Cerebral Infarcts in the Setting of Eosinophilia

Three Cases and a Discussion

Hartej S. Sethi, MBBS; James W. Schmidley, MD

Objective: To describe 3 cases of stroke associated with hypereosinophilic syndrome and discuss the pathogenesis of such strokes.

Design: Retrospective medical record review.

Setting: University hospital.

Participants: Three patients who had strokes temporarily correlating with eosinophilia with no other obvious causes of stroke.

Intervention: Retrospective review of the hospital course, laboratory data, imaging, treatment, and outcome.

Results: All 3 patients had multiple strokes in both hemispheres. Two patients with modest eosinophilia that was controlled quickly had infarcts mostly in arterial border zones and had good outcomes. The third patient with severe and more refractory eosinophilia had a poor outcome.

Conclusions: Cardiac emboli and direct eosinophil toxicity contribute to strokes in hypereosinophilic syndrome. Prognosis is variable with use of anticoagulation and antiplatelet agents but rapid lowering of the eosinophil count results in a better outcome.

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REPORT OF CASES

CASE 1

A 52-year-old, right-handed man presented 4 days after sudden onset of right-sided weakness and slurring of speech. His medical history included hypertension, emphysema, smoking, and alcohol abuse. On neurological examination, he had dysarthria, right facial droop, and right-sided weakness affecting the leg more than the arm. His white blood cell (WBC) count was 16,900/µL (to convert to \( \times 10^9/\text{L} \), multiply by 0.001) with 44.6% eosinophils. Results of cerebrospinal fluid testing were normal. Magnetic resonance imaging (MRI) of the brain showed multiple areas of restricted diffusion, representing infarctions, in anterior and posterior border zones (Figure 1). Findings of magnetic resonance angiography of the head and neck and transesophageal echocardiography were unremarkable. An extensive search for the cause of eosinophilia including stool testing for ova and parasites, cryptococcal antigen, thyroid studies, human immunodeficiency virus, and bone marrow biopsy were unremarkable. The patient was treated with aspirin. The eosinophil count declined over the following few weeks without intervention. Two months after discharge, he had minimal residual right-sided weakness and his WBC count was 9,500/µL with 26% eosinophils. The patient did not keep further return appointments.

CASE 2

A 47-year-old previously healthy man presented with right flank and leg pain. On examination, he was febrile with trace pedal edema, positive Homan sign, and benign findings on abdominal examination. Findings of neurological examination were unremarkable. His WBC count was 27,000/µL with 70% eosinophils. Electrocardiogram and cardiac enzyme testing revealed anterior wall myocardial infarction but findings of coronary angiography were normal. Venous dopplers of the legs revealed bilateral deep venous thrombosis. With initiation of anticoagulation, the pain resolved and the patient was discharged. A week later he was back with shortness of breath and bilateral leg weakness. Neurological examination...
A 46-year-old woman presented to a community hospital with chest pain. She reported having had flulike symptoms and a diffuse red rash 2 weeks prior. Findings of electrocardiogram and cardiac enzyme testing were consistent with inferior wall myocardial infarction. Coronary angioplasty with stent placement did not relieve her chest pain. Two days later, she became somnolent and developed spasticity in all extremities. At this point, she was transferred to our institution. On examination, she did not respond to verbal stimuli but painful stimulation induced moaning and decorticate posturing. All extremities were severely spastic, with exaggerated reflexes and bilateral ankle clonus. Her WBC count was 73,000/µL with 93% eosinophils. No cause for eosinophilia was discovered. Transthoracic echocardiogram showed an ejection fraction of 45% with no mural thrombi or valve abnormalities. Bone marrow aspiration did not show any abnormal cell populations. Magnetic resonance imaging of the brain revealed multiple acute strokes (Figure 2). She did not respond to steroid treatment. Imatinib therapy was initiated, and her eosinophil count slowly trended down. Three weeks into her hospital course, she developed generalized flaccidity. Nerve conduction studies showed severe axonal neuropathy. No eosinophilic infiltrate or inflammation was seen in the nerve biopsy. Muscle biopsy showed fiber size variation and minor denervation changes. Seven months after initial presentation, her eosinophil count was normal. She was still in a nursing home, with minimal improvement. She could only say “yes” and “no” reliably, was unable to lift any limb against gravity, and was hypotonic and areflexic.

The presence of an absolute eosinophil count greater than 1500/µL for 6 months without any known triggers or evidence of related end-organ damage are the criteria for HES.1

A large series of patients with HES in 19722 noted high prevalence of neurological sequelae, mainly peripheral neuropathy, stroke, and encephalopathy.

