Hypereosinophilic Syndrome Presenting As an Unusual Triad of Eosinophilia, Severe Thrombocytopenia, and Diffuse Arterial Thromboses, With Good Response to Mepolizumab

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Case Report

A previously healthy 47-year-old man presented with 3 weeks of bilateral hand numbness, tingling, cyanosis, and newly onset lower extremity edema and petechiae. On examination, both hands were dusky, cold, and exquisitely tender. Bilateral radial pulses and left popliteal pulse were not palpable. No lymphadenopathy, organomegaly, or masses were detected. Initial workup revealed severe eosinophilia and thrombocytopenia (white blood cell count, 20.3 × 10^3/µL; eosinophil count, 10.9 × 10^3/µL; platelet count, 8 × 10^3/µL), and normal hemoglobin of 15.2 g/dL. A peripheral blood smear (PBS) showed markedly increased eosinophils and decreased platelets. No platelet clumps, schistocytes, or blasts were seen. A magnetic resonance angiography (MRA) of the extremities revealed multiple arterial thromboses involving both upper extremities and the left lower extremity.

An investigation for underlying causes of eosinophilia and thrombophilia was pursued. There was no recent travel history or use of suspicious medications. Parasitic infestation was ruled out with serial stool ova and parasites test (O&P), and serology was negative for strongyloides, toxoplasma, toxocara, entamoeba, and trichinosis, among others. Serologic studies for connective tissue disease and vasculitides were negative. Serum interleukin-5 (IL-5) and tryptase were normal. Immunoglobulin E (IgE) was slightly elevated at 178 IU/mL (reference, 0–100 IU/mL).

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Complement studies were normal. Fluorescence in situ hybridization (FISH) screening for *FIP1L1-PDGFRA* rearrangement was negative. A bone marrow biopsy revealed a normocellular marrow, with marked eosinophilia (47%), adequate numbers of megakaryocytes, and no increase in blasts, mast cells, or reticulin fibrosis. Cytogenetic studies showed no abnormalities. Peripheral blood flow cytometry did not identify monoclonal cell populations, and no underlying T-cell clone was detected using a T-cell receptor gene rearrangement polymerase chain reaction (PCR) study. Serum protein electrophoresis, serum immunofixation electrophoresis, and urine immunofixation electrophoresis were all negative. Cryoglobulins were not detected. Hepatitis serologies were negative. Extensive hypercoagulability workup was unrevealing. There was no evidence of disseminated intravascular coagulation (DIC) or thrombotic thrombocytopenic purpura (TTP). Computed tomography (CT) of the chest, abdomen, and pelvis did not show evidence of malignancy. An echocardiogram was normal, with no evidence of intracardiac thrombus, patent foramen ovale, or cardiomyopathy. Given the lack of a readily apparent cause for secondary eosinophilia and the presence of thrombotic complications, the patient was diagnosed with life- and limb-threatening hypereosinophilic syndrome (HES), without evidence of cardiac, renal, or pulmonary involvement.

The patient was given 1 gram of intravenous (IV) methylprednisolone, which was followed by prednisone 1 mg/kg/day. Due to his extensive arterial thromboses, anticoagulation with IV heparin was initiated, and he underwent multiple thrombectomies. The anticoagulation was later transitioned

to warfarin. The platelet count recovered within 2 weeks and the eosinophil count normalized within 3 weeks. Prednisone was slowly tapered over the following month. When the dose was down to 20 mg/day, he developed chest pain and recurrent eosinophilia and thrombocytopenia, requiring a dose increase in prednisone back to 1 mg/kg/day, with a prompt symptom resolution and normalization of eosinophil and platelet counts. Two subsequent attempts in tapering the prednisone were unsuccessful and complicated by recurrent eosinophilia, thrombocytopenia, and new extremity arterial thromboses. Interferon-α (IFN-α) was started as a steroid-sparing agent at an initial dose of 3 million units subcutaneously 3 times weekly (TIW), and was later increased to 5 million units TIW due to persistent digit ischemia and eosinophilia, but was subsequently discontinued due to lack of efficacy. A trial of imatinib (Gleevec, Novartis) 400 mg/day was pursued, without noticeable added benefit and worsening thrombocytopenia, prompting its discontinuation after 2 weeks. At 7 months from diagnosis, IV mepolizumab 750 mg every 4 weeks was started. Adequate control of eosinophilia and thrombocytopenia was achieved; however, in spite of this and the warfarin treatment, the patient developed recurrent thrombosis, which resulted in index finger necrosis, infection, and subsequent amputation. Pathology of the amputated finger revealed an organized blood clot with no evidence of vasculitis. His anticoagulation was changed to low-molecular-weight heparin (LMWH), and with the third mepolizumab dose, hydroxyurea 500 mg twice daily (BID) was started. Since then, prednisone was slowly and successfully tapered, and ultimately discontinued at 18 months from the time of diagnosis. At 44 months from diagnosis, the patient continues to do well without steroids, and has not experienced recurrence of thrombosis, thrombocytopenia, or eosinophilia. He remains on monthly mepolizumab, now once-daily hydroxyurea, and lifelong anticoagulation with LMWH.

