

Cardiovascular Manifestations of Hypereosinophilic Syndromes

Princess U. Ogbogu, MD^{a,*}, Douglas R. Rosing, MD^b,
McDonald K. Horne III, MD^c

^a*Allergy and Immunology, National Institute of Allergy and Infectious Diseases,
National Institutes of Health, Room B1-05, Bldg. 4, Bethesda, MD 20892, USA*

^b*Cardiology Branch, National Heart, Lung, and Blood Institute, National Institutes
of Health, Room 5-3330, CRC, Bldg. 10, Bethesda, MD 20892, USA*

^c*Hematology Service, Department of Laboratory Medicine, W.G. Magnuson
Clinical Center, Room 2C306, Bldg. 10, National Institutes of Health,
Bethesda, MD 20892, USA*

The hypereosinophilic syndromes (HES) are characterized by persistent marked eosinophilia (>1500 eosinophils/mm³), the absence of a primary cause of eosinophilia (such as parasitic or allergic disease), and evidence of eosinophil-mediated end organ damage [1]. Cardiovascular complications of HES are a major source of morbidity and mortality in these disorders. Whereas earlier studies reported that up to 84% of patients who have HES have signs and symptoms of cardiac disease, more recent reports suggest that the frequency is closer to 40% to 50% [1–3].

The most characteristic cardiovascular abnormality in HES is endomyocardial fibrosis, initially described in 1936 by Loeffler [4], who called it “fibroplastic parietal endocarditis with blood eosinophilia.” Patients who have HES also may develop thrombosis, particularly in the cardiac ventricles, but also occasionally in deep veins. Because of the rarity of these disorders, specific guidelines for the management of the cardiac and thrombotic complications of HES are lacking. This article reviews the diagnosis and management of the cardiovascular manifestations of HES.

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* Corresponding author.

E-mail address: ogbogup@niaid.nih.gov (P.U. Ogbogu).

Differential diagnosis

The differential diagnosis of cardiac disease with peripheral eosinophilia includes HES, Churg-Strauss syndrome (CSS), early giant cell myocarditis, hypersensitivity reactions (usually medication induced), parasitic infection [5], Loeffler's or tropical endomyocardial fibrosis (TEF), and malignancy [6]. Although there is considerable overlap in the cardiac manifestations of HES with the other entities listed above, some distinguishing features do exist. For example, TEF and HES are almost identical in presentation, except that TEF occurs in long-term residents of tropical or subtropical regions and is likely, at least in some cases, secondary to the eosinophilia of helminth infection [7]. Therefore, an appropriate travel history in a patient who has endomyocardial fibrosis and peripheral eosinophilia should prompt an evaluation for helminth infection. Similarly, cardiovascular involvement in CSS includes many of the common manifestations of HES, such as eosinophilic endomyocarditis, congestive heart failure, and valvular disease. Other manifestations, such as coronary arteritis, sometimes resulting in myocardial infarction or sudden death, and pericarditis are highly suggestive of CSS [8–10].

Cardiac pathology

Traditionally, the cardiac pathology of HES has been divided into three stages: acute necrosis, thrombosis, and fibrosis [11,12]. Previous studies indicate that the acute necrotic stage is observed when the duration of illness is short (mean duration 5.5 weeks), whereas the thrombotic stage occurs when the mean duration of eosinophilia is 10 months. The third, late fibrotic stage is described after approximately 24.5 months of disease duration [12].

The acute necrotic stage is characterized by eosinophilic infiltration of the myocardium associated with myocardial necrosis due to release of toxic cationic proteins from degranulating eosinophils [13,14]. In one series, patients had prominent splinter hemorrhages during the necrotic stage [12]; however, it often is difficult to diagnose cardiac disease at this stage because the patient may not have cardiac symptoms, and electrocardiography and echocardiography often are unremarkable. Endomyocardial biopsy may be required for diagnosis at this stage, although cardiac MRI may be useful in demonstrating preclinical involvement.

The acute myonecrosis is followed by formation of mural thrombi, often involving both ventricles, the ventricular outflow tracts, and the subvalvular regions. This process may lead to atrioventricular valvular incompetence [15]. In patients who have HES, the most obvious stimulus for thrombosis is ventricular wall vascular damage. Disruption of the normally anticoagulant endothelial lining exposes von Willebrand factor, collagen, and tissue factor (TF). von Willebrand factor and collagen bind platelets, and TF binds activated factor VIIa to start the biochemical reactions that generate

a fibrin thrombus [16,17]. In HES, the stimulation of fibrin formation by TF may be especially important because eosinophils contain TF in their specific granules, and they can induce endothelium to express it [18,19]. Secreted eosinophil proteins also may impair the anticoagulant properties of the endothelial membrane by binding to thrombomodulin [20]. There is some evidence that eosinophil granule proteins can activate factor XII and platelets and that mononuclear cells from patients who have HES have enhanced procoagulant activity [21–23]. Therefore, blood hypercoagulability also may contribute to the pathogenesis of thrombosis in HES. In the cardiac chambers, flow at the endomyocardial surface is relatively static, particularly in the ventricular apices, and becomes more static in areas of hypokinesis. Stasis is a major stimulus for thrombosis because it allows activated clotting factors to accumulate to thrombotic concentrations.

