

Case study

Hypereosinophilic syndrome: Case presentation and update

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Persistent peripheral blood eosinophilia can be associated with a variety of diseases, ranging from parasitic infection to gastrointestinal disease to vasculitis to the hypereosinophilic syndrome (HES). Mucosal ulcerations are a variant presentation of the HES that appear to be markers for a mutation that characterizes a subgroup of patients with HES responsive to treatment with imatinib mesylate. We present a patient with peripheral blood eosinophilia and severe recurrent mucosal ulcers and discuss his presentation in the context of new information about the evaluation, disease progression, and treatment of HES. (*J Allergy Clin Immunol* 2004;113:50-8.)

Key words: Eosinophil, hypereosinophilic syndrome, HES, skin lesions, mucosal ulcers, imatinib mesylate, *FIP1L1PDGFRA* gene

CASE PRESENTATION

A 26-year-old white man was well until April 1979, when he developed recurrent blistering lesions on the glans and shaft of his penis. Later that year, in September, he consulted an otorhinolaryngologist and a dermatologist for a painful throat, oral ulcerations, and scalp scaling. His leukocyte count was 20,000/mm³, with 30% eosinophils (calculated eosinophil count of $6 \times 10^9/L$). He was treated with prednisone, erythromycin, and chlortetracycline without improvement.

In March 1980, he was reevaluated with persistent blistering of his lips and penis, along with the development of folliculitis-like lesions on his lower extremities and subungual hyperkeratosis of his thumb nails. He had a leukocyte count of 18,000/mm³ with 40% eosinophils (calculated eosinophil count of $7.2 \times 10^9/L$). Laboratory studies, summarized below, did not reveal a cause for his clinical presentation. A repeat leukocyte count and differential showed 12,500/mm³ white blood cells, with 52% eosinophils (calculated eosinophil count of $6.5 \times 10^9/L$). He was not treated after this evaluation, and his symptoms gradually improved, save for the genital ulcerations.

In May 1981, he sought consultation with an infectious disease specialist, and another series of tests (summarized below) were performed. Again, no specific treat-

Abbreviations used

HES: Hypereosinophilic syndrome

MBP: Major basic protein

ment was advised. In July 1981, he had severe leg and buttock pain, and an arteriogram was performed. This study (Fig 1) revealed an occluded distal aorta with prominent collateral circulation. Treatment with warfarin sodium, prednisone, and cyclophosphamide was commenced. He did well on this treatment from July 1981 through September 1983.

In September 1983, anemia and marked macrocytosis developed, resulting in discontinuation of cyclophosphamide. Prednisone was also tapered and discontinued. In October, colchicine was started for the diagnosis of Behçet's syndrome. He showed an initial favorable response with clearing of his lesions. However, in February 1984, his skin lesions recurred along with fever. His leukocyte count was 12,300/mm³, with 52% eosinophils (calculated eosinophil count of $6.4 \times 10^9/L$). He was hospitalized and treated with intravenous antibiotics, indomethacin, hydroxyzine hydrochloride, cyproheptadine hydrochloride, and prednisone, with topical care to mucosal ulcers of aluminum sulfate and calcium acetate (Burrow's) solution and Kenalog (triamcinolone acetonide) in Orabase (Bristol-Myers Squibb, New York, NY). His lesions resolved.

Two months later, in April 1984, skin and mucosal lesions, including conjunctival lesions, redeveloped, and fever recurred. His spleen was palpable, and his leukocyte count was 69,900/mm³, with 49% eosinophils (calculated eosinophil count of $34.25 \times 10^9/L$). Examination revealed marked conjunctival erythema with purulent secretions, adherent white fibrinous exudate overlying oral ulcerations, purulent secretion around his nares, and yellow crusts overlying lip erosions (Fig 2, A). His penis showed bloody crusts and purulent secretions overlying ulcers (Fig 2, B). Numerous hemorrhagic perifollicular crusts, ulcers, and plaques were present on his extremities (Fig 2, C). His toenails showed subungual hyperkeratosis and onycholysis with periungual erythema (Fig 2, D). Splenomegaly was present on abdominal examination, and a mitral regurgitant murmur was identified on auscultation. No lower extremity peripheral pulses were present, which is consistent with distal aortic thrombosis. His leukocyte count was 53,200/mm³, with 32% eosinophils (calculated eosinophil count of $17 \times 10^9/L$). Other laboratory evaluations are summarized below. Sys-

