Observation

Cerebral Arteriolar Thromboembolism in Idiopathic Hypereosinophilic Syndrome

Mikayel Grigoryan, MD; Scott D. Geisler, MD; Erik K. St. Louis, MD; Gary L. Baumbach, MD; Patricia H. Davis, MD

Objective: To describe imaging findings as well as post-mortem brain and cardiac pathology in a patient with fulminant idiopathic hypereosinophilic syndrome.

Design: Case report.

Setting: University hospital.

Patient: A 48-year-old right-handed man with hypereosinophilia, rapidly progressive encephalopathy, and focal neurological deficits who died 22 days after presentation.

Main Outcome Measures: Physical examination, radiologic, and neuropathologic examination results.

Results: Imaging of the brain revealed bihemispheric ischemic changes in and beyond the watershed distributions. Pathology review demonstrated mural cardiac thrombus that likely caused cardioembolism as well as diffuse microangiopathy despite resolution of the hypereosinophilia.

Conclusions: Timely recognition of idiopathic hypereosinophilic syndrome may enable aggressive treatment prior to widespread cardioembolism and degranulation that result in devastating cerebrovascular complications.

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DIOPATHIC HYPEREOSINOPHILIC syndrome (IHES) is characterized by a persistent eosinophilia greater than 1500/µL (to convert to ×10³/L, multiply by 0.001) for more than 6 months, causing systemic dysfunction of multiple organs without evidence of associated allergic reactions, parasitic infections, connective tissue diseases, or malignancies. neurologic involvement is common in IHES. Moore et al documented neurologic dysfunction in 65% of their 52 patients with IHES. Of these, 50% had peripheral neuropathy, 12% had cerebrovascular ischemia, and 10% had encephalopathy. We report post-mortem brain and cardiac pathology from a patient with a rapidly progressive encephalopathy due to IHES.

REPORT OF A CASE

A 48-year-old right-handed man with a history of hypertension and obesity presented to his primary care physician with a 5-month history of an unintentional 60-pound weight loss and a 5-day history of distal lower extremity paresthesias and fatigue. His fasting blood glucose concentration was 388 mg/dL (to convert to millimoles per liter, multiply by 0.0555). He was treated with glyburide. The next day, the patient had brief episodes of disorientation and unsteadiness and was admitted to another hospital. Neurological and general medical examination results were normal. Laboratory testing demonstrated a white blood cell count of 17,900/µL with hypereosinophilia of 4100/µL (normal range, 0-200/µL), or 23% of all white blood cells. Head computed tomography (CT) showed an old left internal capsule lacunar infarct.

On the third day following presentation, the patient became more somnolent and disoriented and developed left-sided hemiparesis and hemispatial neglect. Results of a repeated head CT were unchanged. An electroencephalogram demonstrated mild generalized background slowing without epileptiform activity. Carotid duplex study results were unremarkable.

The next day, the patient developed dysarthria and right hemiparesis. Another head CT showed new ischemic changes in the centrum semiovale. He was transferred to our hospital.

On admission, the patient was somnolent and could not follow commands. No cranial nerve deficits were noted. Motor examination showed diffuse hypotonia and weakness, worse in the arms. Muscle stretch reflexes were normal in the upper extremities and reduced in the legs with bilateral extensor plantar signs.

Author Affiliations: Departments of Neurology (Drs Grigoryan, Geisler, St. Louis, and Davis), and Pathology (Dr Baumbach), University of Iowa Hospitals and Clinics, Iowa City.
Hematologic studies showed persistent leukocytosis and eosinophilia (peaking at 5700/µL). Troponin I and creatine kinase–MB concentrations were significantly elevated. The patient’s erythrocyte sedimentation rate was 58 mm/h (normal, 0-15 mm/h) and C-reactive protein concentration was 9.3 mg/L (normal, <0.5 mg/dL) (to convert to nanomoles per liter, multiply by 9.524). Liver enzyme levels were moderately abnormal. Hemoglobin A1C was 8.2% (normal, 4.8%-6.0%). Abnormal indices of immune function included an IgE concentration of 3168 µg/L (normal, 0-1500 µg/L) (to convert to milligrams per liter, multiply by 0.001), an IL-4 (interleukin 4) count of 4000 (normal, 0), and an IL-5 (interleukin 5) count of 250 (normal, 0). A peripheral blood smear demonstrated increased eosinophils with rare immature and partially degranulated forms. Results of other tests, including those for cytoplasmic antineutrophil cytoplasmic antibody, perinuclear antineutrophil cytoplasmic antibodies, IgG, thyroid-stimulating hormone, free T4, free T3, and rheumatoid factor, were normal.

Contrast-enhanced magnetic resonance imaging revealed ischemic changes in and beyond the watershed distributions (Figure 1). Catheter cerebral angiography results were normal. A head CT performed 3 days after magnetic resonance imaging showed new lesions outside of the watershed distribution.

On cardiac evaluation, an electrocardiogram showed sinus tachycardia with diffuse anterolateral ST segment depression. A transesophageal echocardiogram demonstrated mild left ventricular dysfunction (ejection fraction, 40%) with segmental inferior and posterior hypokinesia and biventricular enlargement, without evidence of cardiac or aortic mural thrombus or vegetations.