Thrombus formed on denuded myocardium is replaced by fibrosis (Fig. 1). Patients who have HES may not be diagnosed with cardiac involvement until this final pathologic stage of their disease, when they present with scarring of the chordae tendinae and endocardium leading to a restrictive or dilated cardiomyopathy and progressive valvular incompetence [24]. The valvular pathology observed most commonly in HES includes dysfunctional, regurgitant atrioventricular valves because of restriction of valve leaflet mobility. Aortic and mitral stenosis have been reported much less commonly [25].

Clinical manifestations of cardiac pathology

Clinical evidence of cardiac involvement in HES includes signs and symptoms of heart failure, intracardiac thrombus, myocardial ischemia, arrhythmias, and rarely, pericarditis [3,26]. In an early review of 65 cases of HES in the English literature, the most common presenting symptom was dyspnea, occurring in 60% of the patients. Seventy-five percent of the 55 patients who could be evaluated had signs and symptoms of congestive heart failure, and 4% had evidence of pericarditis [3]. In the same review of 26 patients who had HES and were followed prospectively at the National Institutes of Health (NIH), 42% had dyspnea, 27% had chest pain, 12% had cough, 8% had palpitations, and 4% had embolic events [3]. Subsequently, these patients were found to have mitral regurgitation (42%), congestive heart failure (38%), aortic regurgitation (4%), and aortic stenosis (4%). Myocardial infarction is a rarely reported complication of HES, but it has been described to occur as the result of an embolic event because of endomyocardial fibrosis and thrombus in the left ventricular outflow tract [27].

Early descriptions of risk factors for cardiac disease in patients who have HES included male gender, HLA-Bw44 positivity, splenomegaly, thrombocytopenia, elevated serum vitamin B12, dysplastic eosinophils (hypogranular or vacuolated), and the presence of abnormal early myeloid precursors

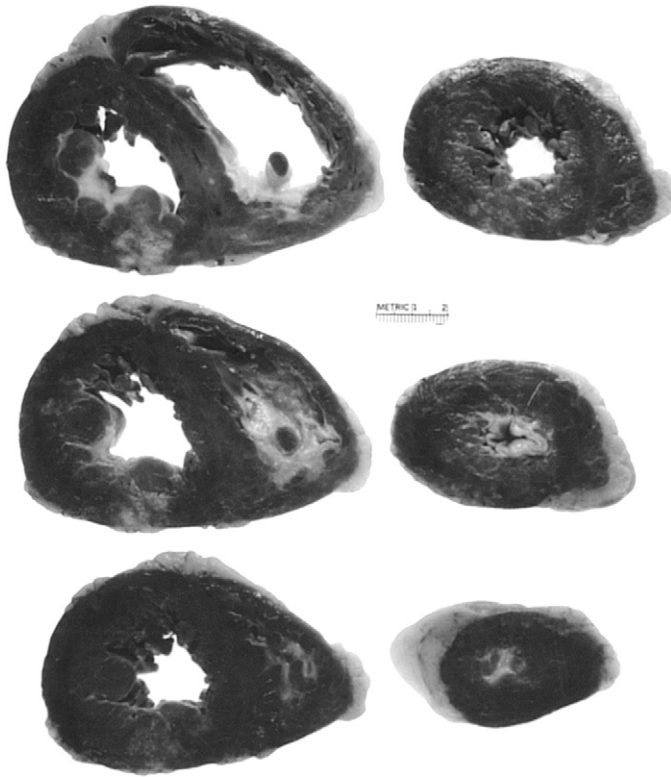


Fig. 1. Fatal endomyocardial fibrosis in a patient who had HES and FP mutation. White areas denote areas of fibrosis. (From Stone RM, Gilliland DG, Klion AD. Platelet-derived growth factor receptor inhibition to treat idiopathic hypereosinophilic syndrome. *Semin Oncol* 2004;31(2 Suppl 6):13; with permission.)