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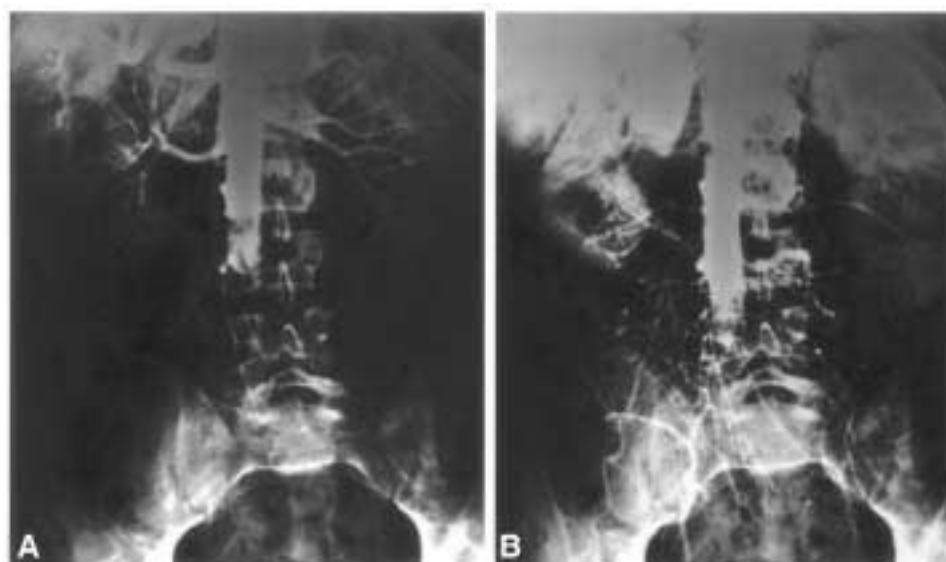


FIG 1. Image of distal aorta thrombotic occlusion in the patient: **A**, arteriogram showing occlusion of the distal aorta at the iliac bifurcation; **B**, later arteriography views showing prominent collateral vessels to lower extremities.



FIG 2. Skin lesions typical of the mucosal ulceration variant of HES: **A**, lower face of patient, with prominent crusting overlying erosions in perioral distribution, on cheeks, and with eyelid swelling; **B**, hemorrhagic crusting of erosions on glans penis, with lesions on fingers also present; **C**, hemorrhagic follicular crusts, with ulcers and plaques on arms (similar lesions on legs); **D**, toenails showing subungual hyperkeratosis and onycholysis with periungual erythema.

temic treatments included allopurinol, hydroxyurea, prednisone, and warfarin sodium. He also received 2 units of packed red blood cells for anemia and underwent therapeutic leukopheresis to decrease the number of cir-

culating eosinophils. Topical treatments included Kenalog in Orabase, zinc oxide ointment, wet dressings, viscous lidocaine, gentian violet, and carbol-fuchsin topical solution (Castellani's paint). His lesions improved sub-

TABLE I. Differential diagnosis of orogenital ulcers

Behçet's syndrome*
Recurrent aphthous stomatitis
Mucous membrane pemphigoid
Pemphigus
Erythema multiforme
Stevens Johnson syndrome
Lichen planus
Lupus erythematosus
Herpes simplex virus
Candidiasis
Crohn disease*
Ulcerative colitis*
Reiter syndrome*
Syphilis
Gonococcal infection
HIV
Strachan syndrome†

*Might be associated with thromboses.

†Orogenital ulcerations, sensory neuropathy, and amblyopia.

stantially, and his leukocyte count decreased to $5100/\text{mm}^3$, with 30% eosinophils (calculated eosinophil count of $1.53 \times 10^9/\text{L}$). Recommendations for ongoing therapy included prednisone, hydroxyurea, allopurinol, warfarin sodium, folic acid, dipyridamole, docusate sodium, and topical glucocorticoids.

In December 1984, a splenectomy was performed for hypersplenism. Over the next year, recurrent lesions developed, and mucosal ulcerations were particularly debilitating because of pain. In late December 1985, the patient experienced massive intracerebral bleeding and died.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses in this case were causes of orogenital ulcers (Table I), including those that develop in association with thromboses, and skin diseases with peripheral blood eosinophilia (Table II). Behçet's syndrome was a strong diagnostic consideration because many of the features that this patient had occur in that disease; however, peripheral blood eosinophil counts are not typically increased in patients with Behçet's syndrome, particularly to the degree found in this patient.