Discussion

Persistent eosinophilia can be reactive (cytokine-driven in response to allergy, inflammation, or neoplasms), clonal (in which the eosinophils themselves are considered neoplastic), or idiopathic. Evaluation must include a complete history (including travel and medications) and physical exam. Serial stool cultures (especially for strongyloides, other ova, and parasite testing) and serologic studies for specific parasites should be obtained. Evidence for underlying allergy, connective tissue disease, vasculitis, organ-restricted eosinophilic disorders (pulmonary or gastrointestinal eosinophilic disease), adrenal insufficiency, and malignancy should be considered and pursued.

The lack of a readily apparent cause of reactive eosinophilia should raise concern for clonal eosinophilic proliferations. Evaluation for these should include a careful review of the PBS, measurement of serum tryptase (for evidence of underlying myeloid malignancies), IL-5, bone marrow biopsy, screening for *FIP1L1-PDGFRA* rearrangement (if positive, a working diagnosis of *FIP1L1-PDGFRA*–associated neoplasm is made), cytogenetic studies (in search of clonal eosinophilia mutations), and peripheral blood lymphocyte phenotyping and T-cell receptor gene rearrangement studies (to exclude lymphocytic-variant hypereosinophilia).[1] Of note, *FIP1L1-PDGFRA* fusion is often karyotypically occult, which makes FISH screening mandatory. If this workup is unrevealing, idiopathic HES should be considered.

The diagnosis of HES is established by fulfilling 3 criteria: 1) hypereosinophilia (blood eosinophilia with or without tissue eosinophilia), 2) hypereosinophilia-related organ damage, and 3) absence of an alternative explanation for the observed organ damage.[2] Eosinophil-related organ damage refers to eosinophil infiltration associated with organ dysfunction that is seen with 1 or more of the following: fibrosis (lung, heart, gastrointestinal tract, skin, or others); thrombosis with or without thromboembolism; cutaneous and mucosal erythema, edema/angioedema, ulceration, or eczema; peripheral or central neuropathy with chronic or recurrent neurologic deficit; and other less common organ manifestations. In our patient, the major organ damage was a consequence of arterial thromboses.

Thrombocytopenia or thrombocytosis are noted in approximately 31% and 16% of HES cases, respectively.[3] Severe thrombocytopenia, as in our patient, is very infrequent, and appears to correlate with disease severity and treatment refractoriness.[3] Approximately 25% of patients develop thromboembolic complications, most commonly venous (pulmonary, cutaneous, cerebral, hepatic, or portal veins) or intracardiac.[4,5] Arterial thrombosis, especially with resultant digit necrosis, is exceedingly rare.[4,6-9] Most arterial occlusions in reality reflect peripheral embolism from intracardiac thrombi or the presence of vasculitis. Rare cases of DIC or TTP have also been reported.[5] In our patient, the arterial thromboses were not associated with vasculitis, and intracardiac thrombi were not identified by echocardiogram. It is possible, however, that small intracardiac thrombi may have been present and could not be visualized. A similar case of HES with thrombocytopenia and thrombosis was reported by Sherer and associates.[10] However, their patient had venous thrombosis instead of arterial, and the thrombocytopenia was not as severe ($69 \times 10^3/\mu L$). Their patient responded well to steroids, in contrast to our patient, who had a much more protracted course and required multiple lines of therapy prior to being able to stop steroids.

The underlying mechanisms driving the HES hypercoagulability are not fully understood. It is thought that main granule proteins released by eosinophils promote endothelial damage and activation of the platelets and the coagulation cascade.[5] The development of recurrent thromboses in our patient, even after the eosinophilia had been controlled, may reflect residual endothelial damage from prolonged eosinophilia, warfarin failure, or potentially eosinophil-independent mechanisms that have yet to be identified.