[12]. More recently, it has become apparent that these features are characteristic of a myeloproliferative variant of HES that includes chronic eosinophilic leukemia (CEL) associated with the *FIP1L1-PDGFR* (FP) fusion tyrosine kinase [28].

Diagnosis of hypereosinophilic syndrome–associated heart disease

The most frequently used modalities to evaluate cardiac disease in HES include electrocardiography, echocardiography, cardiac MRI, and endomyocardial biopsy. The most common electrocardiogram findings in HES are nonspecific and include T wave inversions, left atrial enlargement, left ventricular hypertrophy, incomplete right bundle branch block, and left axis deviation [3]. Other reported electrocardiogram abnormalities include ventricular premature complexes, poor R wave progression, nonspecific S-T and T wave abnormalities, and first-degree atrioventricular block [3].

There is a single case report of a patient who had HES presenting with second-degree atrioventricular block [29]. In general, electrocardiography is a screening tool that detects changes related to the underlying cardiac pathology in HES, especially left ventricular hypertrophy, but it does not reveal any abnormalities that are specific for HES.

Echocardiography has long been a useful noninvasive diagnostic tool in the evaluation of cardiac disease in HES. The traditional modality for cardiac evaluation is two-dimensional echocardiography. Recent reports suggest that transthoracic, transesophageal, and contrast echocardiography play complementary roles in the evaluation of HES. Contrast echocardiography allows for delineation of the left ventricular shape and quantitation of left ventricular hypertrophy [30]. The classic echocardiographic findings in HES include endomyocardial thickening, left and right ventricular apical thrombus formation, and posterior mitral leaflet involvement (Fig. 2) [2]. Often, there are progressive features of a restrictive cardiomyopathy with regurgitation of the atrioventricular valves secondary to subvalvular damage [15]. Doppler pulsed tissue and flow velocities and indices of left ventricular compliance should be evaluated and can be used to follow the severity of the restrictive process. In an NIH study of 22 patients who had HES, 68%

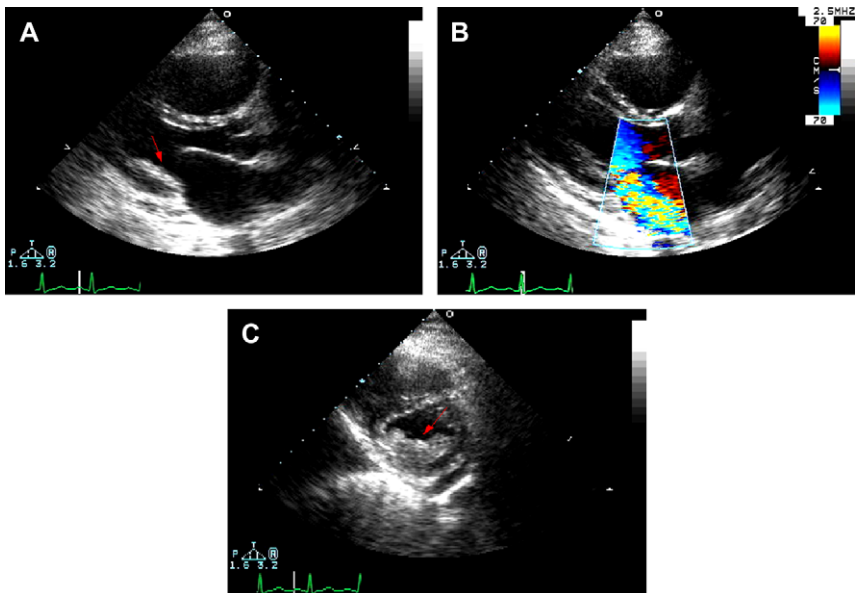


Fig. 2. Echocardiogram of the same patient presented in Fig. 1. (A) In the parasternal long-axis view, an area of increased echo density (arrow) denotes thrombus or fibrosis along the basal posterior wall of the left ventricle that also involves the posterior leaflet of the mitral valve. (B) Color Doppler flow mapping in the same view demonstrates significant mitral regurgitation. (C) In the short-axis view shown during diastole, there is extensive thrombus or fibrosis on the posterior wall (arrow) with compromise of the left ventricular cavity size. (Courtesy of Dr. Vandana Sachdev, Bethesda, MD.)

showed echocardiographic features of left ventricular free wall thickening, 37% showed an increase in left atrial transverse dimension, and 27% showed an increase in right ventricular transverse dimension [3]. Unsuspected pericardial effusions were found by echocardiography in 32% of these patients [3]. In a Mayo Clinic series of 51 patients who had HES, 49% had cardiac disease by echocardiography. This group with echocardiographic evidence of HES also had higher rates of embolization, clinical heart failure, and cardiac surgery [2].