LABORATORY AND OTHER TESTING-PROCEDURES

This patient had persistent and, when untreated, progressive eosinophilia. Table III chronologically recaps his eosinophil counts. Other evaluative studies are summarized as follows.

- March 1980. Normal or negative laboratory study results: chemistry panel, leukocyte alkaline phosphatase, Venereal Diseases Research Laboratory test for syphilis, total hemolytic complement, C3, C4, antinuclear antibody, rheumatoid factor, karyotype, and Philadelphia chromosome. Procedure results: normal

TABLE II. Differential diagnosis of cutaneous diseases with peripheral blood eosinophilia*

Atopic dermatitis
Parasitic diseases
Immunobullous diseases
Drug reactions
Hypereosinophilic syndrome
Eosinophilia myalgia syndrome
Toxic oil syndrome
Eosinophilic fasciitis
Prurigo nodularis
Episodic angioedema associated with eosinophilia (EAE)
Nodules, eosinophilia, rheumatism, dermatitis, swelling (NERDS)
Urticaria and angioedema
Urticaria pigmentosa (mastocytosis)
Cutaneous T-cell lymphoma
Eosinophilic panniculitis
Reactions to arthropod bites and stings
Kimura disease and angiolymphoid hyperplasia with eosinophilia
Granuloma faciale
Wells syndrome (eosinophilic cellulitis)
Eosinophilic folliculitis
Eosinophilic pustulosis (Ofugi disease and erythema toxicum neonatorum)
Eosinophilic ulcer of the tongue

*Adapted from Leiferman KM, Peters MS, Gleich GJ. Eosinophils in cutaneous diseases. In: Freedberg IM, Eisen AZ, Wolff K, Austen KF, Katz SI, Goldsmith LA, editors. Fitzpatrick's dermatology in general medicine. 6th ed. New York: McGraw-Hill; 2003. p. 959-66.

TABLE III. Eosinophil counts ($\times 10^9/\text{L}$)

April 1979	March 1980	February 1984	April 1984	May 1984
6	7.2	6.4	34.25	1.53
	6.5		17	

2-dimensional echocardiography, bone marrow examination revealing hyperplastic marrow with eosinophilia and increased polymorphonuclear leukocytes and fibrosis, and biopsy of an oral lesion showing acute and chronic nonspecific inflammation with pseudoepitheliomatous hyperplasia.

- May 1981. Normal polymorphonuclear leukocyte function test results (chemiluminescence and chemotactic assays), negative herpes simplex virus serology results, and normal total IgE level but increased specific IgE (RAST) to various grass pollens, dust, ragweed, and foods.
- July 1981. Distal occlusion of aorta on arteriography (Fig 1).
- April 1984. Normal or negative laboratory study results: chemistry panel, urinalysis, hepatitis B surface antigen serology, glucose 6-phosphate dehydrogenase levels, blood cultures, increased eosinophil major basic protein (MBP) levels of 5381 and 8390 ng/mL 3 days apart (normal reference, <680 ng/mL). Procedure results: normal 2-dimensional echocardiography and bone marrow biopsy showing hypercellular marrow without

