronic eosinophilic leukemia and Loeffler syndrome with an initial presentation of ventricular tachycardia. (JACC Case Rep 2024;29:102461) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Hypereosinophilic syndrome (HES) is a rare and complex disorder marked by elevated levels of eosinophils, infiltration of tissues, and the release of cytokines that result in damage to various organs.[1,2] Multiple etiologies have been described, including primary neoplastic, secondary reactive, and idiopathic causes.[2] Eosinophilic endomyocardial disease, also known as Loeffler syndrome, is a manifestation of HES characterized by eosinophil-mediated cardiac damage, leading to diverse clinical presentations.[3-5] Arrythmias of unknown origin including ventricular tachycardia have been reported in a few cases in the literature as an initial presentation of Loeffler syndrome.[6]

LEARNING OBJECTIVES

- To recognize ventricular tachycardia as an initial presentation of eosinophilic myocarditis.
- To note that suspicious CMR findings with subendocardial fibrosis should prompt thorough investigations for unusual etiologies of infiltrative cardiomyopathy like myeloproliferative syndrome.
- To understand that early diagnosis of rare infiltrative cardiomyopathy and early therapy can significantly reduce the short- and long-term morbidity and mortality of such conditions.

HISTORY OF PRESENTATION

A 38-year-old, physically active, and otherwise healthy man presented to the cardiology department for preoperative clearance prior to lithotripsy. On review of his records, cardiac magnetic resonance conducted at an outside hospital revealed nonspecific late gadolinium enhancement in the anteroseptal and inferoseptal segments. Incidentally, he was noted to have peripheral eosinophilia of 49 $\times$ 10^3/uL for which he was empirically treated with a short course of steroids with transient normalization of his eosinophilic count. His only complaint in the office was lower limb swelling that had been ongoing for several

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ABBREVIATIONS AND ACRONYMS

HES = hypereosinophilic syndrome

SMCD-eos = systemic mast cell disease associated with eosinophilia

VT = ventricular tachycardia

months, responsive to diuresis. His electrocardiogram showed normal sinus rhythm with premature ventricular complex, incomplete right bundle branch block, and nonspecific ST-T-wave abnormalities (Figure 1). Transthoracic echocardiography revealed a mildly dilated right ventricle, mild biatrial dilatation, normal left ventricular size, and function, trace mitral, and tricuspid regurgitation. He was advised to continue his diuretic dose, cleared for lithotripsy, and referred to hematology and the allergy and immunology clinic.

Two weeks later, he presented to the hospital with right and left upper quadrant abdominal pain, along with anasarca. Physical examination was pertinent for wheezes and rales on lung auscultation, pan systolic murmur consistent with tricuspid regurgitation, tender splenomegaly and hepatomegaly, and 3+ lower limb edema.