In recent years, cardiac MRI has emerged as a highly useful noninvasive modality for the diagnosis of cardiac involvement in HES. Cardiac MRI is more sensitive to and specific for the detection of ventricular thrombi than is transthoracic or transesophageal echocardiography (Fig. 3) [31]. Delayed-enhancement gadolinium imaging is capable of detecting myocardial fibrosis and inflammation (Fig. 4) [32]. Cardiac MRI uses inversion-recovery prepared T1-weighted gradient-echo sequencing after the intravenous administration of gadolinium chelate to demonstrate nonviable tissue as delayed enhancement [33]. Delayed enhancement resulting from fibrosis is more intense than delayed enhancement due to inflammation [31]. There are several recent case reports describing cardiac MRI as an adjunct diagnostic modality in HES [24,31,33,34]. One report describes the use of cine-MRI to aid in right ventricular endomyocardectomy in a patient who had HES [35].

Despite steadily improving noninvasive methods to aid in the diagnosis of HES, endomyocardial biopsy remains the diagnostic gold standard (Fig. 5). Serial myocardial biopsies are used to provide information on the clinical course of cardiac disease and the response to treatment. The

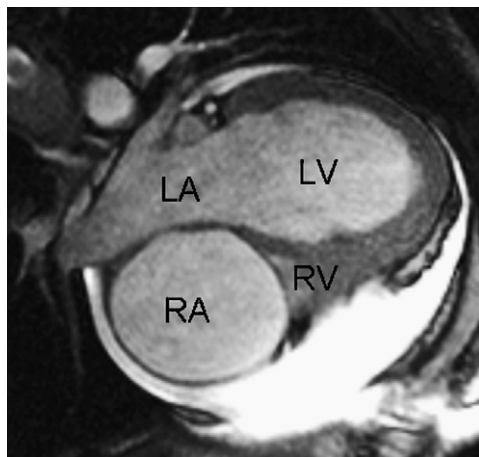


Fig. 3. Cine-MRI in a four-chamber view of the same patient presented in Fig. 1 using a steady-state free precession technique. Note that the right ventricular cavity is nearly obliterated. *Abbreviations:* LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (Courtesy of Drs. Patricia Bandettini and Andrew Arai, Bethesda, MD.)

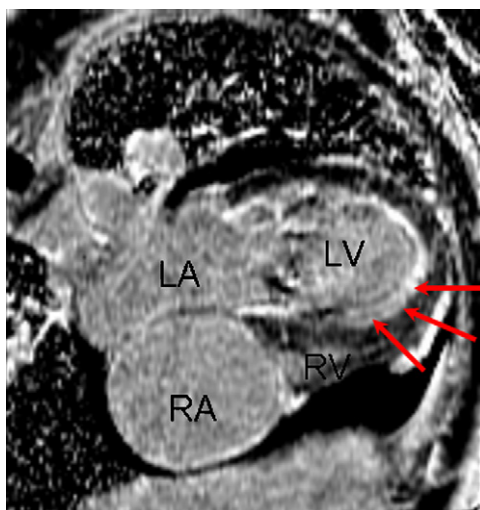


Fig. 4. Delayed hyperenhancement images of the same patient presented in Fig. 1 obtained 20 minutes after administration of gadolinium contrast using an inversion recovery gradient-echo technique validated for imaging myocardial infarction. There is a bright white rim of enhancement lining the left ventricle (arrows), which is consistent with endomyocardial fibrosis. *Abbreviations:* LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (Courtesy of Drs. Patricia Bandettini and Andrew Arai, Bethesda, MA.)

histopathologic features of HES endomyocardial diseases include fibrotic thickening of the endocardium; mural thrombosis; and fibrinoid change, thrombosis, and inflammation of the small intramural coronary vessels. Lastly, infiltration of eosinophils into the myocardium and sometimes endocardium also may be detected [11]. Although endomyocardial biopsy is the gold standard, the high resolution of cardiac MRI permits tissue characterization, which makes this technique a promising, and perhaps, more practical method to follow and potentially diagnose cardiac disease in HES.

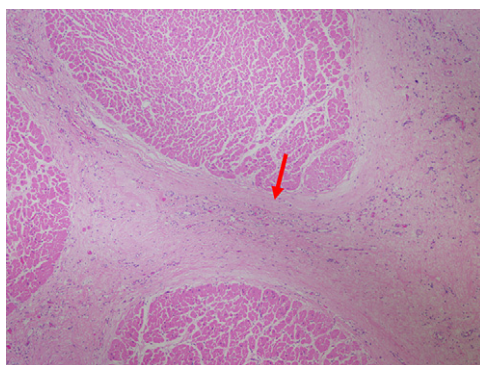


Fig. 5. Histology of fatal endomyocardial fibrosis in the same patient presented in Fig. 1. Arrow denotes areas of intracardiac fibrosis bordered by areas of unaffected myocardium.

