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The Underrecognized Cardiac Manifestation of Hypereosinophilic Syndrome

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Inflammation

Hypereosinophilic syndrome (HES) is a rare systemic disease in which cardiac manifestations are the leading cause of morbidity and mortality. HES involvement of the heart can often clinically mimic acute coronary syndrome (ACS) with the patient undergoing repeat cardiac catheterizations when no conclusive diagnosis is arrived at, and no effective treatment is suggested to alleviate recurrent symptoms of chest discomfort. Here we present an elusive case of eosinophilic myocarditis (EM) and advocate that a detailed review of history as well as obtaining all medical records be done to avoid unnecessary and repeated invasive investigations in order to provide safe, cost effective, and efficient care for our patients.

Case Presentation

A 69-year-old man with history of hypertension, anxiety, benign prostatic hyperplasia, ulcerative colitis (UC) diagnosed 30 years ago, and hyperesosinophilic syndrome (HES) restricted to the colon presented to the emergency room with worsening mid-sternal chest pressure. The chest pressure initially started several hours ago when patient was getting out of bed, however in the thirty minutes prior to presentation it turned to chest pain with associated with shortness of breath, lightheadedness, warmth, and numbness of the left arm. On admission, symptoms did not worsen with exertion or positioning, and recent history was negative for fever, chills, flushing, rash, abdominal pain, or diarrhea. Initial physical examination was unremarkable, however laboratory studies were significant for elevated troponin I (0.15, 0.14, and 0.14), WBC 16.7, Absolute Eosinophil Count (AEC) 7800, and ESR 100. EKG revealed no ST or T wave abnormalities concerning for ongoing ischemia. Renal function and liver function were noted to be within normal limits, along with serum electrolytes, and patient was not found to be anemic.

The patient was initially triaged and planned to be managed as a case of Non-ST-Elevation-MI and subsequently was being evaluated for initiation of a Heparin drip and coronary angiogram. Patient was given aspirin 325 mg, supplemental oxygen, intravenous fluids, beta-blocker, a diuretic, and a statin in addition to patient's home medications, which notably included aspirin 81 mg, mesalamine, montelukast, prednisone 10 mg daily, ranitidine, and tamsulosin. The patient was admitted to General Medicine Service, and Cardiology Service was consulted. On further history patient revealed he had two similar episodes of chest pain in the past where he was evaluated in two different emergency departments.In both occurrences, the patient was admitted for further cardiac work-up secondary to elevated troponins.

Outside records were obtained and it was discovered our patient recently underwent cardiac catheterization which revealed non-obstructive coronary artery disease.

Next, we noted the seemingly unrelated diagnosis of hypereosinophilic involvement of the colon was made in 2007 after patient continued to have refractory symptoms of diarrhea despite adequate treatment for UC. Biopsies of the cecum, ascending, transverse, descending, and sigmoid colon all revealed marked eosinophilic and plasmacytic infiltration. Rectal biopsy showed mild eosinophilic and plasmacytic infiltration. No ova or parasitic infestation was noted and serum AEC was mildly elevated at 1000. The patient did not manifest any other symptoms aside from the diarrhea and therefore a diagnosis of hypereosinophilic involvement of the colon was established at that time.

Patient's diarrhea resolved with the initiation of Prednisone 20 mg daily. The prednisone dose was eventually tapered down to a maintenance dose of 10 mg and a leukotriene inhibitor, montelukast was added to the regimen which allowed patient to remain symptom free. A bone marrow biopsy demonstrated increased eosinophils without mutations in *JAK2 V617F*, *MPL*, or *CALR*, which are associated with classic myeloproliferative neoplasms.

With our additional history, an unremarkable physical exam, and complete resolution of chest pain in the emergency department, our suspicion for an NSTEMI event decreased and the patient was not started on a Heparin drip. An investigation to uncover the underlying disease process was initiated. Given patient's clinical presentation despite a normal cardiac catheterization, his prior hypereosinophilic infiltration of the colon, along with supporting laboratory abnormalities, a diagnosis of hypereosinophilic myocarditis was entertained as the most likely etiology for our patient's clinical presentation. Hematology Service was consulted and prednisone was increased to 50 mg (1 mg/kg in our patient who weighs 54 kg).

After initiation of the high dose steroids, our patient remained asymptomatic for the subsequent 48 hours. Moreover, he remained clinically and hemodynamically stable and was found to be stable for discharge with outpatient follow up. All recent records, including cardiac catheterization and echocardiography, were reviewed and patient was advised on risk factor modification and initiated on ibuprofen 800mg three times a day and colchicine 0.6mg once daily and prednisone 50 mg once daily by mouth until follow up appointment. All home medications were continued after discharge including statin, and low dose Aspirin.An outpatient appointment was scheduled for 2 weeks to trend labs, specifically cardiac enzymes (troponins, CK-MB), and AEC, as well as to evaluate for areas of inflammation and eosinophilic infiltrates via a cardiac MRI study.

