The Idiopathic Hypereosinophilic Syndrome

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The idiopathic hypereosinophilic syndrome (HES) is a leukoproliferative disorder, or more likely disorders, marked by a sustained overproduction of eosinophils. The distinctiveness of the syndrome, in addition to its eosinophilia, is its marked predilection to damage specific organs, including the heart. Such cardiac pathology is not unique to the idiopathic HES, because it may develop with eosinophilia associated with other diseases with identifiable etiologies. Conversely, yet enigmatically, not all patients with hypereosinophilia develop the organ damage characteristic of the HES. There are no specific tests diagnostic of the HES rather, the syndrome is defined by the combination of unexplained prolonged eosinophilia and evidence of organ involvement. We first review the more common and variable hematologic and clinical manifestations of this disorder because these are the features encountered clinically and that must be explained by investigation of the pathogenesis of HES. After considering the current understanding of the etiology and pathogenesis of the manifestations of HES, we review the therapies that may be used for HES.

DEFINITION

Although cases of the HES have been reported since before 1900,1 Hardy and Anderson in 19682 reported three patients with hypereosinophilia, hepatosplenomegaly, and cardiac or pulmonary symptoms and first suggested that these patients had a nonmalignant disorder that belonged within a spectrum of diseases they termed “hypereosinophilic syndromes.” Further progress on delineating this syndrome arose from eosinophilic patients referred to the Laboratory of Clinical Investigation at the National Institutes of Health (NIH). From analyses of these and other reported HES patients, Chusid et al3 presented the three defining features of HES that remain valid today. First, the patient must have sustained blood eosinophilia of greater than 1,500/μL present for longer than 6 months. Second, other apparent etiologies for eosinophilia must be absent, including parasitic infections and allergic diseases. Although not specified as such in Chusid et al’s initial report, by analogy, patients with eosinophilic syndromes that are clinically distinct from HES, whether they have apparent etiologies, such as the L-tryptophan–associated eosinophilia myalgia syndrome, or remain idiopathic, such as eosinophilic pneumonia, should be excluded. Third, by definition, patients must have signs and symptoms of organ involvement. This last criterion excludes patients who have eosinophilia that is clinically benign. Such eosinophilic patients, who may be underrepresented in eosinophilic patients studied at referral centers, can remain asymptomatic for decades. These three criteria, involving sustained eosinophilia without an apparent etiology or disease association and with evidence of organ involvement, constitute the defining features of HES.

Although early analyses of patients with HES suggested that they did not have eosinophilic leukemia, Bousser’s analyses4 provided further evidence indicating that only a minority with marked eosinophilia exhibited features suggestive of a malignant leukemic process and that most with HES did not. The composite experiences with series of HES patients have been reported from the NIH,5-10 by Dr Christopher Spry et al in London,11-13 and by French investigators.14 Other reviews of HES have been presented.15-18

MANIFESTATIONS

HES is more common in men than women (9:1) and tends to occur between the ages of 20 and 50, although a few cases have been reported in children.19,20 Clinically, HES is a heterogenous disease with varied manifestations. Not only is the etiology of HES unknown, but it is likely to include a range of diseases. This may contribute to the clinical heterogeneity in HES and complicates the understanding of its etiology and pathogenesis.

The presenting manifestations of HES may be caused by sudden cardiac or neurologic complications but tend to be more insidious and present for months or longer. In the NIH series of 50 patients, 12% of HES patients had their eosinophilia detected incidentally. Other presenting symptoms in this series were tiredness (26%), cough (24%), breathlessness (16%), muscle pains or angioedema (14%),
rash or fever (12%), and retinal lesions (10%).

Sweating and pruritus are quite common, and HES patients may experience fevers that are usually low-grade. HES patients do not exhibit a propensity to bacterial or other infections and are not anergic. Weight loss or cachexia is not seen, unless there is secondary malnutrition or end-stage congestive heart failure. Some HES patients experience alcohol intolerance with abdominal pain, flushing, nausea, weakness, or diarrhea. HES has developed in patients with human immunodeficiency virus-I (HIV-1) infections and eosinophilia can occur with human T-lymphotropic virus-II (HTLV-II).

**Hematologic Manifestations**

The defining hematologic abnormality is sustained eosinophilia. Often total leukocyte counts are less than 25,000/µL with between 30% and 70% eosinophils, but extremely high leukocyte counts (>90,000/µL) develop in some patients and are associated with a poor prognosis. Eosinophils in the blood may be mature or less commonly can include numbers of eosinophilic myeloid precursors. Eosinophils often exhibit morphologic abnormalities, including at the light microscopic level diminutions in granule numbers and sizes, cytoplasmic vacuolization, and nuclear hypersegmentation. At the ultrastructural level, there may be loss of granule contents, either the major basic protein (MBP)-containing crystalline core or the matrix of specific granules, fewer and smaller specific granules, increased tubulovesicular structures, and increases in cytoplasmic lipid bodies.

Although not often emphasized, many patients with HES will have an absolute neutrophilia along with their eosinophilia further contributing to elevations in the white blood cell (WBC) count. Band forms and less mature neutrophilic precursors, at times with alterations in nuclear segmentation and in cytoplasmic granules, may be present in the peripheral blood. Basophilia, usually mild, is seen in some HES patients. Leukocyte alkaline phosphatase levels may be abnormal, and these are as likely to be elevated as decreased. Serum vitamin B12 and vitamin B12 binding proteins may be normal or elevated.

Platelet numbers may be increased or decreased in 16% and 31%, respectively, of those seen at the NIH. Anemia is present in about 50% of HES patients, and teardrop and nucleated erythrocytes can be found in the peripheral blood. Bone marrow findings demonstrate increased numbers of eosinophils, often 30% to 60%, with a shift to the left in eosinophil maturation. Increased numbers of myeloblasts are not usually seen. Myelofibrosis is encountered in a minority of patients.

Chromosome studies are normal in many patients, with abnormal findings in only 1 of 18 in a British series and 8 of 33 patients at the NIH. Occasionally, a Philadelphia chromosome is found, but the commonest abnormality is aneuploidy in a minority of mitoses. Reported chromosomal abnormalities with HES or eosinophilic leukemia, some of which now might be considered to have HES, are diverse and have been reviewed.

Splenomegaly is found in about 40% of individuals (Table 1). Patients with splenomegaly may experience hypersplenism contributing to their thrombocytopenia and anemia, and infarction of the spleen (Fig 1) can lead to amelioration of the hypersplenism. Splenic pain, caused by capsular distention and/or infarcts, is frequent in those with enlarged spleens. When localization of radiolabeled eosinophils has been studied in these patients, the spleen has been a prominent site of sequestration.

**Clinical Manifestations**

**Cardiac manifestations.** Cardiac disease, frequent with HES (Table 1), is a major cause of morbidity and, especially in previous decades, mortality. The damage to the heart, ranging from early necrosis to subsequent thrombosis and fibrosis, occurs identically whether the eosinophilia is caused by HES or by multiple other etiologies, including eosinophilic leukemia, eosinophilia with carcinomas or Hodgkin’s or non-Hodgkin’s lymphomas, or eosinophilia from granulocyte-macrophage colony-stimulating factor (GM-CSF) administration or drug reactions, or from parasites such as trichinosis, visceral larva migrans, loiasis, or other filarial infections. Although diverse eosinophilic diseases can cause identical forms of cardiac disease, some patients with sustained eosinophilia never develop cardiac disease. Thus, the pathogenesis of eosinophil-mediated cardiac damage involves both the presence of increased eosinophils and other as yet ill-defined stimuli for recruitment and/or activation of these leukocytes. Pathologically, eosinophilic endomyocardial fibrosis, originally described by Loeffler, is identical to tropical endomyocardial fibrosis, although blood eosinophilia is often absent in the latter group of patients. It is likely that the absence of eosinophilia in the tropical disorder reflects the fact that patients are seen late in their disease and the eosinophilia has subsided. In the tropics, although there is not always perfect concordance between the prevalence of helminthic infections and endomyocardial fibrosis, in general it is believed that eosinophilia, elicited by infections with endemic filarial or other helminthic infections, is responsible for initiating the progressive cardiac dysfunction.