Prednisone (1 mg/kg/day) is the cornerstone of HES management and usually induces a rapid decline in the eosinophil count within 1 month of treatment. Unfortunately, many patients recur when steroids are tapered, as in the case presented. In these patients, the addition of hydroxyurea and/or IFN-α is indicated as steroid-sparing therapy. Patients with *PDGFR* rearrangements usually respond to imatinib. Selected patients without *PDGFR* rearrangements may benefit from high-dose imatinib, but responses tend to be partial and short-lived.[11] Cytotoxic drugs have been used with variable success. For refractory HES, there has been increased interest in the humanized monoclonal antibodies mepolizumab (anti–IL-5) and alemtuzumab (anti-CD52). IL-5 plays a crucial role in differentiation, activation, and survival of eosinophils. In a recent randomized clinical trial,[12] 36 of 43 (84%) prednisone-dependent HES patients were able to decrease their prednisone dose to 10 mg/day or less for 8 weeks or more when mepolizumab was added. The presence of *FIP1L1-PDGFRA* rearrangement or pretreatment IL-5 levels do not appear to predict response.[13] In another study, alemtuzumab induced hematologic remission in 10 of 11 (91%) treated patients; however, response was not sustained once therapy was discontinued.[14] To date, monoclonal antibodies remain investigational.

The case described illustrates an unusual presentation of HES, with a triad of severe eosinophilia, severe thrombocytopenia, and diffuse arterial thromboses in spite of adequate anticoagulation and successful control of eosinophilia. To our knowledge, occurrence of diffuse arterial thrombosis without evidence of vasculitis or intracardiac thrombi has never been described in the HES literature. In addition, the degree of thrombocytopenia observed in our patient was more severe than what is usually reported in HES. Concomitant thrombocytopenia may be a marker of disease severity and refractoriness, as suggested in the study by Flaum and colleagues.[3] Finally, although the use of monoclonal antibodies in HES remains investigational, our case adds to the growing evidence that the addition of mepolizumab can effectively help control refractory HES. Even though treatment with hydroxyurea and LMWH certainly contributed, it was not until the addition of mepolizumab that our patient could decrease his high-dose prednisone requirements and eventually discontinue the drug, without disease recurrence to date. As further evidence on these agents becomes available, monoclonal antibodies may prove very beneficial in patients with refractory, steroid-dependent HES.

References

1. Tefferi A, Gotlib J, Pardanani A. Hypereosinophilic syndrome and clonal eosinophilia: point-of-care diagnostic algorithm and treatment update. *Mayo Clin Proc*. 2010;85:158-164.
2. Valent P, Klion AD, Horny HP, et al. Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. *J Allergy Clin Immunol*. 2012;130:607-612.
3. Flaum MA, Schooley RT, Fauci AS, Gralnick HR. A clinicopathologic correlation of the idiopathic hypereosinophilic syndrome. I. Hematologic manifestations. *Blood*. 1981;58:1012-1020.
4. Ogbogu PU, Rosing DR, Horne MK 3rd. Cardiovascular manifestations of hypereosinophilic syndromes. *Immunol Allergy Clin North Am*. 2007;27:457-475.
5. Ohguchi H, Sugawara T, Harigae H. Thrombotic thrombocytopenic purpura complicated with hypereosinophilic syndrome. *Intern Med*. 2009;48:1687-1690.
6. Novack SN, Kun TL, Goldberg LS. Arterial calcification associated with hypereosinophilic syndrome. *Ann Intern Med*. 1971;74:99-101.
7. Ferguson GT, Starkebaum G. Thromboangiitis obliterans associated with idiopathic hypereosinophilia. *Arch Intern Med*. 1985;145:1726-1728.
8. Johnston AM, Woodcock BE. Acute aortic thrombosis despite anticoagulant therapy in idiopathic hypereosinophilic syndrome. *J R Soc Med*. 1998;91:492-493.
9. Hachulla E, Hatron PY, Janin A, Robert Y, Devulder B. Digital arteritis, thrombosis and hypereosinophilic syndrome: an uncommon complication. *Rev Med Interne*. 1995;16:434-436.
10. Sherer Y, Salomon O, Livneh A, Pras M, Langevitz P. Thromboembolism in a patient with transient eosinophilia and thrombocytopenia. *Clin Lab Haematol*. 2000;22:247-249.
11. Butterfield JH. Success of short-term, higher-dose imatinib mesylate to induce clinical response in FIP1L1-PDGFR alpha-negative hypereosinophilic syndrome. *Leuk Res*. 2009;33:1127-1129.
12. Rothenberg ME, Klion AD, Roufosse FE, et al. Treatment of patients with the hypereosinophilic syndrome with mepolizumab. *N Engl J Med*. 2008;358:1215-1228.
13. Gotlib J. World Health Organization-defined eosinophilic disorders: 2011 update on diagnosis, risk stratification, and management. *Am J Hematol*. 2011;86:677-688.
14. Verstovsek S, Tefferi A, Kantarjian H, et al. Alemtuzumab therapy for hypereosinophilic syndrome and chronic eosinophilic leukemia. *Clin Cancer Res*. 2009;15:368-373.