Cerebrospinal fluid analysis demonstrated an elevated protein concentration (138 mg/dL; normal range, 15-45 mg/dL) with a normal cell count and glucose concentration. Bacterial, fungal, and acid-fast bacilli cultures and cryptococcal antigen analysis results were negative. Electromyography documented an axonal polyneuropathy with acute denervation of the patient’s distal leg muscles.

Bone marrow aspirate revealed hypercellular marrow and marked eosinophilia (30%) without evidence of clonality or karyotypic abnormalities. Results of CT of the chest, abdomen, and pelvis were normal.

Treatment with intravenous methylprednisolone was initiated. The patient’s eosinophil count normalized within a day while his troponin I concentrations decreased but remained mildly elevated. Despite 12 days of treatment, the patient remained unresponsive and quadraparetic. He received palliative care and died 22 days following presentation.

The autopsy was limited to the brain and heart. Multifocal subcortical regional softening and hemosiderin staining were seen in the frontal, parietal, and left temporal lobes. On microscopic examination (Figure 2), there were multifocal small-vessel ischemic infarctions of varying ages with fibrin and platelet occlusion of small-caliber arterioles. No intravascular eosinophils or parenchymal eosinophilic infiltrates were noted.

Examination of the heart showed multifocal myocardial infarction of the anterior and posterior ventricles and septum. Careful gross inspection of the endocardium revealed no lesions. However, several organizing thrombi on the endocardial surface were identified in microscopic sections (Figure 3). In addition, several small arterioles were occluded with platelets. No eosinophilic infiltrates were seen.

**COMMENT**

To our knowledge, there are only 3 previous reports of brain pathology in IHES. Surgical biopsy findings from 1 patient demonstrated infarction with abundant intra-
vascular eosinophils. Autopsy cases have shown acute and chronic ischemic brain lesions in borderzone areas as well as endocardial fibrosis and a mural thrombus in the left ventricle, suggesting cardioembolism as an etiology of cerebrovascular complications.

Pathologic investigation in our patient demonstrated endocardial mural thrombosis that was only identified after a careful review of microscopic sections; it was not detected by echocardiography or gross visualization of the heart in the autopsy. This endocardial mural thrombosis was likely the etiology of the borderzone infarctions identified early on; however, multiple lesions, identified by repeated CT, were outside the watershed distribution. Pathologic examination of the vessels did not reveal whether the endothelial changes were due to in situ thrombosis or tiny emboli. There were no intraluminal or parenchymal eosinophils in the brain or heart. Furthermore, the patient failed to improve clinically despite normalized eosinophil counts following immunosuppressive treatment, implying that steroids were given at a time when damage may not have been reversible. This suggests that cerebrovascular endothelial injury and neurotoxicity from eosinophilic degranulation could also have directly contributed to the encephalopathy in our pa-
tient. With this mechanism of clinical deterioration, antithrombotic therapy could be considered in similar cases in the future.

The characteristic manifestations of cerebral eosinophilic neurotoxicity were initially described as the Gordon phenomenon from intraventricular injection of Hodgkin disease aspirates into rabbit cerebrospinal fluid. Eosinophil-derived neurotoxin, a ribonuclease, was later identified as the primary mediator. Two eosinophil ribonucleases with deleterious effects on axons have been identified: major basic protein and eosinophilic cationic protein. Major basic protein toxicity is nonspecific and damages multiple cell types and organs. Intravascular release of major basic protein damages endothelial cells, causing thrombosis and embolic infarctions. Eosinophilic cationic protein has been shown to be responsible for a hypercoagulable state, which may further potentiate thromboembolic phenomena. Endothelial damage in peripheral nerves causes edema and axon loss.

The etiology of IHES has not been elucidated. Interleukin 5, which has a selective role in eosinophil maturation, differentiation, mobilization, activation, and survival, appears to contribute to the pathogenesis of some phenotypes of the IHES, thus making its inhibition a logical therapeutic target. Recently, a randomized, double-blind, placebo-controlled trial evaluated the safety and efficacy of an anti–IL-5 monoclonal antibody enabling physicians to provide 2 aggressive treatments prior to widespread cardioembolism, which could result in irreversibility. The pathology in our patient demonstrated mural cardiac thrombus that likely caused cardioembolism. Prompt recognition of IHES may enable physicians to provide 2 aggressive treatments prior to widespread cardioembolism, which could result in irreversible cerebrovascular complications.

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Correspondence: Mikayel Grigoryan, MD, Department of Neurology, University of Iowa Hospitals and Clinics, 200 Hawkins Dr, Iowa City, IA 52242 (mikayel-grigoryan@uiowa.edu).

Author Contributions: Study concept and design: Grigoryan, Geisler, St. Louis, and Davis. Acquisition of data: Grigoryan, Geisler, St. Louis, and Baumbach. Analysis and interpretation of data: Grigoryan, Geisler, St. Louis, Baumbach, and Davis. Drafting of the manuscript: Grigoryan, Geisler, and St. Louis. Critical revision of the manuscript for important intellectual content: Grigoryan, Geisler, St. Louis, Baumbach, and Davis. Administrative, technical, and material support: Grigoryan, Geisler, St. Louis, and Baumbach. Study supervision: Davis.

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