Eosinophil-mediated heart damage can evolve through three stages. The first is an acute necrotic stage in which...
the duration of illness has been short, a mean of 5.5 weeks.68 The second is a later thrombotic stage found in those with a mean 10-month duration of eosinophilia. The third stage is the late fibrotic stage encountered in those with illness for about 24.5 months.68 The early necrotic stage of cardiac disease is usually neither recognized clinically nor diagnosed as it occurs in HES. In this stage, there is damage to the endocardium and infiltration of the myocardium with eosinophils and lymphocytes with histopathologic evidence of myocardial necrosis and eosinophil degranulation and eosinophil microabscesses.81 A similar acute eosinophilic myocarditis can develop with hypersensitivity reactions and may be more fulminant.82-84 In those with HES and acute-stage myocardial necrosis, splinter hemorrhages may be prominent but clinical cardiac findings are often absent, although rare deaths caused by acute progressive cardiac disease can occur.27 Echocardiography and angiography detect no abnormalities in this stage and endomyocardial biopsy, usually from the right ventricle, is needed to make the diagnosis.29 Corticosteroid therapy during the acute stage may help control and prevent the evolution of myocardial fibrosis.29,85

The second stage of heart disease involves formation of thrombi along the damaged endocardium of either or both ventricles and occasionally the atrium.86 Outflow tracts near the aortic and pulmonic valves are usually spared, although rarely thrombus may involve these valves87 and thrombus may form on atrioventricular valve leaflets.88 Finally, in the fibrotic stage, progressive scarring develops that may lead to entrapment of chordae tendineae with the development of mitral and/or tricuspid valve regurgitation and to endomyocardial fibrosis producing a restrictive cardiomyopathy. HES patients often present at the later thrombotic and fibrotic stages. Common manifestations include dyspnea, chest pain, signs of left and/or right ventricular congestive heart failure, murmurs of mitral regurgitation, cardiomegaly, and T wave inversions.8 Two-dimensional echocardiography is valuable in detecting intracardiac thrombi (Fig 2) and the manifestations of fibrosis, which include thickening of the posterior mitral valve leaflet and its attachment to a thickened posterior wall as well as increases in intensities of endomyocardial echoes in areas of endomyocardial fibrosis.17,26,89-91 Cardiac catheterization demonstrates increased right and left ventricular end diastolic pressures, and angiography can demonstrate valvular incompetence as well as delineate apical obliteration or irregularities.29,92 Cardiac biopsies confirm the diagnosis, although with intense fibrosis in late disease biopsy instruments may fail to obtain samples. Most patients with late-stage eosinophilic heart disease can benefit from standard medical therapies for congestive heart failure or for arrhythmias,93 and will benefit from valve replacement when hemodynamically necessary (vide infra).
The risks of developing cardiac disease for the 50 HES patients from the NIH were not related to the extent of eosinophilia or duration of HES, nor were they for French HES patients.\textsuperscript{16,19} Rather, those who developed evident cardiac disease were more likely to be male and HLA-Bw44 positive and to have splenomegaly, thrombocytopenia, elevated levels of vitamin B\textsubscript{12}, hypoglycan or vacuolated eosinophils, and abnormal early myeloid precursors in their blood.\textsuperscript{19} Those HES patients free of cardiac disease tended to be female and have angioedema, hypergammaglobulinemia, elevated serum levels of IgE, and circulating immune complexes.\textsuperscript{16}

HES heart disease can also present as a dilated cardiomyopathy.\textsuperscript{9,95} Variant angina with normal coronary arteries,\textsuperscript{95} asymmetric septal hypertrophy,\textsuperscript{97} constrictive pericarditis,\textsuperscript{97} and cyanosis, platypnea, and orthodeoxia caused by right-to-left shunting across an atrial septal defect\textsuperscript{97} have been noted rarely with HES.

**Neurologic manifestations.** Neurological complications, also frequent in HES (Table 1), may be of three types.\textsuperscript{18} The first type of neurologic disease is caused by thromboemboli. With the propensity for intracardiac thrombus formation, thromboemboli may originate from the left ventricle or uncommonly with a patent foramen ovale from the right ventricle.\textsuperscript{96} In addition, local intravascular thrombosis might develop within cerebral vessels, but any role for this hypothetical mechanism has been difficult to corroborate. Patients can experience embolic strokes or transient ischemia episodes, either of which can be multiple and recurrent. Such thromboembolic episodes may develop before cardiac disease is demonstrable by echocardiography and can be the presenting manifestation of HES. Although anticoagulation with coumadin and antiplatelet agents is usually instituted, recurrences of emboli in adequately anticoagulated HES patients are not infrequent.\textsuperscript{18,19}

The second type of HES-associated neuropathy is primary central nervous system dysfunction. Patients exhibit changes caused by a distinct encephalopathy, including changes in behavior, confusion, ataxia, and memory loss, and exhibit upper motor neuron signs with increased muscle tone, deep tendon reflexes, and a positive Babinski.\textsuperscript{19} Impaired cognitive abilities may persist for months.\textsuperscript{1} Seizures, intracranial hemorrhages, dementia, and organic psychoses occur less frequently.\textsuperscript{18,19,101-103} The anatomic or pathologic basis for this form of diffuse central nervous system disease remains unknown, and autopsies in four patients have failed to identify lesions in the brain.\textsuperscript{19} Eosinophilic menigitis has been noted uncommonly with HES.\textsuperscript{102} However, infiltration of eosinophils into the brain or meninges is more suggestive of eosinophilic leukemia than of HES.\textsuperscript{27}

The third type of neurologic dysfunction in HES is peripheral neuropathies, which occur in about half of HES patients who have neurologic manifestations.\textsuperscript{18} Symmetric or asymmetric sensory polyneuropathies manifest by sensory deficits or painful paresthesias or mixed sensory and motor deficits are common,\textsuperscript{18,19,106-111} although pure motor neuropathies have been noted.\textsuperscript{112} Mononeuritis multiplex occurs with HES,\textsuperscript{108,113} as do radiculopathies\textsuperscript{18} and muscle atrophy caused by denervation.\textsuperscript{18,107} In some patients, neuropathies have improved coincident with steroid or other therapies, whereas in others peripheral neuropathies have been stable or progressive despite therapy. Some deficits have resolved or improved slowly over time. Biopsies of affected nerves generally show an axonal neuropathy with varying degrees of axonal loss and no evidence of vasculitis or direct or contiguous eosinophil infiltration.\textsuperscript{16,19,106-109,114} However, a few patients have experienced polyneuropathy with biopsy evidence of vasculitis,\textsuperscript{16,108} although the infiltrating cells in one patient were lymphoplasmacytoid and not eosinophils.\textsuperscript{106}