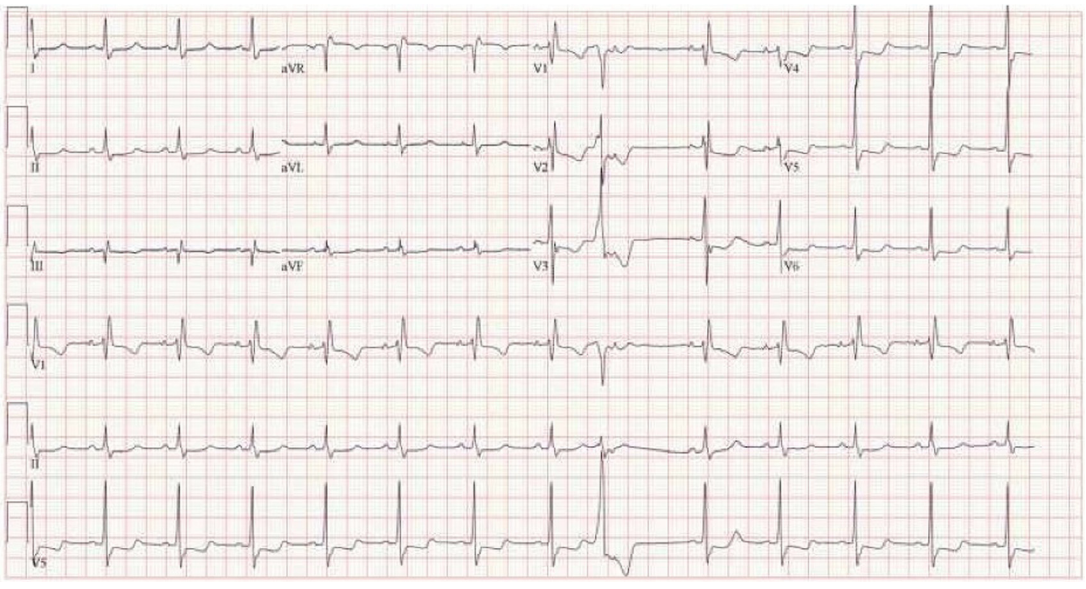
PAST MEDICAL HISTORY

His past medical history was significant for Wolf-Parkinson-White syndrome, status post ablation 12 years ago, incessant monomorphic ventricular tachycardia (VT) 1 year ago, status post ablation × 2 (left basal to mid inferior wall and mid to distal inferior septum), and automated implantable cardioverter-defibrillator for secondary prevention. Family history was unremarkable. His chronic medication included sotalol (80 mg, twice daily) and furosemide (20 mg, once daily). He denied any intake of supplements and had no history of substance abuse. He had no history of recent viral prodrome, urticaria, rash, eye symptoms, exposure to sick contacts, history of parasitic infestations, or travel.

DIFFERENTIAL DIAGNOSIS

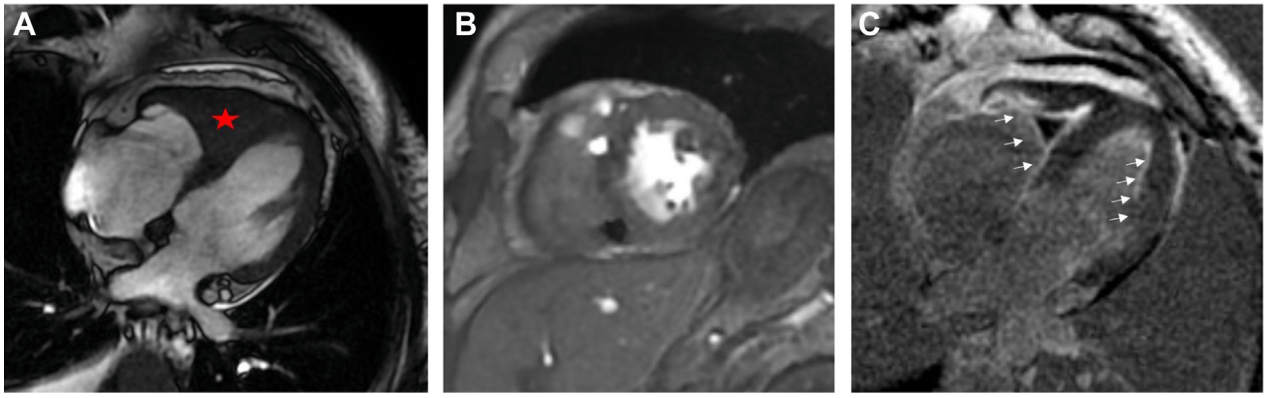
History of VT and signs of right ventricular failure in an otherwise healthy young patient raise concerns for Ebstein anomaly, inherited arrhythmic conditions, arrhythmogenic right ventricular dysplasia, focal noncompaction, and sarcoidosis. The presence of peripheral eosinophilia and late gadolinium enhancement on cardiac magnetic resonance raise concerns for an underlying infiltrative process. In this case, eosinophilic myocarditis was highest on the differential diagnosis.