On initial follow up, our patient continues to do well without recurrence of chest pain or pressure. A test for the *PDGFRA* mutation was also arranged in order to determine if imagine could confer a further therapeutic benefit in our patient. Unfortunately, our patient was lost to subsequent follow up and did not complete a cardiac MRI to help confirm the diagnosis.

A presentation of any patient with chest pain in the emergency department must be approached with a sense of urgency, where the work-up and management are often started concomitantly. In patients with recurrent and refractory symptoms, we recommend that after initial stabilization, the differential diagnosis should be explored beyond the more commonly established diagnosis of cardiac ischemia. Eosinophilic myocarditis (EM), for example, is such a disease state and often presents as emergent chest pain under the guise of an NSTEMI. However, management and outcomes vary tremendously.

The Condition

Hypereosinophilic syndrome (HES) is a rare disease with limited epidemiological data [1]. Previously defined as a collection of heterogeneous disorders characterized by eosinophilia in the periphery, in tissue, or both in the setting of various clinical manifestations, many subtypes of HES have been elucidated [2]. These include clonal hypereosinophilia, chronic eosinophilic leukemia, lymphocytic HES, myeloproliferative HES, organ-restricted HES, and idiopathic HES.

Subsequently, the definition of HES has been refined to include an Absolute Eosinophil Count (AEC) greater than 1500 eosinophils/mm^3 for greater than six months. The leading cause of morbidity and mortality in patients with HES continues to be cardiac disease, specifically myocarditis [3]. Albeit cardiac diseases have been reported in up to 50% of HES cases, eosinophilic myocarditis (EM) is largely underrecognized and patients are often not only underdiagnosed, but also not fully treated. Over time, repeated uninhibited myocyte infiltration may lead to conduction system damage which can then progress to fulminant heart failure [4]. Treatment of HES depends on the presence or absence of the *FIP1L1-PDGFRA* mutation, which leads to constitutively active tyrosine kinase. A near complete cure rate with imatinib therapy has been reported for patients with the mutation; whereas patients without the mutation are managed with glucocorticoids primarily, and hydroxyurea/IFN-alpha reserved for refractory cases [1,5].

Discussion

In healthy individuals, eosinophils are absent from most tissues, except for lymphatic tissue (thymus, spleen, lymph nodes), bone marrow, uterus and gastrointestinal tract [6]. Broadly, hypereosinophilic syndrome can be characterized as reactive, lymphocytic, and myeloproliferative. While the pathogenesis of eosinophilia and end organ damage are similar in all HES subtypes, treatment varies depending on the specific etiology.

The pathogenesis of HES is thought to involve eosinophil expansion, recruitment, degranulation, and delayed-type hypersensitivity reactions. CD34+ pluripotent myeloid progenitors are stimulated by IL-3 and GM-CSF with terminal differentiation of eosinophils driven by IL-5 [7]. Expansion of circulating eosinophils has been attributed to (1) IL-3, IL-5, or GM-CSF-induced proliferation by activated T-cells or (2) cytogenetic abnormalities leading to constitutional signal transduction such as that seen in the *FLIP1-PDGFR* fusion gene [8].Once in circulation, eosinophils are trafficked to various sites throughout the body. Common mediators such as VLA4 and PSGL-1 have been implicated in eosinophil margination and adhesion, although chemokine mediators of organ-specific homing remains poorly understood [9]. Upon tissue extraversion, eosinophils are aberrantly activated and degranulate cytotoxic compounds which mediate tissue damage. The mechanisms causing eosinophil degranulation is largely unknown with implicated mediators consisting of IL-5, IFN-g and sIgA to name a few [10].

Cytotoxic proteins released during degranulation include major basic protein, ECP, EPO, and EDN; all of which promote cellular damage and fibrosis of the involved organs [11]. Delayed-type hypersensitivity reactions involve Th1 recruitment, IL-5 release, and subsequent eosinophil differentiation from progenitor cells.

HES can affect any organ system causing clinical symptoms that range from a cough to peripheral neuropathy. Presenting symptoms in one case series included fatigue, cough, breathlessness, muscle pain/angioedema, rash/fever and retinal lesions [12]. With disease progression, HES typically involves the cardiovascular, pulmonary, gastrointestinal, and peripheral nervous systems. Greater than 50% of patients with HES have cardiac involvement in the form of eosinophilic myocarditis, which may include tissue necrosis, endomyocardial thrombosis, and even myocardial fibrosis [13]. During the necrotic stage, eosinophilic degranulation can cause micro-abscess formation in the myocardium with little functional effect. After sufficient damage to the endocardium, thrombi tend to form along the ventricles and atrioventricular valve leaflets leading to cardiac functional abnormalities and increased risk of cardio-embolic strokes in advanced disease. Furthermore, with untreated cardiac disease, progressive myocardial scarring will develop which can lead to entrapped chordae tendinae causing mitral and tricuspid regurgitation in addition to restrictive cardiomyopathy [12].