The etiology of the peripheral neuropathy is largely undefined. Monaco et al\textsuperscript{111} have suggested that damage to endothelial cells leads to capillary leakage and increased endothelial pressure causing axonal damage. Others have speculated that specific eosinophil granule proteins may be responsible for the nerve damage. Some of the eosinophil granule cationic proteins can exhibit neurotoxicity, but it must be borne in mind that this neurotoxicity was demonstrable only by injecting eosinophils or purified eosinophil granule proteins into the brains of test animals. This was performed to delineate the basis for the Gordon phenomenon, a cerebrocerebellar dysfunction in rabbits first reported to be elicited by intracranial injection of lymph nodes from Hodgkin’s disease patients.\textsuperscript{115} The Gordon phenomenon was shown subsequently to be mediated by eosinophils infiltrating such lymph nodes\textsuperscript{106} and thereafter by specific eosinophil granule proteins,\textsuperscript{117} including one named after the test, eosinophil-derived neurotoxin (EDN).\textsuperscript{118} EDN is an approximately 16-kD, markedly cationic polypeptide, which has ribonuclease activity and homology to another eosinophil cationic granule constituent, eosinophil cation protein (ECP).\textsuperscript{119} ECP is as potent as EDN in causing the Gordon phenomenon upon injection intrathecally in rabbits,\textsuperscript{119} but is less potent when injected intrathecally in guinea pigs.\textsuperscript{120} The brain histopathology in test animals shows spongiform lesions in the white matter and loss of Purkinje cells.\textsuperscript{117} Although these eosinophil granule proteins would be candidates to cause neurologic damage to human central or peripheral nerves, to date there is no direct proof that these eosinophil constituents mediate neurologic damage of the types observed in humans with HES. The pathology of biopsied peripheral nerves is not directly comparable to the lesions in rabbit brains, and eosinophil ECP and ECP have not been demonstrated as yet at sites of HES neuropathology. For one other eosinophil-related disease, neuropathies are common in the Churg-Strauss syndrome but are presumably based on the demonstrable underlying vasculitis.\textsuperscript{12} In contrast, in other eosinophilic diseases, including eosinophilic menigitides,\textsuperscript{122} the types of peripheral and central neurologic manifestations of HES characteristically do not develop (with the exception that any associated cardiac endomyocardial thrombosis might cause thromboembolic complications). Thus, the pathogenesis of both the central encephalopathic and peripheral neuropathies of HES remain unknown.

**Cutaneous manifestations.** The skin is one of the most frequently involved organs in HES, with cutaneous manifestations occurring in more than 50% of patients (Table 1).\textsuperscript{3,6,13} The most common skin manifestations are of two types, either angioedematous and urticarial lesions or erythema-
The Hyper eosinophilic syndrome infiltrates may be diffuse and angioedema and urticaria are likely to have benign courses without cardiac or neurologic complications and either to not require systemic therapy or to respond to prednisone alone.\textsuperscript{11,12} Some patients with angioedema and eosinophilia are now recognized to have a syndrome, episodic angioedema and eosinophilia that is distinct from HES.\textsuperscript{123,124} In HES patients with papular or nodular lesions, dermal biopsies usually show a mixed cellular infiltrate\textsuperscript{4} that is not solely eosinophilic and is devoid of vasculitis. Perivascular infiltration with eosinophils and mild-to-moderate perivascular neutrophilic and mononuclear infiltrates are found.\textsuperscript{5} These lesions usually improve in parallel with responses to systemic therapies of HES.\textsuperscript{6} HES patients with aquagenic pruritus\textsuperscript{65} and numerous indurated papules and nodules\textsuperscript{125,126} have been reported who have had beneficial responses to PUVA treatment.\textsuperscript{43,127,128} Papulonodular lesions unresponsive to prednisone but responsive to treatment with dapsone\textsuperscript{129} and pruritic erythematous eruptions responsive to sodium chromoglycate\textsuperscript{130} have occurred with HES. Also, blistering skin lesions and small bowel necrosis caused by dermal microthrombi and mesenteric thrombi and vasculitis,\textsuperscript{131} lesions caused by cutaneous microthrombi,\textsuperscript{132} vesiculo-bullous lesions,\textsuperscript{133} ulcerations with dermal arteriolar microthrombi,\textsuperscript{31,134} generalized erythroderma,\textsuperscript{135} and erythema annulare centrifugum\textsuperscript{136-138} have been reported with HES. Three patients with apparent HES later developing lymphomatoid papulosis were reported by Whitaker et al.\textsuperscript{139} Particularly incapacitating mucocutaneous manifestations of HES are mucosal ulcers, which may be an early\textsuperscript{139} or later manifestation of HES. These ulcerating lesions can occur in the mouth, nose, pharynx, penis, esophagus, stomach, and anus.\textsuperscript{139,140} Biopsies demonstrate only a nonspecific mixed cellular infiltrate without a prominence of eosinophils and no evidence of vasculitis or microthrombi\textsuperscript{139} (Weller, Dvorak, and Bubley, unpublished observations). Mucosal ulcerations do not correlate with use of cytotoxic drugs, do not respond to topical or systemic glucocorticosteroids, and mucocutaneous disease can flare independent of other hematologic or clinical manifestations of HES.

Pulmonary manifestations. Overall, pulmonary involvement is reported in about 40\% of HES patients (Table 1). The commonest respiratory symptom in patients with HES is a chronic, persistent, generally nonproductive cough. The basis for this may be sequestration of eosinophils in pulmonary tissues. Most of these symptomatic individuals have clear chest radiographs. Although bronchospasm has been noted to occur in HES in some series,\textsuperscript{135} Spry has remarked on the rarity of asthma in HES patients. Pulmonary involvement in HES may be secondary to congestive heart failure or pulmonary emboli originating from right ventricular thrombi or may reflect primary infiltration of the lungs by eosinophils; and chest radiographs may show abnormalities associated with each of these processes.\textsuperscript{141} In earlier series in which frank congestive heart failure was more common, pleural effusions were the commonest abnormality.\textsuperscript{3} Although these are transudative, rarely an eosinophil-containing exudative pleural effusion may occur.\textsuperscript{142} Infiltrates (Fig 3) are seen in 14\% to 28\% of HES patients.\textsuperscript{3,35} The infiltrates may be diffuse or focal without a predilection for any region of the lungs, in contrast to the often peripheral infiltrates in chronic eosinophilic pneumonia.\textsuperscript{143} Biopsies of the infiltrates in HES show eosinophilic parenchymal accumulations and occasionally infiltration and cuffing of small pulmonary arteries.\textsuperscript{144} These infiltrates may or may not improve with prednisone administration. Pulmonary fibrosis may develop over time, especially in those with cardiac fibrosis.\textsuperscript{13} Bronchoalveolar lavage may recover large numbers of eosinophils in HES,\textsuperscript{145} but this does not distinguish HES from other eosinophilic pneumonias that also may yield large numbers of eosinophils in the lavage fluid.\textsuperscript{146-148}

Ocular manifestations. Visual symptoms, most commonly blurring, can be experienced by patients with HES.\textsuperscript{13} Even in those without visual symptoms, fluorescein angiography demonstrated that more than 50\% of HES patients had choroidal abnormalities, including patchy and delayed filling, and retinal vessel abnormalities.\textsuperscript{25} Although retinal arteritis\textsuperscript{140} can develop with HES, most of the ocular abnormalities are presumed to be caused by microemboli or possibly by local thrombosis.\textsuperscript{123,150} Adie’s syndrome (pupillotonia)\textsuperscript{151} and keratoconjunctivitis sicca and episceritis, both of which improved with systemic prednisone therapy that effectively suppressed eosinophilia,\textsuperscript{152} have been recorded with HES.

