CLINICAL VIGNETTE

A Traveler with Eosinophilia

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Case

A 78-year-old male visiting from Europe presented to the emergency department with several days of epigastric pain, weakness, and shortness of breath. His past medical history includes hypertension, coronary artery disease and well controlled asthma. After leaving Europe to visit family, exertional shortness of breath progressively worsened, prompting ED evaluation.

He denied fevers, chills, night sweats, rashes, dysphagia, visual disturbances, abdominal pain, diarrhea or chest pain. On ED arrival, he was afebrile, hypotensive to 102/78, and tachycardic at 95. He appeared comfortable with normal respiratory effort. Cardio respiratory exam was unremarkable and abdomen was soft without masses or organomegaly. Neurological exam was significant for decreased sensation to light touch on the dorsal aspect of the right foot with normal reflexes and intact strength.

Initial labs were remarkable for increased WBC of 27.17, with an elevated absolute eosinophil count of 14.3. Platelets were 465k. Troponin was elevated to 11, erythrocyte sedimentation rate >130mm, C-reactive protein 7.0mg/dl, procalcitonin 0.10 ug/l, and B-type natriuretic peptide 412. Creatinine and urinalysis were normal.

EKG showed ST abnormality and lateral ischemia and echocardiogram showed left ventricular ejection fraction of 40-45% with mildly enlarged right ventricular size and normal systolic function with severe bi atrial enlargement.

Extensive infectious disease testing including fungal, parasitic, TB and routine infectious etiologies returned negative. Autoimmune labs included negative C-ANCA, P-ANCA, proteinase-3 ab, myeloperoxidase ab and ANA.

At this point the differential diagnosis included eosinophilic granulomatosis polyangiitis (EGPA) vs. hypereosinophilic syndrome (HES). A bone marrow biopsy was ordered to rule out myeloproliferative-type HES. Hospital course left heart catheterization showed no occlusive disease or plaque rupture. Because of a history of contrast allergy, intravenous methylprednisolone was given as a premedication before his catheterization. The steroid transiently improved his absolute eosinophil count from 14000 to 700 after which, the eosinophil count continued to increase.

Cardiac MRI showed a small focus of subepicardial delayed enhancement along the mid cavity inferolateral and subendocardial apical septal and inferior walls consistent with nonspecific fibrosis. CT chest revealed diffuse bronchial wall thickening and post obstructive subsegmental atelectasis in the bilateral lower lobes thought to be related to asthma/COPD overlap. During hospitalization, the patient developed left sided foot drop concerning for mononeuritis multiplex but neuroimaging was negative. A cardiac biopsy was deferred due to procedural high risk. He was discharged with a presumptive diagnosis of eosinophilic granulomatosis polyangiitis (EGPA), supported by his history of asthma, eosinophilia, eosinophilic myocarditis, elevated inflammatory markers, and dramatic response to steroids with resolution of symptoms and eosinophilia. He was started on 60mg of prednisone with a plan for further evaluation after returning home to Europe.

One-week post-discharge, his bone marrow biopsy returned positive for a mutation in JAK2 -V617F consistent with a myeloproliferative disorder with thrombocytosis, with the unusual finding of marked eosinophilia. His prednisone dose was decreased, and he was started on hydroxyurea 500mg daily with significant decline in eosinophil count to 0.36 and WBC to 11.

Discussion

Eosinophilic granulomatosis polyangiitis, previously known as Churg Struss syndrome, was first described in 1951 as a form of necrotizing vasculitis occurring exclusively in patients with asthma and tissue eosinophilia.[1] EGPA is a disease that falls into dual categories of ANCA associated vasculitis (AAV) and the hypereosinophilic syndromes (HES).[2,3] HES are a group of disorders marked by overproduction of eosinophils, following which the eosinophilic infiltration and subsequent mediator release can cause damage to multiple organs.

Our patient presented with hypereosinophilia and myocarditis with worsening chest tightness and shortness of breath, and subsequently developed mononeuritis multiplex concerning for EGPA vs. HES.