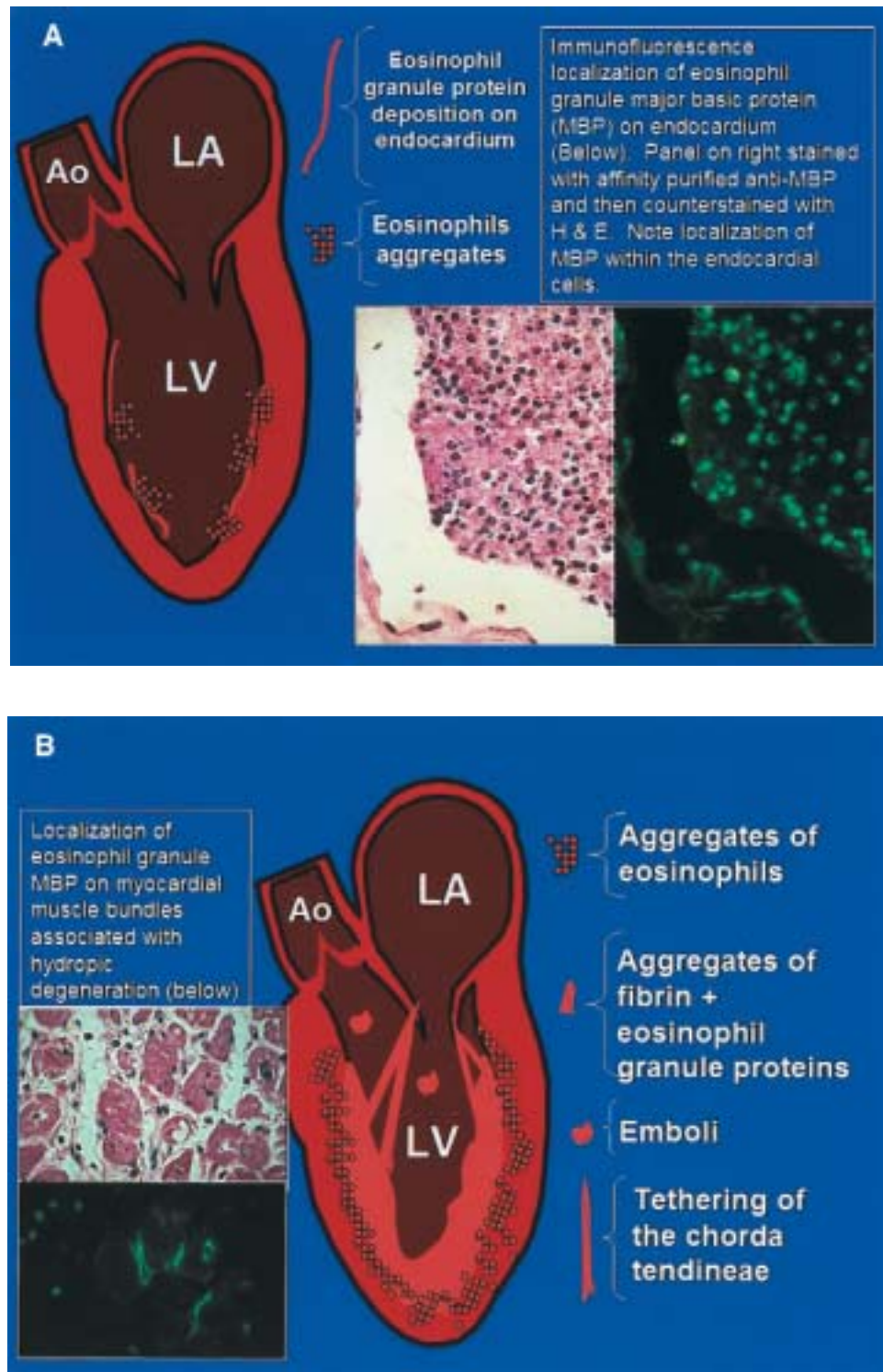


FIG 3. The phases of eosinophilic endomyocardial disease. **A**, The initial phase of disease in which eosinophils become adherent to endocardium and release granule proteins on the endothelial cells. The *insert* shows eosinophil granule MBP staining, which is present beneath the endocardial surface and apparently within the cytoplasm of the endocardial cells, as well as within eosinophils. **B**, The thrombotic phase of the disease with fibrin and eosinophil granule protein deposition encroaching on the ventricular cavity, tethering of the chorda tendinae, and release of emboli. The *insert* shows MBP deposition on myocardial bundles in association with hydropic change as noted on H&E counterstain in upper panel of insert. (Fig continued on following page.)