FIGURE 1 Electrocardiogram at Presentation



Electrocardiogram showing normal sinus rhythm with premature ventricular complex, incomplete right bundle branch block, and nonspecific ST-T abnormalities.

FIGURE 2 Cardiac Magnetic Resonance Images



(A) Steady-state free precession procession 4-chamber image demonstrating right ventricular apical mass (star). (B) Gradient echo short-axis image demonstrating right ventricular mass. Implantable cardioverter-defibrillator lead is noted on the right side. (C) On delayed gadolinium enhancement 4-chamber image, there is diffuse subendocardial fibrosis of the right ventricle (arrow). There is subendocardial fibrosis noted of the left ventricle (arrow). Right ventricular thrombus is noted at the right ventricular apex.

INVESTIGATIONS

Initial laboratory results were significant leukocytosis of 115,000 $\times$ $10^3/\mu L$, a left shift with neutrophilia of 73,000 $\times$ $10^3/\mu L$, and an eosinophil count of 27,000 $\times$ $10^3/\mu L$, hemoglobin was 11.7 g/dL, and platelet count was 79,000 $\times$ $10^3/\mu L$. Tryptase was abnormally elevated at 16.6 μg/L (0-11.4 μg/L), and B_{12} was >2,000 pg/mL. Peripheral smear analysis indicated myelocytes, metamyelocytes, and promyelocytes, raising concern for a myeloproliferative disorder. Chest and abdominal computed tomography scans showed pleural effusion, hepatomegaly, and splenomegaly. Transthoracic echocardiography indicated a normal left ventricular size and systolic function, thrombotic obliteration of the right ventricle's lumen, and severe tricuspid regurgitation. Cardiac magnetic resonance revealed delayed gadolinium enhancement with diffuse biventricular subendocardial fibrosis and advanced scarring of the right ventricle (Figure 2). Additionally, a right ventricular thrombus was noted. The constellation of signs and symptoms observed is characteristic of Loeffler syndrome.

A bone marrow biopsy revealed markedly hypercellular marrow (90%) with granulocytic hyperplasia, eosinophilia with a spectrum of maturation stages, and increased abnormal mast cells count, consistent with myeloid neoplasm. Subsequent molecular testing was positive for *CHIC2* (4q12) deletion (*FIP1L1*/PDGFRA fusion), and negative for CSF3R mutation, KIT Asp816Val mutation, and *BCR*/*ABL1* mutation.

MANAGEMENT

A multidisciplinary team, including heart failure specialists and hematologists, was consulted. The patient was initially started on high-dose methylprednisolone (1 g daily), resulting in an initial decline in eosinophil count to 4,700 $\times$ $10^3/\mu L$, followed by a quick rebound to 17,000 $\times$ $10^3/\mu L$ in 2 days, which prompted the initiation of empirical imatinib at 400 mg daily, resulting in a significant reduction in eosinophil count to 0.1 $10^3/\mu L$. Intravenous diuresis, and therapeutic anticoagulation with warfarin for right ventricular thrombus and anasarca, were also implemented. The patient was safely discharged.

DISCUSSION

HES is characterized by the presence of hypereosinophilia and eosinophil-mediated organ dysfunction not attributable to other causes.[1] It is a rare condition with a prevalence of 0.3 to 6.3 per 100,000 people, with most patients 50 to 70 years of age, and is equally prevalent in both sexes.[1] Primary HES consists of clonal proliferation of eosinophils due to myeloid or stem cell neoplasms of which the myeloproliferative HES variant is caused by mutations in the *PDGFR*, *FGFR1*, and *JAK2* genes.[2] Secondary or reactive HES occurs in the setting of parasitic infections, in the setting of solid tumors, and in association with eosinophilic granulomatosis with polyangiitis, inflammatory bowel disease,

sarcoidosis, human immunodeficiency virus infection, hyperimmunoglobulin E syndrome, and immunoglobulin G4-related disease.[2] In this report, we discuss a case of myeloproliferative HES in the setting of *CHIC2* gene (4q12) deletion resulting in *FIP1L1*/*PDGFRA* fusion genes. This mutation is present in 11% of all HES cases.[7] Patients with *FIP1L1*/*PDGFRA* fusion present with phenotypic and genotypic features suggesting an overlap between myeloproliferative HES, also known as chronic eosinophilic leukemia, and systemic mast cell disease associated with eosinophilia (SMCD-eos).[8]