Rheumatologic manifestations. Arthralgias and large joint effusions can occur with HES.\textsuperscript{31} Long-standing rheumatoid arthritis or nonerosive polyarthritis involving large joints and causing a synovial fluid eosinophilia have been noted.\textsuperscript{153-156} Patients with HES may experience cold-induced Raynaud’s phenomenon\textsuperscript{157,158} and can develop digital necrosis of fingers or toes. We have seen three patients with digital necrosis, one of whom was HIV infected. Reported cases have occurred in those with HES alone\textsuperscript{159} and in a patient with eosinophilia and acquired immunodeficiency syndrome (AIDS) who had arteriographic evidence of digital vasculitis.\textsuperscript{160} Although myalgias are frequent, HES with focal myositis\textsuperscript{161} or polymyositis\textsuperscript{157,162} occurs only uncommonly.

Digestive system involvement. Gastrointestinal tract involvement can accompany HES, and 20\% of patients at some time may have diarrhea.\textsuperscript{3,31} Eosinophilic gastritis, enterocolitis, or colitis may be present.\textsuperscript{163,168} Pancreatitis and sclerosing cholangitis occur rarely.\textsuperscript{163,169} Hepatic involvement with HES includes chronic active hepatitis\textsuperscript{170,171} and the Budd-Chiari syndrome from hepatic vein obstruction.\textsuperscript{172,173}

Immunologic Manifestations

The associated immunologic abnormalities suggest the heterogeneity of HES. Serum Ig levels assayed in 21 HES patients at the NIH found elevations in IgG, IgA, and IgM in only 3, 1, and 7 patients, respectively.\textsuperscript{9} In contrast, 38\% had extremely elevated IgE levels.\textsuperscript{9} The subgroup with increased IgE required no therapy or responded very well to prednisone, so enhanced IgE levels are a good prognostic factor and suggest the existence of a distinct subgroup of HES patients.\textsuperscript{9} Although Clq-binding circulating immune complexes were elevated in 32\%, this finding did not correlate with prognosis or response to therapy.\textsuperscript{9} Antinuclear antibodies and lupus erythematosus cell preparations are negative. Erythrocyte sedimentation rates were elevated in 6 of
22 patients. Studies of T- and B-lymphocyte numbers and blastogenic responses have shown no striking or consistent abnormalities.3

ETIOLOGY OF HES

Relationship Between HES and Eosinophilic Leukemia

Before the recognition that most patients with hypereosinophilia did not have a truly malignant disease, patients with HES were reported as having eosinophilic leukemia. The distinction between these disease processes, the truly malignant and the more usual nonmalignant HES, can be difficult in some patients who present with acute HES. Acute eosinophilic leukemia can be distinguished from HES when there is a marked increase in the number of immature eosinophils in the blood and/or marrow, with more than 10% blast forms in the marrow, infiltration of tissues with immature cells of predominantly eosinophilic type, and a clinical course similar to other acute leukemias, including pronounced anemia and thrombocytopenia and susceptibility to infections.1 The cardiac and neurologic complications of HES can develop in acute eosinophilic leukemia, as in other eosinophilic diseases, so these are not distinguishing clinical features. Features that are more distinctive for eosinophilic leukemia include central nervous system invasion by eosinophilic cells and a tendency to produce myeloblastomas in bones.1

Although, as noted above, chromosomal abnormalities can occur with eosinophilia because of HES or leukemias, eosinophilic leukemia is often associated with chromosomal abnormalities described in other acute nonlymphocytic leukemias, including trisomy-1, 8;21, and 10p+11q− translocations.174-177 Also, eosinophilic leukemia has been described as a variant of the M-4 phenotype of acute myelomonocytic leukemia, including having the common M4 characteristic of chromosomal 16 abnormalities.177-179 Other instances in which the diagnosis of eosinophilic leukemia is clear are those associated with leukemias developing after another hematopoietic malignancy, in which abnormalities of chromosomes 5 or 7 are common.180,181 A preleukemic setting such as a myelodysplastic syndrome has also been described before the development of eosinophilic leukemia.182 One eosinophilic leukemia has been reported with a chromosomal abnormality at 5q31, the site of the interleukin-5 (IL-5) gene,183 but this region also encodes a number of other hematopoietic growth factors, hormone receptors, and proteins involved in signal transduction or transcriptional regulation.184

Relationship of Hypereosinophilia to Lymphomas

Although eosinophilia may accompany some lymphomas, including Hodgkin’s disease,185 T-cell lymphoblastic lymphoma,186 and adult T-cell leukemia/lymphoma,187 this eosinophilia is usually modest. However, several patients with the typical clinical and hematologic features of HES have been reported who later developed T-cell lymphomas188-191 or acute lymphoblastic leukemia.192-195 Eosinophilia occurring in three patients with T-cell lymphomas has been correlated with GM-CSF, IL-3, or IL-5 production by the lymphomas.196,197

Relationship of HES to Myeloproliferative Disorders

In series of HES patients analyzed by both French35 and NIH11,13 investigators, 17 of 40 and 16 of 32 HES patients, respectively, exhibited features common to myeloproliferative disorders, including elevated B12 levels, abnormal leukocyte alkaline phosphatase scores, splenomegaly, cytogenetic abnormalities, myelofibrosis, anemia, erythrocyte abnormalities including teardrop forms, myeloid dysplasia, and basophilia. Patients with these features were less likely to respond to prednisone and more likely to require cytotoxic therapy.7,11,13,35 However, HES patients rarely have expansions of other cell lines besides eosinophils to the extent seen in myeloproliferative disorders and do not develop myelofi-
brosis severe enough to cause pancytopenia or acute leukemia. A couple of HES patients have had concomitant polycythemia vera. Some HES patients do develop blast crises similar to chronic myelogenous leukemia, or evolve into chronic myelogenous leukemia-like diseases. Although in a few instances it has been possible to demonstrate that eosinophils are part of the clonal proliferation in chronic myelogenous leukemia, for analyses of HES there are no specific markers that can be applied to ascertaining the clonality of eosinophils. Studies of eosinophil colony formation with blood cells from HES patients have yielded varying results, but none suggestive of colony growth characteristics of acute or chronic myelogenous leukemia.

**Etiology of Nonmalignant HES**

Because the diagnostic and hematologic hallmark of HES is a dysregulated overproduction of eosinophils, in patients with HES who lack malignant disorders several mechanisms may be hypothesized to account for the observed eosinophilia in both the blood and marrow. First, there may be overproduction of eosinophilopoietic signals and such might involve abnormalities in T-cell clones producing such eosinophilopoietic cytokines. Second, there may be abnormalities in the eosinophilopoietic cytokines, enhancing or prolonging their biologic activities. Third, there may be defects in receptors for these cytokines, or, fourth, there may be defects in signal transduction mediated by these cytokine receptors. Finally, there may be defects in normal suppressive regulatory steps, active either within eosinophils or on the cells generating the eosinophilopoietic cytokines. Although prolonged survival of mature eosinophils might heighten numbers of cells in the blood or tissue, this mechanism by itself would not explain the enhanced eosinophilopoiesis demonstrable in the marrow of HES patients. One mother with typical HES, including splenomegaly, pulmonary infiltrates, sustained eosinophilia for 10 years, and endomyocardial fibrosis, delivered a child who was markedly eosinophilic at birth (63% eosinophils, 88,000 WBC/L) and remained eosinophilic at 4 (42% eosinophils, 30,000 WBC/L) but not at 8 months of age. The nature of the transplacentally transferred eosinophilic stimulus was not defined, but the persistence of eosinophilia for more than 4 months would seem prolonged to be accounted for by a prenatally transferred polypeptide eosinophilopoietic cytokine.