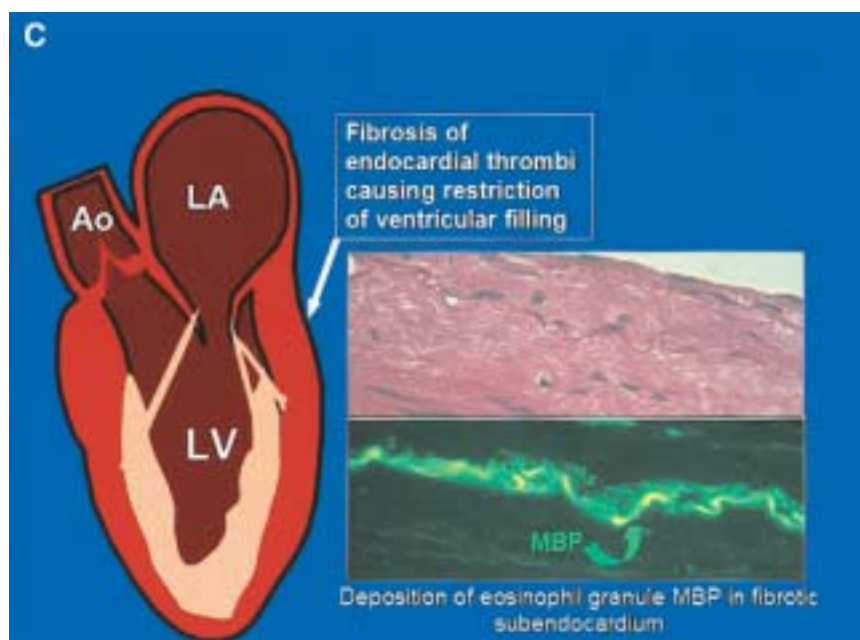


FIG 3. C. The fibrotic phase, showing dense fibrous tissue in the subendocardium. The *insert* shows MBP in this area in the absence of recognizable eosinophil infiltration; fibrosis is observed in H&E counterstain in upper panel of insert.

myelofibrosis, foreign cells, or granulomata with slightly decreased erythropoiesis and increased granulopoiesis, including approximately 60% eosinophils.

FINAL DIAGNOSIS WITH TREATMENT-MANAGEMENT PLANS

The patient was finally given a diagnosis of the mucosal ulceration variant of the hypereosinophilic syndrome (HES).¹ At the time he presented for care, the main treatments available were prednisone and hydroxyurea. These treatments apparently helped control his eosinophilia for a time. The management of his case was complicated by major thromboses requiring anticoagulation. The arteriogram of the patient's thrombosed distal aorta (Fig 1) is dramatic evidence of this phenomenon. In addition, he had a heart murmur of mitral regurgitation. Although this patient's echocardiograms did not reveal abnormalities, formation of thrombi in the heart and embolization to a distant site is common in HES.

Considerable information supports an important role for eosinophils and their products in the pathophysiology of eosinophilic endomyocardial disease.²⁻⁴ Initially, endomyocardial biopsy specimens from patients with HES show focal aggregates of eosinophils along the endocardial surface, with extracellular deposition of eosinophil granule MBP. MBP is present on the surface of the endocardium, beneath endocardial cells, and within the cytoplasm, as shown in Fig 3, A.⁵ These findings suggest that eosinophils adhere to the endocardium, although the mechanism of this localization is not known. Subsequently, the eosinophil releases its granule proteins either

by means of regulated or piecemeal degranulation⁶ or by means of frank cytolysis,⁷ and granule proteins are deposited on the surrounding tissues. The intensity of the MBP immunofluorescence in the endocardial cells is striking (Fig 3, A) and is in keeping with a concentration of approximately 5×10^{-5} mol/L.⁸ On the basis of the biologic properties associated with MBP at such concentrations, namely its ability to activate cells⁹⁻¹² and cause cell damage,¹³ these MBP concentrations likely adversely alter the endocardial cells,⁹⁻¹² although the specific effects of MBP on endothelial cells have not been studied. The eosinophil peroxidase also binds to the endocardium, and it potently mediates damage in a Br⁻-specific and H₂O₂-specific manner, as expected from the known preference of the peroxidase for this anion.¹⁴ Moreover, exposure of isolated rat hearts to eosinophil peroxidase in the presence of Br⁻ and H₂O₂ caused acute heart failure, suggesting that eosinophil peroxidase bound to endocardium could damage the heart during the course of the HES.¹⁴

As the pathologic process continues, aggregates of fibrin and eosinophil granule proteins are deposited on the endocardial surface and form a thrombus. Intact eosinophils and, more impressively, eosinophil granule proteins are present in the adherent thrombus.¹⁵ Fig 3, B, schematically shows progression of damage to the endocardium and myocardium, the deformation of chordae tendinae, and the deposition of thrombus onto the surface of the endocardium, with gradual extension of this process culminating in reduction of the volume of the ventricular cavity. MBP is strikingly deposited throughout the thrombus, mainly outside of eosinophils.¹⁵ The role of eosinophil granule proteins in the formation of the