Stroke is the most devastating neurological consequence of eosinophilia. Stroke incidence in HES has been estimated to be around 12%.3,4 Case series of eosinophilia-related strokes have projected a common theme: multiple strokes in different vascular territories.4 In early HES, strokes are small and occur in the arterial border zones. If eosinophilia persists, larger cortical and subcortical areas are involved. Cardiac embolism is the likely cause. Eosinophilia can damage the endocardium and myocardium, rendering the heart a potential source of emboli.5 Toxicity by release of eosinophilic basic proteins initiates endomyocardial necrosis. Autopsies of these patients have shown eosinophils and their products in the endomyocardium and in the endothelium of coronary vessels.6 This damage occurs early in the course and is usually subclinical. It progresses in 4 to 6 weeks to a second, thrombotic, stage that results from excessive release of tissue factor by the damaged tissue and from eosinophils,5,7 causing distant embolism. This is followed by the final stage of endomyocardial fibrosis. At this stage, TTE reveals a restrictive cardiomyopathic pattern. Cardiac MRI may be the more sensitive noninvasive modality for de-
Protecting ventricular thrombi and myocardial inflammation. Endocardial biopsy remains the criterion standard for diagnosis of endomyocardial fibrosis.

In the first 2 stages of HES, when a patient presents with stroke, TTE findings are typically nonrevealing, as in our cases. Half of patients with eosinophilia have cardiac abnormalities by echocardiography. Lack of evidence of cardiac disease in some patients with HES suggests that alternate causes must contribute to some of the early strokes. Eosinophils have the potential to cause local thrombogenicity. They store tissue factor in their specific granules, and they can induce tissue factor secretion by the endothelium. This could be an important cause of small strokes that are limited to the border zones early in HES. Such small infarcts were seen in our first 2 patients and are generally associated with a good prognosis. Patients with multiple emboli tend to have a poor prognosis, as seen in our third patient.

A syndrome of generalized encephalopathy has been described in a small percentage of patients with HES. The hallmark of this is behavioral disturbances and upper motor neuron signs. Most of these studies were from the pre-MRI era. An imaging series published in 2001 described 3 patients with eosinophilia-related encephalopathy in whom sequential MRIs of the brain revealed multiple lesions in border zones that worsened with increasing eosinophilia and improved with treatment. Pathology on one of these cases was consistent with cerebral infarctions. It seems likely that multiple small infarcts cause eosinophilic encephalopathy, although they are not always recognized clinically.

Not surprisingly, treatment with anticoagulants has been used but the response to anticoagulation alone has been dismal. This underscores the importance of rapacuronium and other muscle relaxants. Patients with multiple emboli tend to have a poor prognosis, as seen in our third patient.

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Not surprisingly, treatment with anticoagulants has been used but the response to anticoagulation alone has been dismal. This underscores the importance of rapidly lowering the eosinophil count. For effective treatment strategies to lower eosinophil count, better understanding of the pathophysiology of HES is needed. It can be divided on the basis of etiology into lymphocytic and myeloproliferative variants. The former, which is more common, results from increased secretion of eosinophilic cytokines like interleukin 5 by T lymphocytes. Nearly 30% of patients with idiopathic HES have the lymphocytic variant. The eosinophilia in these patients is typically less severe than in those with myeloproliferative HES but is harder to treat. The myeloproliferative variant is found in 3% to 27% of HES cases in different series. It results from clonal expansion of eosinophil precursors due to various mutations. The best studied of these is the FIP1L1 gene translocation to platelet-derived growth factor receptor α (PDGFRα) gene, resulting in a fusion product. This product constitutively activates a tyrosine kinase domain on PDGFRα, activating the downstream second messenger systems and enhancing proliferation and survival of eosinophil precursors. PDGFRα tyrosine kinase is competitively inhibited by imatinib mesylate. It binds to the adenosine triphosphate–binding site on PDGFRα tyrosine kinase and prevents tyrosine phosphorylation. Its potential cardiotoxicity notwithstanding, imatinib has been extremely successful in the treatment of HES related to FIP1L1 mutation. In the absence of this specific cause, steroids and nonspecific immune suppression remain the mainstays of treatment.

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Correspondence: Hartej S. Sethi, MBBS, Department of Neurology, University of Arkansas for Medical Sciences, 4301 W Markham St, Slot 500, Little Rock, AR 72205 (dhartejesinh@gmail.com).

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REFERENCES