With regard to eosinophilopoietic cytokines, three currently recognized cytokines, IL-5, IL-3, and GM-CSF, are active in stimulating eosinophilopoiesis. IL-3 and GM-CSF act on other cell lineages of marrow-derived cells, whereas IL-5 in humans is restricted to stimulating eosinophil production. In the human, in contrast to the mouse, IL-5 does not appear to have major B-cell stimulatory activities, although some enhancement of B-cell-dependent antibody production is demonstrable in vitro with human IL-5. Thus, overproduction of IL-5 would be a candidate mechanism for explaining HES; and its dysregulated production by T-lymphocyte clones could represent an underlying mechanism for the hypereosinophilia. Indeed, increased IL-5-like bioactivity, neutralizable with anti-IL-5 antisera, has been detected in the sera from three corticosteroid-unrespon-

sive HES patients. However, because eosinophils themselves have been shown to contain IL-5 mRNA transcripts and to exhibit immunocytochemically detectable IL-5 protein, increased IL-5 levels in HES cannot be interpreted simply at the present time as evidence of overproduction by T cells. Whereas eosinophil numbers are uniformly elevated, some HES patients also have increased numbers of neutrophils. Because IL-5 does not directly stimulate neutrophil production, it is possible that other cytokines are contributing, alone or in combination with IL-5. Eosinophils themselves may elaborate GM-CSF and IL-3, and conceivably the release of these cytokines from stimulated HES eosinophils during or after their intramedullary development might contribute to the neutrophilia.

In other human diseases associated with eosinophilia, including helminthic infections, T-cell lymphomas with eosinophilia, and eosinophilia after IL-2 administration, it has been possible to demonstrate enhanced IL-5 mRNA transcripts and/or production of IL-5 as the candidate eosinophilpoietin contributing to the eosinophilia. In HES, cloned CD4+ CD8+ T cells obtained from HES patients have been shown to release eosinophilopoietins, specifically IL-5 and, to a lesser extent, GM-CSF. Thus, it is possible that some patients with HES have overproduction of IL-5 from T lymphocytes. Elevated levels of soluble IL-2 receptors present in the sera of HES patients have been suggested to indicate that lymphocyte populations are activated in HES. Because human eosinophils express functional high-affinity receptors for IL-2 and the elevated levels of soluble IL-2 receptors detected in HES, however, might also be derived from eosinophils and not lymphocytes.

IL-5 transgenic mice have developed massive, long-term eosinophilia, but in all studies to date have remained healthy, without evidence of the cardiac or other organ damage usually found in HES, suggesting that more than IL-5-mediated eosinophil overproduction may be needed to cause the organ damage found in HES. Of the other potential mechanisms involved in the development of HES, there is very little information as yet. The IL-5 receptor has been cloned and characterized. Interestingly, a dominant transcript encodes a soluble IL-5 receptor that lacks the transmembrane region. This soluble IL-5 receptor binds IL-5 and inhibits its activity. The role of such binding of IL-5 in vivo in regulating the availability of active IL-5 remains to be defined. The existence of another novel type of downregulatory mechanism governing eosinophilia is suggested by studies in IL-5 transgenic mice that normally have pronounced and sustained eosinophilia in conjunction with IL-5 overproduction. When these IL-5 transgenic mice were infected with a parasite that itself elicits eosinophilia, *M. oestruea* in both the blood and marrow declined despite sustained high serum IL-5 levels. This downregulatory regulatory mechanism, whose nature is not known, exemplifies areas that are not yet understood but may be relevant to understanding the production dynamics of eosinophils in patients with HES.

**PATHOGENESIS OF HES**

In addition to having sustained eosinophilia, HES is characterized by damage to specific organs. As discussed above,
the pathogenesis of the central and peripheral neuropathies in HES are not known, although neurotoxicity mediated by one of the eosinophil’s cationic granule proteins, EDN, is often suggested. In addition to this cationic protein, the eosinophil is capable of causing damage or dysfunction to host cells by a number of mechanisms. Specific granules contain four cationic proteins, eosinophil peroxidase, MBP, ECP, and EDN. Each can exert toxicities on host cells, as recently reviewed.238 The eosinophil can undergo a respiratory burst to generate oxidative products that alone or in concert with eosinophil peroxidase may further cause oxidant-mediated damage.239-241 Human eosinophils are also capable of elaborating a number of cytokines that might contribute to inflammation and fibrosis, including transforming growth factor-α (TGF-α),242 TGF-β,243,244 tumor necrosis factor-α (TNF-α),245 IL-1α,246 macrophage inflammatory protein-1α,245 IL-6,247 IL-8,248 as well as the hematopoietic cytokines, IL-5,216,217 IL-3,230 and GM-CSF.217,218,221 Eosinophils circulating in the blood of HES patients exhibit a number of functional and biochemical measures, indicating that they are “activated,” as also found with varying percentages of blood eosinophils in other diseases associated with eosinophilia.249 These changes include increased metabolic activity,252,251 diminished density (“hypodense”),252 enhanced antibody-mediated cytotoxicity,253 enhanced leukotriene C4 formation,254 and morphologic alterations, including cytoplasmic vacuolization, alterations in granule numbers and size, and losses within specific granules of MBP-containing cores or matrix.51 In HES, the extent of cytoplasmic vacuolization and hypogranularity has been well correlated with the development of cardiac disease.1,13 A number of cytokines, including GM-CSF,225 IL-3,230 and IL-5,257 cause eosinophils to become hypodense and functionally “activated.”249 Serum of HES patients, which stimulates eosinophils to become hypodense, contains activity with prolonged eosinophil viability in vitro and is neutralizable with antisera to IL-5.258,259 Thus, blood eosinophils in HES exhibit alterations compatible with their exposure in vivo to activating stimuli, such as IL-5.

The most striking organ damage in HES and some other secondary eosinophilias is to the heart, culminating in thrombosis and fibrosis. That eosinophilia itself does not uniformly cause this damage is indicated by experience with patients with syndromes such as eosinophilic pneumonia and episodic angioedema with eosinophilia that characteristically are devoid of cardiac damage. With regard to thrombus formation, one eosinophil cationic protein, ECP, has been reported to enhance urokinase-induced plasminogen activation279 and enhance factor XII-dependent reactions.280 In contrast, the opposite was reported in another study: eosinophils, ECP, MBP, and eosinophil peroxidase were found to inhibit activation of factor XII.281 HES patients have elevated serum levels of MBP282 and ECP283 and have been noted to require more heparin to achieve anticoagulation.284 There are reports of enhanced procoagulant activity from HES monocytes,283,284 but most investigators have failed to find any consistent systemic alterations in coagulation or fibrinolysis.11 HES patients do not have a predilection for deep venous thromboses in sites such as the legs, but rather thrombi generally occur in the heart and small vessels, such as retinal vessels.

In cardiac tissues of patients with acute eosinophilic myocarditis or early necrotic and thrombotic stages of HES-related cardiac disease, eosinophils have infiltrated the endocardium and myocardium and their cationic proteins, including MBP and ECP, can be found to be deposited in these sites.84,285 An early requisite step in this recruitment of eosinophils to the heart likely involves adherence of eosinophils to the endocardium or the cardiac microvascular endothelium. Eosinophils may use several adherence pathways to bind to endothelial cells, including binding to ICAM-1 and ICAM-2, E-selectin, VCAM, and P-selectin.286 By means of their expression of VLA-4, which binds to VCAM, selectivity of local adherence for eosinophils and lymphocytes, without neutrophils, might be achieved.267 The early cellular infiltrate in eosinophilic heart disease includes both lymphocytes and eosinophils.51 To date, no data are available on which adherence proteins may be induced to become expressed on the endocardium or cardiac vascular endothelium in HES. Such knowledge would be germane in helping to define mechanisms of preferential targeting of eosinophils to the heart, might help explain the propensity for endomyocardial fibrosis to develop in the trabeculated regions and not smooth outflow tracks of the ventricles, and might afford opportunities for therapeutic intervention.