thrombus is not definitely established, although MBP and eosinophil peroxidase are potent stimuli of platelet activation and aggregation¹⁶ and are able to alter the clotting process by interfering with endothelial cell surface thrombomodulin.⁵ Thus their presence might explain, in part, the continuing thrombus formation. Moreover, MBP and eosinophil peroxidase are able to alter myocardial cell functioning; peroxidase deposition causes acute heart failure,¹⁴ and MBP causes hydropic degeneration of myocardial cells.¹⁵ Fig 3, B, shows the association between MBP deposition on myocardial cells and hydropic degeneration of these cells, strongly supporting the conclusion that the eosinophil, through its toxic granule proteins, is causing damage to the myocardium. Furthermore, MBP and the eosinophil cationic protein are able to activate cardiac mast cells,^{17,18} and mast cell products could deleteriously affect cardiac function. With encroachment of the thrombus on the ventricle, restriction of ventricular filling, and tethering of the chordae tendinae, patients with HES commonly present with the murmur of mitral insufficiency, and echocardiography typically reveals thrombus deposited in the ventricle and on the valve. During this phase, pieces of thrombi might dislodge as emboli and cause tissue damage throughout the body, especially in peripheral limb vessels and in the central nervous system. The events leading to eosinophilic endomyocardial disease might also occur in large and small vessels in the HES and other eosinophil-associated syndromes.¹⁹ Either emboli or large-vessel eosinophilic endothelial disease were likely causes of the aortic occlusion in the patient presented here.

Later in the pathogenic process, the mural thrombus becomes fibrotic, with restriction of filling of the left ventricle and continued deformation of the mitral valve. At this late fibrotic stage, extracellular MBP can still be found in the subendocardial fibrous tissue (Fig 3, C),¹⁵ suggesting that eosinophils continue to play a role in the pathogenic process. Notably, eosinophils are strikingly associated with various fibrotic diseases throughout the body,²⁰⁻²² and therefore the finding of eosinophil degranulation with fibrosis, as shown in Fig 3, C, suggests a role for the eosinophil in the evolution of the endocardial disease, possibly through production of TGF- β .²³ Remarkably, in this late stage of the disease, prominent MBP staining is present, but few intact eosinophils in the subendocardial fibrous tissue are discernible.

The cardiac findings described above are classically associated with HES. However, it appears that any disease that results in prolonged and marked eosinophilia can be associated with endomyocardial disease. For example, endomyocardial disease has occurred during the course of helminth infections²⁴ and also in various malignancies associated with marked eosinophilia.^{5,25} Thus patients with marked eosinophilia are at risk for the development of cardiac disease, and it is important that clinicians be alert to this possibility.

An important question regards what level of peripheral blood eosinophilia should prompt therapy to reduce the number of eosinophils (and to guard against the like-

lihood of endomyocardial disease). The answer to this question is not clear, but as a general rule, eosinophil counts of greater than $2 \times 10^9/L$ for prolonged periods are concerning. Patients might tolerate higher peripheral blood eosinophil counts, between $2 \times 10^9/L$ and $10 \times 10^9/L$, over many months without the development of cardiac disease. However, certain patients have presented with cardiac disease at much lower peripheral blood eosinophil levels. It is important to monitor patients with increased eosinophil counts every few months by means of echocardiography for the development of eosinophil endomyocardial disease. It is also important to keep in mind the syndrome of acute necrotizing eosinophilic myocarditis.²⁶ This syndrome occurs with viral infections and results in a striking infiltration of eosinophils into the myocardium, with dramatic deposition of eosinophil granule proteins in association with myocardial muscle cell necrosis. The syndrome is frequently fatal within days and should be distinguished from the chronic and slowly progressive eosinophilic endomyocardial disease described above.

Anticoagulation has been indicated in the treatment of thrombotic complications of HES. Ironically, the patient presented here died of an intracerebral hemorrhage, a risk with warfarin therapy. Shortly after the patient died, IFN- α was found to be efficacious²⁷ in the treatment of HES, including the mucosal ulceration variant. Before IFN- α therapy, patients with this HES variant had a bleak prognosis, as attested to by the present case and other cases.²⁸ Very recently, patients with mucosal ulcerations and HES have shown excellent responses to imatinib mesylate (vide infra).

SUMMARY

The term *hypereosinophilic syndrome* was introduced by Hardy and Anderson²⁹ in 1968 to describe patients with marked eosinophilia. They reported 3 patients, all men between the ages of 34 and 47 years, who had cardiopulmonary symptoms, fever, sweats, weight loss, and marked eosinophilia. Two patients died, and at autopsy, their hearts were enlarged and showed mural thrombi. Hardy and Anderson postulated that these patients represented one extreme of a syndrome that varied in severity from serious and often fatal to benign. Using the terminology of that time, they suggested that HES spanned a spectrum from disseminated eosinophilic collagen vascular disease or eosinophilic leukemia to Loeffler endocarditis and to the pulmonary infiltrates with eosinophilia syndrome. They further postulated that HES was more likely the result of a hypersensitivity cause than a malignant proliferation of eosinophils. This speculation was supported by the observation that the hematologic picture in patients with HES most commonly shows a striking increase of mature eosinophils. The failure of patients with HES to show immaturity in the eosinophil lineage, such as one observes in chronic myeloid leukemia, prompted this speculation and discouraged belief that HES was due to a malignant proliferation of eosinophils.