Management of hypereosinophilic syndrome heart disease

The initial approach to the cardiac evaluation of a patient who has HES includes a good history and a thorough physical examination looking for evidence of cardiovascular involvement, particularly cardiac decompensation or peripheral thromboembolic events. A baseline electrocardiogram, two-dimensional echocardiogram, and chest radiograph should be obtained. The common findings on electrocardiogram generally are nonspecific and include nonspecific S-T and T wave abnormalities, and, in later stages, evidence of left ventricular hypertrophy. Two-dimensional echocardiography with Doppler flow measurements is essential to evaluate the degree of ventricular hypertrophy, the presence of valvular abnormalities, the presence of mural or apical thrombi, and to estimate ventricular systolic and diastolic function. If initial transthoracic echocardiography is normal, it should be repeated at a minimum of 6-month intervals. If evidence of cardiac disease is found, more frequent echocardiograms may be warranted. The electrocardiogram should be repeated at a similar frequency. If there is evidence of endocardial thickening or difficulty obtaining optimal images, transesophageal echocardiography or cardiac MRI should be performed. If a question of disease involvement or severity still remains, a cardiac biopsy is necessary.

All patients who have evidence of myeloproliferative HES (MHES) or cardiac involvement should be screened by fluorescence in situ hybridization or polymerase chain reaction for the FP mutation, because the tyrosine kinase inhibitor, imatinib, is the treatment of choice for patients with this mutation. Although imatinib therapy is associated with clinical, hematologic, and molecular remission in most patients who have FP-associated CEL, signs and symptoms of congestive heart failure in patients who have endomyocardial fibrosis remain unaffected in most cases [36]. This is likely due to the presence of irreversible structural damage as a result of chronic fibrosis and emphasizes the need for prompt treatment with imatinib in these patients. It is recommended that screening be performed with a baseline serum troponin T level before the initiation of imatinib therapy. Pretreatment with steroids should be initiated before imatinib therapy if the baseline serum troponin T level is elevated or there is evidence of active cardiac disease, because imatinib may be associated with an acute drug-induced cardiomyopathy with resultant clinical decompensation [37–39]. There have been case reports of cardiac toxicity associated with long-term imatinib therapy, although larger clinical databases have not shown similar findings [40,41].

Symptoms of congestive heart failure should be managed with conventional medications, including diuretics, β -adrenergic blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, aldosterone antagonists, and digoxin [42]. Control of concomitant comorbid conditions, such as cardiac dysrhythmias, diabetes mellitus, thyroid dysfunction, anemia, and hypertension should be optimized. Most patients who have clinically significant atrioventricular valvular regurgitation no longer need to

use prophylactic antibiotic treatment before dental and surgical procedures according to the new American Heart Association guidelines; however, if the patient has a prosthetic heart valve, a history of previous infective endocarditis, or certain congenital heart disorders, antibiotic prophylaxis is still recommended [43].

Surgical intervention secondary to progressive valvular dysfunction may become necessary. The experience with valve replacement in patients who have HES is limited because of the rarity of the disease; however, valve replacement and, less frequently, valve repair in patients who have HES have been described [44,45]. Damaged valves can be replaced with mechanical or bioprosthetic valves. Despite anticoagulation, mechanical valve replacement may have a high incidence of thrombosis, whereas bioprosthetic valves may require more frequent replacement because of deterioration. In 1991, Boustany and colleagues [44] reported a collection of eight cases of mitral valve operations for HES. Since then, six other reports have been published [46]. Mitral valve replacement is the most common surgery performed, although one case of mitral valve annuloplasty for HES has been reported [47]. The use of mechanical valves in this patient group incurs a high risk for thrombosis, despite the use of anticoagulation [48]. In the limited number of patients reported with mechanical valve obstructive thrombosis, reoperation was associated with high mortality [45,48]. Obstruction of mechanical valves may occur rapidly and, in some cases, has been reported to develop within days to months of surgery, despite anticoagulant therapy [49]. Repeat surgery often leads to replacement of the mechanical valve with a bioprosthetic valve.