Attempts to demonstrate eosinophil cytotoxicity for human embryonal heart cells have failed to show that eosinophils were more toxic for myocardial cells than neutrophils,288 although recently the capacity of human eosinophils to damage feline endocardium has been reported.289 Local effects within the heart that promote thrombosis could be due to the capacity of MBP and other eosinophil cationic proteins to bind to glycosylated thrombomodulin and inhibit its local anticoagulant activity on the endothelium.270 Eosinophil-derived oxidants may damage endothelium.279,284 and platelets may further be activated by eosinophil-derived MBP271 or PAR.272 Although the mechanisms of fibrosis in eosinophil endomyocardial disease are not known, eosinophilia and eosinophil degranulation occur in a number of syndromes associated with fibrosis.273 Mechanisms for enhancing fibrosis may include the capacity of EDN to stimulate fibroblast proliferation,274 enhanced fibroblast proliferation and extracellular matrix deposition by eosinophil-derived TGF-α275 and TGF-β,276 respectively, and ECP inhibition of proteoglycan degradation in fibroblasts.277

Differential Diagnosis of HES

The differential diagnosis of HES involves the disparate diseases associated with eosinophilia.7 Because a number of the eosinophilic syndromes and diseases are of unknown etiology, distinctions between these and HES must be made on clinical and pathologic bases. Eosinophilic syndromes limited to specific organs, such as eosinophilic pneumonitis143,278 or eosinophilic gastroenteritis,279,280 characteristically do not extend beyond their own target organ, and hence lack the multiplicity of organ involvement often found with HES and do not have the predilection to develop secondary...
THE HYPEREOSINOPHILIC SYNDROME

eosinophil-mediated cardiac damage, for reasons that are not known. These distinct eosinophilic syndromes therefore can usually be separated from HES, although individual patients may on occasion present with overlapping features that confound classification.

Although vasculitis is not a prominent feature of HES, individual patients with HES may exhibit pathologic evidence of vasculitis. The major vasculitis that is associated with eosinophilia is the Churg-Strauss syndrome. A history of asthma, nonfixed pulmonary infiltrates, blood eosinophilia greater than 10%, paranasal sinus abnormalities, mononeuropathy or polyneuropathy, and a biopsied blood vessel demonstrating extravascular eosinophils characterize this syndrome. Biopsies showing necrotizing vasculitis of small arteries and veins and extravascular granulomas are characteristic of the Churg-Strauss syndrome, but not all patients exhibit these pathologic features. Rather, asthma, peak eosinophilia greater than 1,500/μL, and systemic vasculitis of two or more extrapulmonary organs help identify this syndrome.

Neurologic, pulmonary, and, less commonly, paranasal involvement may occur with HES, but asthma is often absent from patients with HES. In individual patients, clear cut distinction between HES and Churg-Strauss syndrome may not be possible. Because patients with the latter syndrome respond usually to oral high-dose prednisone, therapy at the outset would be identical for either syndrome.

For those with cutaneous involvement and eosinophilia, angiolymphoid hyperplasia with eosinophilia or Kimura’s disease, eosinophilic cellulitis (Wells’ syndrome), eosinophilic fasciitis, and eosinophilic pustular folliculitis can be distinguished from HES with the histopathology of the biopsied lesions. The eosinophilia-myalgia syndrome caused by ingestion of contaminated L-tryptophan should be excluded. Another syndrome, episodic angioedema with eosinophilia, is characterized by recurring episodes of angioedema, urticaria, fever, and marked blood eosinophilia.

The clinical course of this disease with its prominent periodic occurrences of angioedema and eosinophilia and its lack of association with cardiac damage distinguish it from HES. Indeed, the milder course noted in a subgroup of HES patients with angioedema in the NIH series may have reflected inclusion of patients with the syndrome of episodic angioedema with eosinophilia that had not been delineated at that time.

The diagnosis of HES also requires that eosinophilias of identifiable etiologies be excluded. These include eosinophil-eliciting parasitic infections that, with the exceptions of two enteric protozoans, Isospora belli and Dientamoeba fragilis, are caused by helminthic parasites. Those more likely to elicit prolonged eosinophilia in adults include filarial infections and strongyloidiasis. Trichinosis may cause an acute, marked eosinophilia, but this does not persist unless there is reinfection from contaminated meat. Strongyloides stercoralis, which may be difficult to diagnose solely by stool examinations, is especially important to exclude not only because of its capacity to cause marked eosinophilia mimicking HES but also because it, unlike other helminthic etiologies of marked eosinophilia, can develop into a disseminated, often fatal, disease (hyperinfection syndrome) in patients receiving immunosuppressive corticosteroids as might be tried for HES therapy. Indeed, HES has been misdiagnosed in patients with unsuspected strongyloidiasis. Serial stool examinations and a serologic test for Strongyloides should be performed. An enzyme-linked immunosorbent assay (ELISA) serology has proven valuable in detecting strongyloidiasis, even when aggressive examinations of stool samples have been unrevealing. Some tissue- or blood-dwelling helminths, not detectable by stool examinations, that can cause marked eosinophilia and require diagnostic examinations of blood or biopsied tissues or specific serologic tests include filarial infections, trichinosis, and visceral larva migrans. In children, with their proclivity for pica and ingestion of dirt contaminated by dog ascidian eggs, visceral larva migrans caused by Toxocara canis is a potential etiology for sustained eosinophilia, especially if reinfection is occurring. ELISA serologic testing can evaluate this possibility.

THERAPIES FOR HES

The early literature was replete with reports of HES patients with a poor prognosis. A 1975 review of 57 published cases noted a mean survival of 9 months and a 3-year survival of 12%. Although these retrospective analyses emphasized the high morbidity and mortality that may be associated with HES, most of these HES patients presented with advanced disease and very significant cardiovascular compromise. Most deaths in these patients were caused by congestive heart failure or other complications of endomyocardial damage, including secondary bacterial endocarditis, progressive atrioventricular valvular incompetence, and thromboemboli. Earlier diagnosis of patients with HES and clinical and echocardiographic monitoring of heart disease, combined with use of cardiac medications and cardiothoracic surgical approaches not available in previous decades, enables the cardiac sequelae of HES to be managed more successfully and has improved the longevity of HES patients. A 1989 report of 40 HES patients from France, including 17 with the more serious features of a myelodysplastic syndrome, noted an 80% survival at 5 years and a 42% survival at 10 and 15 years. For many patients, if the sequelae of organ damage, especially to the heart, can be managed, HES can have a prolonged course over decades.