TABLE IV. HES: Clinical pearls

Diagnostic criteria		
Eosinophil counts $>1.5 \times 10^9/L$ for ≥ 6 months or <6 months with evidence of organ damage	Lack of evidence for parasitic, allergic, or other recognized causes of eosinophilia	Symptoms and signs of organ system involvement
Subtypes and treatment considerations		
Myeloproliferative	Lymphoproliferative	Unclassified
<i>FIP1L1PDGFRA</i> gene, other as yet unfound mutations possible	T-cell clone producing T_H2 cytokines	Necrotizing eosinophilic vasculitis
"Classical HES," male subjects with endomyocardial disease	T-cell clones have occurred in rare cases of EAE	EAE
Mucosal ulcers	T-cell clones have occurred in rare cases of NERDS	NERDS
High serum tryptase level, tissue fibrosis, increased vitamin B12 levels, splenomegaly, and bone marrow biopsy specimens with increased numbers of $CD25^+$, atypical, spindle-shaped mast cells		Variety of other diseases, including eosinophilic gastroenteritis (reviewed in this issue by Rothenberg ⁴⁷)
Most patients responsive to imatinib mesylate therapy with dramatic improvement; also might respond to IFN- α or anti-IL-5	Might be responsive to IFN- α or anti-IL-5; prednisone, hydroxyurea, or both	Control of eosinophilia is important to prevent damaging sequelae from eosinophils

EAE, Episodic angioedema with eosinophilia; NERDS, nodules, eosinophilia, rheumatism, dermatitis, and swelling syndrome.

Since the designation of HES as a disease category, it has attracted considerable attention, with numerous publications devoted to this difficult problem. Many treatments are similar to those used for patients with chronic myeloid leukemia, and at various times, prednisone, hydroxyurea, IFN- α , and combinations of these have been advocated. Additionally, Hardy and Anderson²⁹ did not identify criteria for the diagnosis of HES, and it remained for Chusid and associates³⁰ to formulate such criteria (Table IV). These include the following: (1) persistent eosinophilia of at least $1.5 \times 10^9/L$ for a minimum of 6 months; (2) lack of evidence for parasitic, allergic, or other recognized causes of eosinophilia; and (3) symptoms and signs of organ system involvement. After bone marrow and the heart, the skin is one of the most frequently involved organs in the HES. Skin lesions occur in more than half of the patients with HES.^{28,31} A variety of skin lesions have been described, the most common of which are erythematous pruritic papules and nodules and angioedematous and urticarial lesions; the latter is associated generally with a better prognosis. Other types of skin lesions in HES are blistering lesions and vasculitic lesions that likely result from dermal microthrombi. Mucosal ulcerations, when they occur in HES, can cause significant morbidity, are difficult to treat, and are poorly responsive to therapy, as evidenced in the patient presented here.

Over the past roughly 2 decades, investigators have recognized considerable heterogeneity among patients with HES. For example, in the 1980s, the syndrome of episodic angioedema associated with eosinophilia was recognized and differentiated from typical HES³²; some of the patients with angioedema and eosinophilia who were noted to have a good prognosis might have had this syndrome. Later, the nodules, eosinophilia, rheumatism, dermatitis, and swelling syndrome was also recog-

nized.³³ A further HES subdivision consisted of patients with recurrent mucosal ulcers, a manifestation portending a grave prognosis.¹ More recently, T-cell clones producing the T_H2 cytokine IL-5 have been found in patients satisfying the diagnostic criteria for HES.³⁴⁻³⁶ Perhaps the most striking advance has come about after treatment of patients with HES with the Bcr-Abl kinase inhibitor imatinib mesylate. Imatinib was introduced for chronic myeloid leukemia and has had a remarkable effect in that disease.^{37,38} Treatment of many patients with HES with imatinib causes a dramatic reduction of peripheral blood and bone marrow eosinophils, suggesting that certain patients with HES express a novel kinase sensitive to imatinib.³⁹ Further investigation has revealed the existence of an 800-kb deletion in chromosome 4, bringing together an upstream DNA sequence homologous to a yeast protein, termed FIP1, (and referred to as like FIP1 or FIP1-L1) and the gene for the cytoplasmic domain of the PDGFR α receptor. This fusion gene is transcribed and translated, yielding a novel kinase referred to as FIP1L1-PDGFR α ^{40,41}; FIP1L1-PDGFR α is exquisitely sensitive to imatinib in vitro in parallel with the remarkable sensitivity of patients with HES to this drug.³⁹ The patients responsive to imatinib are those most characteristic of classic HES, namely male patients between the ages of 20 and 50 years who present clinically with marked peripheral blood eosinophilia. These patients go on to have eosinophilic endomyocardial disease, and they strikingly resemble the patients described by Hardy and Anderson.²⁹ Development of eosinophilic endomyocardial disease is classically associated with HES, and considerable evidence links the development of eosinophilic endomyocardial disease to deposition of eosinophil granule proteins onto the endocardium, as described above.^{5,14-18} However, as noted above, any disease with