Clinical manifestations of HES are varied due to involvement of multiple organs, most commonly skin, lungs, and gastrointestinal system.[9] Although uncommon, eosinophilic endocarditis or Loeffler endocarditis is a major cause of morbidity and mortality in patients with HES, mainly due to acute heart failure, arrythmia, and thromboembolism.[3,4] Loeffler endocarditis is more commonly seen in HES due to *PDGFR* gene mutations.[10] Evolution of Loeffler endocarditis occurs in a staged fashion starting with endocardial wall necrosis when the disease is clinically and radiologically silent, followed by thrombus formation due to increased tissue factor production by the damaged endothelial cells, and a last stage of fibroinflammatory remodeling leading to restrictive cardiomyopathy, arrhythmias, and valvular regurgitation.[3-5] VTs rarely occur as an initial presentation of eosinophilic endomyocarditis.[6] VT could occur in late stages as a consequence of heart failure, diuretic use, and valvular dysfunction. However, they are less likely to be related to intracardiac eosinophils and cytokine production, as demonstrated by Cohen et al,[11] who found that the frequency of VTs did not change with variation in intracardiac eosinophilia. This patient's initial presentation of VT is potentially related to eosinophilic endomyocarditis, which should have prompted further investigations in a patient with high-risk clinical features and abnormal cardiac imaging.

Studies have proven the effectiveness of imatinib (Gleevec, Novartis) in the treatment of HES.[7] Because patients with SMCD-eos with *cKIT* mutations are resistant to imatinib, it becomes important to differentiate myeloproliferative HES from SMCD-eos for selection of therapy.[7] Additionally, elevated serum tryptase, as seen in the present case, is associated with tissue fibrosis, poor prognosis, and imatinib responsiveness.[12] A recent study by Pardanani et al[13] showed the effectiveness of imatinib in a subset of patients with SMCD-eos with *FIP1L1*/*PDGFRA* fusion without cKIT mutations. The present case did not respond initially to high-dose steroids but showed normalization of eosinophil and total leukocyte counts after the third day of imatinib 400 mg daily. Regarding the management of Loeffler endomyocarditis, symptomatic management with diuresis, digoxin, and guideline-directed medical therapy for heart failure is usually initiated.[5] Early steroid administration has been shown to reduce the risk of thrombosis and fibrosis.[14] Some studies also used immunosuppressants (eg, cyclophosphamide, azathioprine, methotrexate) either alone or with steroids.[15] Surgical options (eg, endomyocardial resection, valve repair/replacement) have been described; however, there is limited available data on outcomes.[5]

FOLLOW-UP

On follow-up 4 weeks later, the patient was found to be in good health, exhibiting euvolemia, on a stable dose of diuretics. Additionally, he continued to be in remission with a daily imatinib dose of 200 mg. Subsequently, the patient relocated and was lost to further follow-up.

CONCLUSIONS

HES in its myeloid form, also known as chronic eosinophilic leukemia, is a rare myeloid malignancy associated with serious hematological complications and unique organ dysfunction, particularly affecting the cardiovascular system. Increased vigilance is crucial, especially in young patients with arrhythmias of unknown origin, to facilitate early identification and treatment of eosinophilic myocarditis and endocarditis, averting irreversible and life-threatening consequences.

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Dr Baibhav is a speaker for Bristol Myers Squib. Dr Feitell is a consultant for Abbott. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS ***CHIC2*** **locus deletion, chronic eosinophilic leukemia, hypereosinophilic syndrome, Loeffler endocarditis, ventricular tachycardia**