Thus, supportive modalities, not available in prior times, are important in conjunction with therapies directed more specifically at controlling eosinophilia (Table 2). HES for most patients is not a truly malignant disease. Therefore, its therapy should be aimed at controlling organ damage, not solely eradicating or suppressing eosinophilia, and should be predicated upon the patient having a chronic long-lasting disease. Usually, at least at the present time, the goal is chronic maintenance therapy, not aggressive therapy that aims for inducing a “remission” of disease. Disease may subside in severity with time. Furthermore, some manifestations of the disease, such as cardiac damage, do not appear to correlate in severity with the levels or duration of eosinophilia. Although aggressive therapy may be indicated, it must be tailored to the needs and responsiveness of individual patients. Spry has emphasized from his experience that
Table 2. Therapies for the HES

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Indications</th>
</tr>
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<tbody>
<tr>
<td>None</td>
<td>if no evidence of organ involvement, ie, those with eosinophilia but without defining features of HES</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>first-line agent for those with organ involvement; if effective in suppressing blood eosinophilia, dose may be tapered or changed to every other day; response to corticosteroids associated with a better prognosis</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>used in those with organ involvement and eosinophilia unresponsive to corticosteroids; anemia and/or thrombocytopenia common with chronic therapy</td>
</tr>
<tr>
<td>Vincristine</td>
<td>especially useful for acute reductions when total eosinophil counts are excessive (&gt;50,000 to 75,000/µL); can be administered episodically to control HES often with amelioration of thrombocytopenia</td>
</tr>
<tr>
<td>Alkylating agents</td>
<td>chlorambucil and others; may be administered in 4-day pulse doses repeated as dictated by magnitude of blood eosinophilia</td>
</tr>
<tr>
<td>Other</td>
<td>α-interferon; cyclosporin</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>indicated for serious mitral regurgitation with bioprosthetic mitral valve replacement; less commonly, thrombectomy or endomyocardectomy</td>
</tr>
</tbody>
</table>

overaggressive cytotoxic therapy for HES patients may be more deleterious than HES itself for some patients and is not necessarily warranted for many patients. Deaths caused by marrow aplasia induced by cytotoxic therapy have been recorded.3

Initial Therapeutic Options

In patients with eosinophilia that lack evidence of organ involvement, specific therapy need not be administered. Such patients with apparently benign hypeeosinophilia can have prolonged courses without need for any therapeutic interventions. However, because cardiac involvement may develop insidiously, and is not correlated with any specific level of blood eosinophilia,7 such patients should have careful clinical and echocardiographic follow-ups at least initially at 6-month intervals. In the early evaluations of such patients, it can be helpful to administer a short course of prednisone (60 mg/kg/d or 1 mg/kg/d) to ascertain whether the blood eosinophilia is suppressable by corticosteroids. This may provide information pertinent to whether prednisone will be efficacious in case the patient rapidly develops organ involvement necessitating therapy and also has prognostic significance because patients with HES who experience corticosteroid-induced eosinopenia have a better prognosis than those whose eosinophilia is unaffected by corticosteroids.7

In patients with organ involvement, initial therapy is with prednisone (1 mg/kg/d or 60 mg/d in adults). If blood eosinophilia is suppressed, doses may be slowly tapered and attempts at changing to alternate day therapy may be made.7 For some HES patients, more aggressive therapy with prednisone is needed only when their disease becomes active.7,11 If blood eosinophilia is not suppressed by high-dose prednisone, there usually is no reason to continue prednisone for most patients, although a few may have organ involvement (eg, pulmonary infiltrates) that responds to corticosteroid therapy despite its failure to reduce blood levels of eosinophils. The mechanism of action(s) of corticosteroids in reducing blood eosinophils, which generally occurs rapidly within 4 hours,7 are not fully delineated. Steroids may interfere with eosinophilopoiesis,30 although this would not likely account for the rapidity of eosinopenia induced by steroids in normal individuals or patients with allergic and parasitic diseases or those with steroid responsive HES.302,305 Potential redistribution of blood eosinophils into noncirculating compartments, spleen or lymph nodes, has been suggested.302 Moreover, by antagonizing the viability-promoting effects of GM-CSF, IL-5, and IL-3 on developing and mature eosinophils, steroids may promote apoptotic death of eosinophils.305 For those patients with HES with corticosteroid refractory eosinophilia, the mechanisms of such steroid resistance have not been defined, although an absence of normally detectable glucocorticosteroid receptors on eosinophils from such HES patients has been reported.310

In the NIH series, 38% of patients responded well and 31% responded partially to prednisone therapy. Those patients with HES who are likely to respond to prednisone alone are those with episodes of angioedema and urticaria, with increased serum IgE levels, and who experience a prolonged eosinopenic response to a single dose of prednisone.7,10,11 Those less likely to respond to prednisone include those with splenomegaly and with cardiac or neurologic dysfunction at the time of presentation.11

Chemotherapeutic Agents

The decision to use cytotoxic chemotherapy for HES should be made in the context of continued end-organ involvement despite corticosteroid therapy. For most chemotherapeutic and biologic agents, there are only case reports of efficacy, so firm recommendations for treatment for the steroid-unresponsive patient are not possible. However, it is often possible to control the progression of disease and its symptoms in even severely affected patients over a long period of time. Therefore, extremely toxic and especially life-threatening regimens should probably be avoided in most HES patients.

Studies at the NIH initially demonstrated the efficacy of hydroxyurea in the management of steroid-unresponsive patients with HES.11,13 Similarly, individual patients with HES have responded to hydroxyurea.198 This agent, which interferes with DNA synthesis, inhibits the formation of all marrow-derived cells. It is used in a usual dose range of 1 to 2 g/d with a goal of reducing the total leukocyte count to less than 10,000/µL.7 After initiation of daily hydroxyurea, peripheral blood eosinophil counts do not begin to diminish for 7 to 14 days, reflecting the kinetics of eosinophilopoiesis and eosinophil turnover in these patients. Anemia, often requiring red blood cell transfusions, and thrombocytopenia
are complications of therapy and may necessitate lowering doses or cessation of therapy with hydroxyurea. Because of fluctuating rates of eosinophil production in HES and complicating dose-dependent or uncommonly idiosyncratic anemia or thrombocytopenia, dosages of hydroxyurea often need to be adjusted based on weekly leukocyte, red blood cell, and platelet counts.

Vinca alkaloids are effective in HES. Vincristine at a dose of 1.5 to 2.0 mg at 2-week intervals has been shown to be beneficial for several patients.320,319.314 Importantly, this agent usually spares marrow toxicity, especially for platelets. The onset of a decrease in blood eosinophilia is within 1 to 3 days so vincristine is especially efficacious for acute therapy of individuals with markedly elevated eosinophil counts. Furthermore, patients often have a sense of enhanced well-being with vincristine, not elicited with hydroxyurea therapy.25 Vincristine treatment may become limited by its neurologic complications, including paresthesias, which may be difficult to distinguish from the peripheral neuropathies associated with HES.18

Etoposide (VP16-213), a podophyllotoxin derivative and topoisomerase II inhibitor that induces DNA damage, has been used in one patient. Oral and subsequently parenteral etoposide, administered over 18 months after hydroxyurea had to be terminated, effectively controlled symptoms and eosinophil counts, but had to be terminated because of marrow suppression.315

Alkylating agents may be used for HES. We have used oral pulse chlorambucil at doses ranging from 4 to 10 mg/m² daily for 4 consecutive days administered, depending on leukocyte counts, on an approximately every other month schedule. This therapy has been generally effective for more than 2 years and should be considered for HES patients, who are refractory to steroid therapy and unable to tolerate monotherapy with hydroxyurea.

Biologic Response Modifiers

Interferon-α, effective in both chronic myelogenous leukemia and multiple myeloma, has also been used recently to treat several HES patients.316-321 In one patient, HES-associated diarrhea and splenomegaly have subsided and eosinophilia has been suppressed with interferon-α administered subcutaneously at 8 million U/d and later continued at 2 million U/d for several months.319 One patient who initially responded to interferon-α was reported to have progression of HES after 6 months despite continued therapy.318 Successful control of HES with suppression of eosinophilia and reduction of hepatosplenomegaly has been reported in another two patients: one who received 3 years of interferon-α (7 and then 5 million U three times a week) and remained without eosinophilia for 1 year after cessation of interferon-α treatment, and another who, with cardiac disease, had clinical and echocardiographic improvements while on 1 year of interferon-α treatment (3 and then 2 millions U three times a week).322 A single patient with HES has been treated with both interferon-α and granulocyte colony-stimulating factor (G-CSF), but renal failure developed that was reversible after the administration of the two cytokines was stopped.320 Although interferon-α acts to inhibit eosinophilopoiesis, it is uncertain whether it also may exert suppressive effects on the activation of mature eosinophils.