Because of these considerations, the use of bioprosthetic valves has been advocated, despite the frequent young ages of the patients and apprehension about early valve deterioration. The restrictive cardiomyopathy associated with a small left ventricular cavity is an additional concern and favors the use of a low-profile valve [46]. A report of a young boy who had HES requiring several mitral valve operations described recurrent thrombotic events, despite the use of a bioprosthetic valve and documented therapeutic anticoagulation [49]. Because of these concerns, a heterograft bioprosthesis should be used in conjunction with warfarin therapy. It also is highly recommended that the peripheral eosinophilia be controlled before valve replacement or repair. Most case reports of repeat valve thrombosis were before the use of imatinib treatment and may reflect the effects of persistent uncontrolled eosinophilia.

If the restrictive cardiomyopathy progresses or recurrent valve thrombosis occurs, heart transplantation should be considered. The use of orthotopic heart transplant has been described in only three patients who had HES. All patients are reported to be alive (International Society of Heart and Lung Transplantation Registry 2005) [50]. In the most recent case, a 48-year old man who had HES received an orthotopic heart transplant and—despite treatment with tacrolimus and prednisone—required reintroduction of

hydroxyurea treatment 5 weeks after transplant because of uncontrolled eosinophilia. Subsequently, the patient was shown to be positive for the FP mutation and was started on imatinib, which led to resolution of the eosinophilia [50]. After cardiac transplant, graft rejection must be monitored by serial endomyocardial biopsies, which are useful in assessing the degree of eosinophil graft infiltration. As is the case with valve replacement or repair, peripheral eosinophilia should be controlled before heart transplantation is considered.

Thrombotic complications of hypereosinophilic syndrome

Descriptions of thromboembolism in patients who have HES largely have been published in successive literature reviews, each contributing a few more patients [1,3,51–53]. Isolated cases of intra-abdominal, cerebral, and cutaneous thrombosis also have been reported. Some of these had cardioembolic disease involving multiple organs, and occasionally the origin of the thrombi seemed to be multifocal [54–58]. In many cases, a causal link between eosinophilia and the thrombotic event was unclear, although, in a few instances, eosinophilic infiltrates were documented in involved tissues [59–70]. In some, additional predispositions to thrombosis were present, such as immobility, genetic hypercoagulability, or advanced atherosclerosis [71–73].

The best described thromboembolic events and those most clearly related to eosinophilia are the cases of intracardiac thrombus and secondary pulmonary and arterial emboli. In 1975, Chusid and colleagues [1] collected 57 cases of “broadly defined” HES from the English literature and added 14 of their own seen at the NIH. Four of these 14 had arterial emboli (29%); one patient (7%) died of thromboembolic complications. Autopsies performed on 39 of the previously reported patients revealed cardiac mural thrombi in 16 (41%); however, among the 31 patients with a stated cause of death, only 2 (7%) were reported to have died of embolic disease. Fifteen percent of the autopsied cases had “myocardial necrosis associated with thrombi in the smaller coronary vessels,” which presumably contributed to the demise of the 20 of 31 patients who died of myocardial infarction and congestive heart failure. The relationship of the coronary thrombi to the patients’ eosinophilia is unclear. They could have resulted from coincidental atherosclerotic disease or from local eosinophilic infiltrates. The left ventricle more often contained thrombus than the right, and clot tended to be located in the apices of the ventricles, where stasis is more of a factor, rather than in the outflow tracts. Splenic infarcts also were discovered commonly at autopsy. Pulmonary emboli were rare. Microthrombi were found sometimes in cerebral vessels and microemboli in renal vessels.

In 1979, the NIH investigators reviewed 65 cases of HES, including 26 previously unpublished cases of their own. Only one (4%) of the 26 new

cases had had an embolic clinical event [3,51]. At autopsy, this patient did not have intracardiac thrombi, but he had been taking warfarin. One other patient had undergone a postmortem examination, which revealed extensive thrombus in the left ventricle overlying endocardial fibrosis. A third patient developed portal vein thrombosis. Subsequently, 8 out of 50 NIH patients were reported to have had multiple emboli, and they were all in a subgroup of 21 patients who had clinically overt heart disease (38% incidence) [74]. Six of 52 NIH patients had cerebral vascular accidents [52]. Five of these individuals had clinical heart disease secondary to HES.

In 1983, Spry and colleagues [53] in London, reported 15 more patients, 10 of whom had had clinical thrombotic or embolic events (brain, spleen, kidneys, retina), with 3 dying of this complication. At postmortem examination, one of these had widespread arterial and venous thrombi, although no thrombi were found in the cardiac ventricles. The other 2 patients died with endomyocardial necrosis or fibrosis and cerebral infarcts, but apparently no demonstrable intracardiac thrombus.