Serum studies are critical to the diagnosis of HES: an absolute eosinophil count $\geq 1.5 \times 10^9$/L measured on two separate occasions separated by at least 4 weeks or eosinophilia $\geq 1.5 \times 10^9$/L with eosinophil mediated end organ damage and the absence of a more likely diagnosis [6]. The diagnosis and treatment is also largely dependent on ruling out secondary causes of eosinophilia and identifying which HES variant a patient has. The approach to patients with eosinophilia starts with eliminating myeloid neoplasms such as chronic myeloid leukemia, myeloproliferative syndromes and myelodysplastic syndromes as possible diagnoses [1]. If myeloproliferative disease is suspected a bone marrow biopsy, cytology, histology and molecular analysis should be performed. Once hematologic malignancy is excluded from the differential, diagnostic testing is guided by degree of eosinophilia and clinical manifestations. In 2009, the Japanese Circulation Society Task Force Committee on Acute and Chronic Myocarditis created diagnostic criteria for patients with EM. This includes peripheral eosinophilia >500/mm3, cardiac symptoms, elevated cardiac enzymes, ECG changes, and transient left ventricular wall thickening and wall motion abnormality on echocardiography [14]. Further, ACS must be ruled out for the diagnosis of EM to be considered.

Noninvasive cardiac imaging such as echocardiography and cardiac MRI may also be used to aid in the diagnosis of EM. Although no specific echocardiographic findings have been definitively associated with EM, endocardial infiltration and fibrosis, apical thrombus formation, wall thickening or motion abnormalities, and reduced ejection fraction are commonly colocalized [15]. Cardiac MRI is better able to demonstrate the extent of endomyocardial involvement in the form of edema, inflammation, and hyper-enhancement on T2-weighted images [16].

To guide specific treatment after diagnosing HES, it is important to identify the HES variant. To diagnose M-HES a cytogenetic abnormality in PDGFRA, PDGFRB, FGFR or PMC1-JAK2 needs to be identified whereas demonstration of TCR clonality or abnormal T-cell marker expression is required to diagnose L-HES [17,18].

If no cytogenetic markers can be identified a diagnosis of idiopathic HES or HES of undetermined significance can be made. When patients present with urgent or life threatening complications, treatment should not be delayed for a complete diagnostic work-up. Initial treatment of severe disease includes high dose corticosteroids with second line agents including imatinib, cyclophosphamide, hydroxyurea, vincristine and mepolizumab [19]. In non-urgent cases, treatment can be deferred until the HES variant is diagnosed.

Imatinib can be used to treat M-HES with nearly universal remission in patients with *FLIP1PDGFR* fusion genes and mixed results in *FLIP1-PDGFR* negative patients with L-HES [19-21]. First line treatment of L-HES includes high dose corticosteroids and often requires an additional agent. Imatinib can be used to treat L-HES with response rates between 9-60% depending on the case series.

Third line agents for steroid and imatinib resistant M-HES includes hydroxyurea and second or third generation tyrosine kinase inhibitors [19]. Idiopathic HES can be treated with either low or high dose corticosteroids depending on disease severity. If no response to corticosteroids noted, many patients have been shown to respond to hydroxyurea and IFN-a, with a synergistic effect when used in tandem [22, 23].

Lessons for the Clinician

Patients with chest pain and a troponin leak often undergo invasive investigations, including cardiac catheterizations, to exclude ACS. Frequently, the ischemic evaluation is abandoned prematurely in inpatient settings when initial work up is unrevealing and patients are lost to follow up or present to different inpatient settings with the same unresolved chief complaints – as initially occurred in our case. Within the context of a prior diagnosis of HES and our patient's clinical presentation, we considered a diagnosis of eosinophilic myocarditis early in the hospital course.

We intentionally omitted an invasive diagnostic cardiac catherization given our patient recently presented with a similar chief complaint at an outside hospital and completed an extensive unrevealing work up. Instead we concentrated our efforts on obtaining all prior outside medical records and promptly initiated treatment with steroids as we suspected EM as the underlying diagnosis. Consequently, we advocate approaching common acute chief complains with a broad differential diagnosis and considering rare diagnoses concurrent to evaluating the most common pathologies in order to provide safe, cost effective, and efficient care for our patients.

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