Eosinophilic Granulomatosis Polyangiitis

EGPA is classified with ANCA associated vasculitis (AAV) because of the overlapping clinico-pathological features with

other AAV's. However, while ANCA are consistently found in 70–95% of patients with GPA and MPA, their prevalence in EGPA is much lower, 30-60 %. The main fluoroscopic pattern is perinuclear(p-ANCA) with antibodies to MPO.[4]

The most common presenting features of EGPA are asthma, nasal and sinus symptoms and peripheral neuropathy. It is a multiorgan system disease with notable constitutional symptoms especially in the vasculitic phase with a mean age of diagnosis round 50.

Two previous studies have shown that ANCA positive patients tend to have peripheral neuropathy, glomerulonephritis and purpura more frequently compared to the ANCA negative group that had more features of GI, pulmonary and cardiac involvement.[5]

ANCA and Its Significance

EGPA disease manifestations may differ between ANCA-positive and ANCA-negative patients, although confirmatory data is needed.[5] ANCA-positivity is associated with constitutional symptoms, biopsy-proven vasculitis and glomerulonephritis on biopsy. Mononeuritis multiplex was associated with systemic vasculitis and ANCA-positivity, although 22 % of patients with mononeuritis multiplex were ANCA-negative. In terms of ANCA types, 96% were specific for myeloperoxidase and 4% were specific for PR3. In a series of 112 patients with newly diagnosed EGPA, a positive ANCA at diagnosis was associated with renal involvement, peripheral neuropathy, and biopsy-proven vasculitis, whereas a negative ANCA was associated with heart disease and fever.[6]

Hypereosinophilic Syndromes

A panel of experts published consensus recommendation terminology for hypereosinophilic syndromes in 2012.[7] Hypereosinophilia is defined as an absolute eosinophil count (AEC) >1.5 x 10^9/L (or >1500 cells/micro L) in the peripheral blood on two examinations separated in time by at least one month **and/or** pathologic confirmation of tissue hypereosinophilia.[3]

Hypereosinophic syndromes (HES) are subclassified based on pathophysiology as primary, secondary or idiopathic hypereosinophilia. Primary is neoplastic and secondary is polyclonal expansion due to cytokine release such as parasitic infection, solid tumor or T cell lymphoma and idiopathic HES has unclear etiology is unclear despite evaluation.

HES is classified clinically into the following subcategories[8]:

- Myeloproliferative variants of HES (M-HES).
- T lymphocytic variants of HES (L-HES).
- Familial HES
- Idiopathic HES (IHES)
- Organ-restricted hypereosinophilic conditions (single organ involvement)
- Specific/defined syndromes are associated with hypereosinophilia with multiple organ involvement such as EGPA

Clinical presentation can vary. Some patients have insidious onset of symptoms with eosinophilia incidentally noted, whereas others present with severe life-threatening disease. A retrospective multicenter series of 188 patients reported dermatologic findings in a third of the cases, pulmonary and GI symptoms in a quarter each, with cardiac, neurological and asymptomatic hypereosinophilia being rare presenting features of HES.[8]

Cardiac Evaluation

As with our patient, a complete cardiac evaluation should be obtained after diagnosis of EGPA even in the absence of symptoms suggesting cardiac disease. This is because cardiac involvement is the leading cause of mortality due to EGPA, and approximately 40% of asymptomatic patients with a normal EKG have evidence of cardiac involvement with EGPA on TTE.[9,10] Findings on MRI have been reported to correlate with endomyocardial biopsy evidence of eosinophilic infiltration.[11] MR is recommended for initial testing to guide further decisions about endomyocardial biopsy.

Role of Endomyocardial Biopsy (EMB)

Endocardial biopsy is the gold standard, however may not be very sensitive because the infiltration is usually focal.[12] Acute myocardial infarction, left ventricular mural thrombosis, or aneurysm formation are contraindications to EMB. In EGPA the most notable pathological features are inflammatory cell infiltrates of neutrophils, lymphocytes and eosinophils, cellulose-like necrosis, granuloma formation, stenosis, occlusion, and thrombosis.