Review

An Unusual Presentation of Idiopathic Hypereosinophilic Syndrome

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Discussion

Idiopathic hypereosinophilic syndrome (HES) is a diagnosis of exclusion. Specifically, no evidence of a hematopoietic neoplasm or reactive eosinophilia is found. Leon-Ferre and colleagues discuss the diagnostic workup and management of an intriguing case of idiopathic HES with unusual presentation.[1] A young man presented with persistent eosinophilia, severe thrombocytopenia, and diffuse arterial thrombosis as a manifestation of hypereosinophilia-associated tissue damage. There was no cutaneous, cardiac, renal, or pulmonary involvement. Reactive and neoplastic processes were excluded after thorough and extensive clinical and laboratory examination. He responded to the course of corticosteroids, hydroxyurea, mepolizumab, and anticoagulation with low-molecular-weight heparin, and remains well after 44 months.

The presence of severe thrombocytopenia and diffuse arterial thrombosis with eosinophilia is infrequent. Although virtually any tissue or organ can be affected in HES, clinical complications arise frequently in the skin, heart, lungs, and nervous system. The most serious clinical findings are related to endomyocardial fibrosis, restrictive cardiomegaly, valvular scarring/regurgitation, and formation of intracardiac thrombi. Hematologic abnormalities including thrombocytopenia can be seen, though they are more common in *FIP1L1-PDGFRA*–associated HES.[2] Thrombotic complications are usually a manifestation of damage to the endovascular surface by chronic eosinophilia. In HES, patients are thought to have increased activated blood eosinophils. Once activated, eosinophils release a number of cytopathic substances, including major basic proteins (MBP), reactive oxygen species, leukotrienes, prostaglandins, platelet-activating factor, cytokines, matrix-digesting enzymes, and other reactive granule proteins. In addition to its cytotoxicity, MBP is a potent stimulator of platelets, binding to thrombomodulin and reducing its ability to inhibit the clotting cascade.[3] It is likely that eosinophils mediate the vascular endothelial damage central to forming microthrombi. Although venous thrombosis is more frequent in HES, rare cases of digital necrosis associated with occlusion of medium-sized arteries without vasculitis have been reported.[4]

The concept of idiopathic HES is evolving with the identification of novel genetic abnormalities. In the past, there were relatively more cases of this rare disease. Now many cases are reclassified as chronic eosinophilic leukemia as a result of a cryptic deletion of part of chromosome 4q that leads to the *FIP1L1-PDGFRA* fusion gene.[5] The *FIP1L1-PDGFRA* fusion gene encodes a constitutively activated tyrosine kinase, and is a target for therapy by the tyrosine kinase inhibitor imatinib (Gleevec, Novartis). The fusion gene is identified by polymerase chain reaction (PCR) or fluorescence in situ hybridization (FISH).

Recent studies have demonstrated that approximately 17–56% of previously defined HES cases harbor the *FIP1L1-PDGFRA* mutation.[6,7] Elevated serum tryptase and serum vitamin B_{12} levels are observed in patients with *FIP1L1-PDGFRA* disease.[8] Some of the prior HES cases are also recognized as lymphoid and myeloid neoplasms with *PDGFRB* or *FGFR1* rearrangement, systemic mastocytosis, or eosinophilic transformation of myeloproliferative neoplasms or chronic eosinophilic leukemia, not otherwise classified. Thus, testing for clonal rearrangements is mandatory in the investigative schemata for HES.

Of note is a distinct category of lymphocytic variant-HES, a cytokine-secreting lymphocyte population that can lead to eosinophilia. The immunophenotypically aberrant T-lymphocytes overproduce interleukin-5 (IL-5), and this variant can be identified with flow cytometry by its most frequently reported phenotype, CD3-/CD4+.[9] The eosinophils are not part of the clonal process. Roufosse and coworkers estimated that roughly one-fourth of HES patients present with this type.[10] High serum immunoglobulin E (IgE) levels and polyclonal hypergammaglobulinemia are more frequently noted in this disease. Some patients with lymphocytic variant-HES subsequently develop T-cell lymphoma. In addition to corticosteroids, the anti–IL-5 monoclonal antibody mepolizumab can be effective in this variant.