Therefore, the limited literature suggests that perhaps a quarter of patients who have HES develop thromboembolic complications and that 5% to 10% died of them. There also is the suggestion that thromboembolic disease associated with HES is particularly difficult to control. Among the NIH patients, 4 of 5 treated chronically with warfarin with “evidence of good patient compliance” developed recurrent emboli resulting in new neurologic deficits [52]. Among the 10 English patients with thrombotic or embolic complications, 3 developed these “while adequately anticoagulated with warfarin” [53]. In addition to these series, a few case reports promote the same impression. An 11-year-old boy who had eosinophilia and cerebral sinus thrombosis died, despite treatment with heparin [65]. A 65-year-old Japanese woman who had idiopathic hypereosinophilia died 3 months after surgical removal of a large left ventricular thrombus, despite anticoagulation with warfarin [75]. A 26-year-old man who had mitral and tricuspid valve prostheses because of HES-related endocarditis suffered a cerebral embolus, despite taking warfarin, and demonstrated apparent heparin resistance during subsequent cardiopulmonary bypass [76].

Although these reports suggest a pessimistic prognosis for hypereosinophilic patients with thrombosis, they describe a small number of patients, and they give little quantitative data about their level of anticoagulation. Most of the patients on warfarin were monitored with the prothrombin time (PT), rather than the international normalized ratio (INR), which is a more reproducible measurement. In some instances, the patients clearly were underanticoagulated by today’s standards. The goal of anticoagulation for the aforementioned 26-year-old patient, for example, was a PT of only 16.5 seconds, and his resistance to heparin may have represented heparin-induced thrombocytopenia [76]. Therefore, it is difficult to judge how refractory these patients would have been to anticoagulation administered according to current guidelines.

Management of thrombotic complications of hypereosinophilic syndrome

In the complete absence of information about whether anticoagulation could prevent the progression of HES cardiac disease from the thrombotic to the fibrotic stage, prophylactic treatment for this indication cannot be recommended; however, patients who have HES with evidence of intracardiac thrombosis by echocardiography or cardiac MRI should be treated with anticoagulant therapy because of reports, limited though they are, that approximately 25% of these patients develop emboli [1,52,53]. On the basis of the published experience with intracardiac thrombosis associated with HES and the much larger experience following myocardial infarction, it is likely that anticoagulation that conforms to the current recommendations for treating thromboembolic disease in other patient populations can significantly reduce, if not eliminate, the risk for emboli in patients who have HES.

A meta-analysis in 1993, for example, concluded that anticoagulation with heparin, but not antiplatelet therapy, can prevent the formation of echocardiographically demonstrated thrombi after myocardial infarction and reduce the risk for embolization [77]. Preventing thrombi is more difficult than preventing emboli, but emboli are the chief source of morbidity. Twenty-two to 56% of patients receiving up to 1000 U/h of unfractionated heparin developed mural thrombi within 11 days after myocardial infarction, but only 0% to 10% of those patients developed clinically apparent emboli [78–83]. Heparin doses exceeding 1000 U/h were more effective. In 1999, a meta-analysis of 31 trials found that the frequency of strokes after myocardial infarction was reduced by 63% in patients who took warfarin with a target INR of 3 to 5 and by 53% in those with an INR of 2 to 3 [84]. In more recent studies, warfarin with an INR of 2.8 to 4.2 and warfarin with an INR of 2 to 2.5 in combination with aspirin, 75 mg/d, were equally protective against strokes and significantly more protective than aspirin, 160 mg/d, alone [85]. In another study, a slightly lower INR (1.5–2.5) in combination with aspirin, 81 mg/d, provided the same level of protection as aspirin, 162 mg/d, alone [86]. Therefore, on the basis of these studies, the threshold INR to prevent cardioemboli seems to be approximately 3.0, although similar results may be achievable with an INR of 2 to 3 supplemented with aspirin. Treatment of thrombosis should begin with an agent that will damp the prothrombotic mechanisms quickly. For arterial thrombosis this means aspirin, with or without a form of heparin, and for venous thrombosis, a form of heparin [87,88]. In a patient who has active thrombosis, warfarin should not be given until heparin is started, because warfarin will not induce therapeutic anticoagulation for several days. If warfarin is given alone, it even may increase coagulability transiently [89,90].

In most patients, the parenteral anticoagulant of choice is a low molecular weight (LMW) heparin because this drug usually requires no monitoring and can be administered to outpatients [91]. Several LMW heparins are

marketed. They are similar in efficacy and price. Enoxaparin (Lovenox), dalteparin (Fragmin), and tinzaparin (Innohep) are the most commonly prescribed in the United States and are given subcutaneously every 12 or 24 hours. Because these drugs are excreted by the kidney, they should be used with caution in patients who have renal insufficiency. There is more information about the excretion of enoxaparin than the other LMW heparins. It seems that enoxaparin can be administered safely with creatinine clearances as low as 30 mL/min [92]. The dose is weight-based, even in obese patients, although higher doses of LMW heparin may be required for patients in critical care settings [92,93].