In HES the hallmark histologic findings include interstitial infiltrates with prominent eosinophils and other immune cells, myocyte necrosis, and edema in the acute phase. Endocardial thrombosis containing eosinophils are noted in the second phase and endocardial fibrotic thickening without inflammatory infiltrates in the late stage.[13]

Conclusion

In conclusion, the clinical presentation of EGPA and HES is very similar and difficult to differentiate the etiology of eosinophilic myocarditis. Cardiac biopsy may not very sensitive in differentiating the etiology. In our case a diagnosis of EGPA was made based on clinical picture and was confirmed with bone marrow biopsy. Differentiating the etiology is crucial as their management differs.

The overall prognosis of HES with cardiac involvement is poor. Early diagnosis of HES with close clinical and echocardiographic monitoring for heart disease has improved the mean survival.

CLINICAL FEATURES OF EGPA AND HES

CLINICAL FEATURES	EGPA	HES
SKIN	Tender subcutaneous nodules Seen on extensor surfaces (50-75%)	Eczema, lichenification, dermatographism, angioedema, urticaria, mucosal ulcers
MUSCULOSKELETAL	Myalgia, polyarthralgia, frank arthritis (50%), myositis rare	None
LYMPHADENOPATHY	Eosinophilic lymphadenopathy (30-40%) cervical and axillary adenopathy reported	Intrathoracic adenopathy (12%)
CARDIOVASCULAR	Cardiomyopathy (15%), pericarditis (16%) cardiac arrhythmia, endomyocardial involvement	Eosinophilic myocarditis progressing to valvular disease, heart failure, cardiomyopathy
PULMONARY	Asthma (90%), poorly controlled, pulmonary infiltrates, pleural effusions	Infiltrates (37%) pleural effusion (14%), PE (4%)
UPPER AIRWAY/ ENT	Otitis media, sinus polyposis, recurrent sinusitis, allergic rhinitis (85%)	None
THROMBOEMBOLIC	Increased risk of VTE (8%)	venous and arterial thrombi, digital gangrene with Raynaud's
GASTROINTESTINAL	Eosinophilic gastroenteritis in the form of abdominal pain (60%), diarrhea, Gi bleed, colitis	Similar findings to EGPA
RENAL	isolated proteinuria, GN, ARF and microscopic hematuria (22%)	None
NEUROLOGIC	Mononeuritis multiplex, peripheral neuropathy (75%), cranial nerve palsy, including ocular involvement.	thromboembolism, encephalopathy, peripheral neuropathy (50%), rarely mononeuritis
OCULAR	CRAO, CRVA, ischemic optic neuropathy, orbital myositis	Microemboli, local thrombosis, uveitis (rare)

REFERENCES

1. **Churg J, Strauss L**. Allergic granulomatosis, allergic angiitis, and periarteritis nodosa. *Am J Pathol.* 1951 Mar-Apr;27(2):277-301. PMID: 14819261; PMCID: PMC1937314.
2. **Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, Flores-Suarez LF, Gross WL, Guillevin L, Hagen EC, Hoffman GS, Jayne DR, Kallenberg CG, Lamprecht P, Langford CA, Luqmani RA, Mahr AD, Matteson EL, Merkel PA, Ozen S, Pusey CD, Rasmussen N, Rees AJ, Scott DG, Specks U, Stone JH, Takahashi K, Watts RA**. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum*. 2013 Jan;65(1):1-11. doi: 10.1002/art.37715. PMID: 23045170.
3. **Valent P, Klion AD, Horny HP, Roufosse F, Gotlib J, Weller PF, Hellmann A, Metzgeroth G, Leiferman KM, Arock M, Butterfield JH, Sperr WR, Sotlar K, Vandenberghe P, Haferlach T, Simon HU, Reiter A, Gleich GJ**. Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. *J Allergy Clin Immunol*. 2012 Sep;130(3):607-612.e9. doi: 10.1016/j.jaci.2012.02.019. Epub 2012 Mar 28. PMID: 22460074; PMCID: PMC4091810.
4. **Radice A, Bianchi L, Sinico RA**. Anti-neutrophil cytoplasmic autoantibodies: methodological aspects and clinical significance in systemic vasculitis. *Autoimmun Rev*. 2013 Feb;12(4):487-95. doi: 10.1016/j.autrev. 2012.08.008. Epub 2012 Aug 17. PMID: 22921790.
5. **Sablé-Fourtassou R, Cohen P, Mahr A, Pagnoux C, Mouthon L, Jayne D, Blockmans D, Cordier JF, Delaval P, Puechal X, Lauque D, Viallard JF, Zoulim A, Guillevin L; French Vasculitis Study Group**. Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome. *Ann Intern Med*. 2005 Nov 1;143(9): 632-8. doi: 10.7326/0003-4819-143-9-200511010-00006. PMID: 16263885.
6. **Sinico RA, Di Toma L, Maggiore U, Bottero P, Radice A, Tosoni C, Grasselli C, Pavone L, Gregorini G, Monti S, Frassi M, Vecchio F, Corace C, Venegoni E, Buzio C**. Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome. *Arthritis Rheum*. 2005 Sep;52(9):2926-35. doi: 10.1002/ art.21250. PMID: 16142760.