Recent developments and insights into the biology of this disease have drastically changed the therapeutic options for this heterogeneous group under the umbrella diagnosis of HES. Management depends on the disease manifestations/severity and identification of pathogenic variants. For *FIP1L1-PDGFRA*-associated HES, imatinib has undisputedly become the first line of therapy.

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This subgroup frequently presents with cardiac complications, and is at risk for developing acute leukemia. Patients with the lymphocytic variant of HES usually show cutaneous lesions, and should be monitored over the years for the development of T-cell lymphoma.

The small subset of patients with idiopathic HES may represent the clinically overlooked reactive causes, or cases with unique molecular genetic abnormalities that remain undiscovered. Follow-up of such cases is recommended to see how and in which direction the disease evolves. Currently, corticosteroids are administered as first-line therapy in all patients without the *FIP1L1-PDGFRA* mutation. The second-line drugs or steroid-sparing drugs include hydroxycarbamide, interferon-α, and imatinib. For refractory cases, chemotherapeutic agents that have been used with some success include chlorambucil, etoposide, vincristine, 2-chlorodeoxyadenosine, and cytarabine. The advances in the use of monoclonal antibodies in HES offer novel target-specific options. Promising reports have emerged with the use of mepolizumab, the anti–IL-5 monoclonal antibody designed to target eosinophils, and alemtuzumab, a monoclonal anti-CD52 antibody effective against CD3-/CD4+ T-cell subsets.[11,12] As fascinating pathogenic mechanisms have been discovered and new knowledge is gathered, the development of safe and efficacious targeted therapeutic approaches will significantly alter the course of this rare, potentially fatal disease.

References

1. Leon-Ferre RA, Weiler CR, Halfdanarson TR. Hypereosinophilic syndrome presenting as an unusual triad of eosinophilia, severe thrombocytopenia, and diffuse arterial thromboses, with good response to mepolizumab. *Clin Advan Hematol Oncol.* 2013;11:317-319.
2. Vandenberghe P, Wlodarska I, Michaux L, et al. Clinical and molecular features of FIP1L1-PDFGRA (+) chronic eosinophilic leukemias. *Leukemia.* 2004;18:734-742.
3. Rohrbach MS, Wheatley CL, Slifman NR, et al. Activation of platelets by eosinophil granule proteins. *J Exp Med.* 1990;172:1271-1274.
4. Oppliger R, Gay-Crosier F, Dayer E, et al. Digital necrosis in a patient with hypereosinophilic syndrome in the absence of cutaneous eosinophilic vasculitis. *Br J Dermatol*. 2001;144:1087-1090.
5. Swerdlow SH, Campo E, Harris NL, et al. *World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon: IARC Press; 2008:51-53, 67-74.
6. Cools J, DeAngelo DJ, Gotlib J, et al. A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. *N Engl J Med*. 2003;348:1201-1214.
7. Roche-Lestienne C, Lepers S, Soenen-Cornu V, et al. Molecular characterization of the idiopathic hypereosinophilic syndrome (HES) in 35 French patients with normal conventional cytogenetics. *Leukemia*. 2005;19:792-798.
8. Klion AD, Noel P, Akin C, et al. Elevated serum tryptase levels identify a subset of patients with a myeloproliferative variant of idiopathic hypereosinophilic syndrome associated with tissue fibrosis, poor prognosis, and imatinib responsiveness. *Blood*. 2003;101:4660-4666.
9. Roufosse F, Cogan E, Goldman M. Lymphocytic variants hypereosinophilic syndromes. *Immunol Allergy Clin North Am*. 2007;27:389-413.
10. Roufosse F, Cogan E, Goldman M. Recent advances in pathogenesis and management of hypereosinophilic syndromes. *Allergy.* 2004;59:673-689.
11. Rothenberg ME, Gleich G, Roufosse F, et al. Steroid-sparing effects of anti-IL-5 monoclonal antibody (mepolizumab) therapy in patients with HES: a multicenter, randomized, double-blind, placebo-controlled trial. *Blood.* 200;108:373.
12. Pitini V, Teti D, Arrigo C, et al. Alemtuzumab therapy for refractory idiopathic hypereosinophilic syndrome with abnormal T cells: a case report. *Br J Haematol*. 2004;127:477.