Unlike unfractionated heparin, LMW heparin has minimal, if any, effect on the activated partial thromboplastin time (aPTT) because its anticoagulant activity comes largely from its inhibition of activated factor X (fXa), rather than thrombin; however, if LMW heparin does need monitoring (eg, in a patient with marginal renal function), this is possible with an assay that specifically measures anti-fXa activity in U/mL. Blood for the test should be drawn approximately 4 hours after a subcutaneous dose. Therapeutic anti-fXa levels at that point are 0.5 to 1.2 IU/mL.

Unfractionated heparin is advisable for patients at high risk for bleeding or who are critically ill because its anticoagulant activity can be reversed completely with protamine, and it is only partially dependent upon renal excretion [91]. Although dosing recommendations vary, a commonly used regimen for venous thrombosis is an intravenous bolus of 80 U/kg, followed by 18 u/kg/h by continuous infusion [91]. Traditionally, the dosage has been adjusted 6 hours later to prolong the aPTT to 1.5 to 2.5 times the “control” value; however, this practice often results in subtherapeutic anticoagulation because the sensitivity of the aPTT to heparin varies with different reagents [91]. Also, the meaning of “control” often is unclear. It is recommended that each laboratory establish a therapeutic range of aPTT for heparin based upon calibrations with known amounts of heparin. No therapeutic range is appropriate, however, if the patient’s pretreatment aPTT is abnormal. Lupus anticoagulants, which are not rare, can elevate the aPTT to make it especially sensitive to heparin. Such patients will be underanticoagulated significantly if the aPTT is used to adjust their dosage of heparin. Anticoagulation in these patients should be monitored with the anti-fXa assay (therapeutic range, 0.3–0.7 IU/mL, different from that for LMW heparin).

Warfarin should be begun simultaneously with heparin or soon thereafter. Heparin must be continued for at least 5 days and until warfarin has achieved a stable INR between 2 and 3. The transition from heparin to warfarin should not be hurried because unstable anticoagulation at this early stage risks treatment failure.

The downside to antithrombotic treatment, of course, is the risk for bleeding. It has been estimated that 4% to 6% of patients who are treated with standard or LMW heparin for acute deep vein thrombosis develop major bleeding [94–96]. The risk increases with the dosage of anticoagulant and

with the presence of comorbid conditions. About 5% of patients taking warfarin have a major bleed each year [85,97–99]; however, the risk for bleeding on warfarin is greatest during the first 3 months of treatment, increases with comorbidities, and increases sharply at INRs greater than 4.5 [96,97,100]. In a study with more than 12,500 patients, the annual risk for major bleeding from antithrombotic dosages of aspirin (≤ 325 mg/d) was 2.7% [101]. Combining aspirin, 100 mg/d, with warfarin at an INR of 3.0 to 4.5 increased the annual risk for major bleeding in patients with artificial heart valves from 10% to 13% [102]. Therefore, the clinical challenge is to balance these bleeding risks with the potential benefits of administering antithrombotic agents.

Patients who have HES can have thromboembolic events unrelated to or only partially related to their hypereosinophilia [71–73]. Therefore, in deciding about the duration of anticoagulation, consideration must be given to whether the initial clinical event followed surgery or occurred during hospitalization or another period of relative immobility [103]. Testing a patient for genetic predispositions (eg, factor V Leiden, prothrombin G20210A) to thrombosis rarely impacts the decision about the duration of anticoagulation [104].

The recommended duration of anticoagulation is based upon the assumption that the risk for recurrent thrombosis or embolism is high until or unless the inciting cause is eliminated. Therefore, in patients who have HES, the duration of anticoagulation should be determined by the activity of the patient's endomyocardial disease. If this is controlled and if echocardiography reveals the absence of thrombus or resolution of thrombus, it is reasonable to discontinue anticoagulation; however, the balance between the risks and benefits of anticoagulation must be reassessed continuously.

Summary

Cardiovascular manifestations of HES are a common cause of morbidity and mortality in an otherwise uncommon disorder. The management of cardiovascular disorders in HES includes normalization of the peripheral eosinophil count; screening for the FP mutation and treating with imatinib if present; optimizing cardiac function by medical and surgical intervention; initiating anticoagulant therapy in patients who have or at risk for thrombotic complications; and considering heart transplantation for patients who have progressive cardiac disease, despite conventional management.

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