7. **Simon HU, Rothenberg ME, Bochner BS, Weller PF, Wardlaw AJ, Wechsler ME, Rosenwasser LJ, Roufosse F, Gleich GJ, Klion AD**. Refining the definition of hypereosinophilic syndrome. *J Allergy Clin Immunol*. 2010 Jul;126(1):45-9. doi: 10.1016/j.jaci.2010.03.042. PMID: 20639008; PMCID: PMC3400024.
8. **Ogbogu PU, Bochner BS, Butterfield JH, Gleich GJ, Huss-Marp J, Kahn JE, Leiferman KM, Nutman TB, Pfab F, Ring J, Rothenberg ME, Roufosse F, Sajous MH, Sheikh J, Simon D, Simon HU, Stein ML, Wardlaw A, Weller PF, Klion AD**. Hypereosinophilic syndrome: a multicenter, retrospective analysis of clinical characteristics and response to therapy. *J Allergy Clin Immunol*. 2009 Dec;124(6):1319-25.e3. doi: 10.1016/j.jaci.2009.09.022. PMID: 19910029; PMCID: PMC2829669.
9. **Sinico RA, Bottero P**. Churg-Strauss angiitis. *Best Pract Res Clin Rheumatol*. 2009 Jun;23(3):355-66. doi: 10.1016/j.berh.2009.02.004. PMID: 19508943.
10. **Dennert RM, van Paassen P, Schalla S, Kuznetsova T, Alzand BS, Staessen JA, Velthuis S, Crijns HJ, Tervaert JW, Heymans S**. Cardiac involvement in Churg-Strauss syndrome. *Arthritis Rheum*. 2010 Feb;62(2):627-34. doi: 10.1002/art.27263. PMID: 20112390.
11. **Groh M, Pagnoux C, Baldini C, Bel E, Bottero P, Cottin V, Dalhoff K, Dunogué B, Gross W, Holle J, Humbert M, Jayne D, Jennette JC, Lazor R, Mahr A, Merkel PA, Mouthon L, Sinico RA, Specks U, Vaglio A, Wechsler ME, Cordier JF, Guillevin L**. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management. *Eur J Intern Med*. 2015 Sep;26(7):545-53. doi: 10.1016/j.ejim.2015.04.022. Epub 2015 May 9. PMID: 25971154.
12. **Burke AP, Saenger J, Mullick F, Virmani R**. Hypersensitivity myocarditis. *Arch Pathol Lab Med*. 1991 Aug;115(8):764-9. PMID: 1863186.
13. **Take M, Sekiguchi M, Hiroe M, Hirosawa K, Mizoguchi H, Kijima M, Shirai T, Ishide T, Okubo S**. Clinical spectrum and endomyocardial biopsy findings in eosinophilic heart disease. *Heart Vessels Suppl*. 1985; 1:243-9. doi: 10.1007/BF02072403. PMID: 3843586.