Cyclosporin has been reported to be effective in four patients,225-322 and is often used with low-dose corticosteroids, although the duration of therapy has been less than 10 months in the published reports and the long-term efficacy and side effects of cyclosporin in HES patients remain to be ascertained. The rationale for the use of cyclosporin, an immunosuppressant, is based on observations of enhanced release of eosinophilopoietic cytokines from T-cell clones of HES patients.225

Pheresis

Leukapheresis of patients with HES will remove large numbers of eosinophils from the blood, but blood eosinophil levels rebound to their prepheresis levels within 1 day.26,324 An early report of the apparently beneficial application of leukapheresis in a patient with sulfisoxazole-induced hyper-eosinophilia26 is difficult to interpret because the natural history of the potentially self-limited drug-induced eosinophilia is unclear. In patients with HES, whereas single leukaphereses remove large numbers of circulating eosinophils, several pheresis sessions will not usually lead to a decrease in blood eosinophilia.26,324,326 Decreases in blood eosinophilia after five plasma and leukapheresis sessions over 2 weeks occurred in one patient, with a temporal course compatible with the removal of a circulating eosinophilopoietic factor.326 Continued plasma and leukapheresis in this patient was not by itself sufficient to control blood eosinophilia. Decreases in blood eosinophilia, albeit transient, have been noted to be greater with plasma exchange than with leukapheresis, suggesting that a removed plasma factor may have been sustaining the eosinophilia.26 It is unknown whether plasma or leukapheresis, by removing eosinophil-derived proteins circulating in HES patients,12,40 may be beneficial in helping prevent eosinophil-mediated injury to tissues. Thus, leukapheresis has no defined role in the long-term management of HES patients, and its use is usually restricted to emergency situations for patients developing very high eosinophil counts.307

Antiplatelet Agents and Anticoagulation

As noted above, thrombotic and thromboembolic events are frequent serious complications of HES. For this reason, anticoagulation is often administered to those with evidence of thromboemboli or with demonstrable intraventricular thrombi. Whether anticoagulation or antiplatelet agents are effective in this disorder has not been established, because a number of patients have continued to have thromboemboli despite adequate anticoagulation.18,31

Splenectomy

Some patients with HES and splenomegaly have undergone splenectomy. The spleen is a major site of localization of injected radiolabeled eosinophils in HES patients.31,36 and leukocyte and eosinophil counts increase, often dramatically, after splenectomy.27,300 In HES, splenectomy may ameliorate platelet sequestration because of hypersplenism and relieve
pain caused by splenic distention and splenic infarctions, which are common in those with splenomegaly. Although necessary if splenic rupture develops, splenectomy has no established role in the routine management of HES. Splenic irradiation has been without benefit in one patient.5,28

Bone Marrow Transplantation

Bone marrow transplantation has been used in only a few patients.1 One recipient of an allogeneic bone marrow transplant had hematologic recovery, but died 3 months after transplantation from diffuse cytomegalovirus infection.329 The risks of bone marrow transplantation appear not to be justified for HES patients unless they have an extremely aggressive course. A greater understanding of the mechanisms leading to overproduction of eosinophils and the development of organ damage in those with aggressive disease might provide a rationale for bone marrow transplantation, but such knowledge is currently incomplete.

Cardiac Surgery

Because many patients reported before the 1970s succumbed from complications of cardiac disease, a major advance in the care of HES patients with cardiac involvement is modern medical and surgical cardiac therapies. For those with marked valvular compromise or with endomyocardial thrombosis or fibrosis, cardiac surgery can provide substantial benefits. Because the usual valvular deficits arise from fibrosis of the chordae tendineae, mitral and/or tricuspid regurgitation can become severe. Mitral valve replacements, alone1,4,23,31,330,331 or with tricuspid valve repairs332 or replacements,23,333,334 have been reported with more than 50 eosinophilic patients.1 Mitral valve annuloplasty25 and tricuspid valve replacement335 have also been helpful. In addition, endomyocardectomy or thrombectomy, as used in patients with late-stage Loeffler's endomyocardial fibrosis, has been necessary and beneficial in some HES patients.1,4,23,31,331 Interestingly, restricting fibrosis has not recur at ventricular sites of surgical excision.1 One unusual patient with HES had both mitral and aortic stenosis, and because of fibrinous valve leaflet deposits containing eosinophils, fibroblasts, and histiocytes, required insertion of both mitral and aortic prostheses.23,336

A number of patients with HES who had mechanical valves inserted have experienced thrombosis on these valves, necessitating reoperations within months or even days to replace the mechanical valves with bioprostheses.14,57,336 One illustrative HES patient initially receiving a Björk-Shiley mechanical mitral valve prosthesis had a course complicated by recurrent episodes of valve thrombosis necessitating three subsequent reoperations until, finally, a St. Jude bioprostheses was inserted that did not become compromised by thrombus.330 Of three patients who received mitral valve prostheses at the NIH, two received porcine valves and experienced no thromboses, whereas the recipient of a Björk-Shiley mechanical valve developed valve thrombosis necessitating valve replacement after 4 months with a porcine allograft. This patient later died of Staphylococcus aureus prosthetic valve bacterial endocarditis.14 Death caused by thrombotic blockade of a Björk-Shiley mechanical valve has occurred in HES.331 Thus, the combined difficulties in preventing thromboemboli in HES, despite adequate anticoagulation, and the heightened susceptibility of mechanical valves to thrombus formation should lead to the deliberate use of bioprostheses, if such can be physically inserted.330 Patients with HES who have received valve replacements have experienced long-term improvement in their cardiac function and their overall well-being, making cardiac surgery a warranted modality in the longer-term care of HES.

CONCLUSION

HES, a heterogeneous collection of disorders marked by hypereosinophilia and organ damage, presents a number of challenges. The heterogeneity of patients with HES ranges from those with myelodysplastic features (splenomegaly, increased vitamin B12 levels, abnormal leukocyte alkaline phosphatase scores, and cytogenetic abnormalities) to those with benign courses (associated with increases in IgE, angiokeratoma, and corticosteroid-responsive eosinophilia). Given this heterogeneity, it is likely that more than one mechanism will be responsible for causing HES. Definition of the etiologic mechanisms may enable more targeted therapeutic approaches whether they act on IL-5, the IL-5 receptor, T-cell clones elaborating eosinophilopoietins, or other yet to be identified steps. The virtual absence of organ involvement in some with hypereosinophilia contrasts with the typical endomyocardial fibrosis found identically in HES and other eosinophilias. Identification of the factors responsible for cardiac localization of eosinophils may provide new avenues for therapies aimed at blocking eosinophil entry and activation within cardiac tissues. Because HES patients are not uniform, therapies based on current knowledge must be individualized with the goal of controlling organ damage in what remains an idiopathic, yet potentially chronic, syndrome.

ACKNOWLEDGMENT

We dedicate this review to the memory of Sheldon M. Wolff, MD, who, when he was Chief of the Laboratory of Clinical Investigation at the National Institutes of Health, established the research program responsible for investigating the largest series of HES patients at a single referral center and whose studies contributed immensely to delineating the manifestations of HES and establishing new approaches to its therapy. We thank and gratefully acknowledge the assistance and cooperation of a number of eosinophilic patients and their physicians and nurses.

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The idiopathic hypereosinophilic syndrome

PF Weller and GJ Bubley