marked eosinophilia can be associated with endomyocardial disease. Therefore clinicians caring for patients with prolonged eosinophilia must be alert to the possibility of cardiac disease development, regardless of the underlying cause of the eosinophilia.

Three publications have further characterized HES subsets responsive to imatinib.⁴²⁻⁴⁴ The first 2 described patients with HES with increased serum tryptase levels (>11.5 ng/mL) and with tissue fibrosis, poor prognosis, and imatinib responsiveness,⁴² and a later report showed reversal of myelofibrosis.⁴³ These patients also had increased vitamin B12 levels and splenomegaly, and bone marrow biopsy specimens showed increased numbers of CD25⁺, atypical, spindle-shaped mast cells. Patients with this HES subset can be distinguished from patients with systemic mastocytosis and eosinophilia on the basis of their clinical manifestations, the absence of mast cell aggregates, and the presence of the *FIP1L1PDGFRA* fusion gene. All 6 of these patients treated with imatinib showed a clinical and hematologic response, including patients with mucosal ulcerations and HES,¹ as was the case with our presented patient. The third publication reports on patients with systemic mastocytosis, some of whom had eosinophilia.⁴⁴ Three of 5 patients with systemic mast cell disease had the *FIP1L1PDGFRA* gene, and the expression of the *FIP1L1PDGFRA* gene was also documented in enriched eosinophils, neutrophils, and mononuclear cells. All of the patients with the *FIP1L1PDGFRA* gene achieved a complete response to imatinib, whereas patients with the c-kit D816V mutation did not. Whether the patients in the study by Pardanani and associates⁴⁴ differ from those described in the study by Klion and colleagues⁴² is not clear at this time; the clinical features of the patients in the study by Pardanani and associates⁴⁴ were not described in detail, and the morphology of the mast cells was also not described. The observations in that study likely explain the concomitant increases of eosinophils and neutrophils in some patients with HES. The patient reported herein had 2 bone marrow examinations with increased granulopoiesis, including both eosinophil and polymorphonuclear leukocytes.

The patient whose case is presented had many features indicating that he had the HES subtype with the *FIP1L1PDGFRA* gene.^{42,43} Unfortunately, the treatments available at that time were toxic and not very specific for his disease. Less than 2 decades later, a treatment useful for many patients with HES has been found, and on the basis of the response of patients to this treatment, the genetic mutation underlying the disease has been elucidated. Moreover, imatinib mesylate is relatively safe, and although the optimum treatment schedule is yet to be determined, many patients respond to remarkably low doses. Although it is pharmacogenetically best suited to treat patients with HES with the *FIP1L1PDGFRA* gene, some patients with HES evidently without the gene have responded to imatinib therapy. For those patients who do not respond, have other types of HES, or both, new drugs are on the horizon. For example, patients with HES,

including the mucosal ulceration variant, might respond to therapy with anti-IL-5, as reviewed in this issue by Garrett et al⁴⁵; other therapeutic considerations are reviewed in this issue of the Journal by Bochner.⁴⁶ Although HES is a relatively rare disease, many other diseases, including common ones, such as asthma and atopic dermatitis, show evidence of eosinophil involvement. The significant advancements since this lamentable case encourage hope for new and better treatments of eosinophil-associated diseases. Finally, although the role of the eosinophil and its products in asthma still elicit controversy,⁴⁶ the critical participation of the eosinophil in the pathophysiology of HES and eosinophilic endomyocardial disease is strongly supported by the information presented above. Therapies that diminish eosinophils have been effective to the degree that they reduce the numbers of eosinophils and their products in blood and tissues.

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