Cerebral Infarcts in the Setting of Eosinophilia

Three Cases and a Discussion

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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 $10^9/L$, 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 was discharged to inpatient rehabilitation and continued taking low-dose steroids. At the 1-year follow-up, her WBC count had dropped to 18 900/µL with 57% eosinophils (international normalized ratio, 1.9). Computed tomography angiography of the chest revealed multiple small pulmonary emboli. Results of a hypercoagulable panel, rheumatological panel, Coxsackie viral antigen test, parvovirus B19 antigen test, Rocky Mountain spotted fever (RMSF) antigen test, and stool test for ova and parasites were all unremarkable. An MRI of the brain showed multiple small acute infarcts in all arterial border zones (Figure 1). Transthoracic echocardiogram (TTE) revealed mildly reduced ejection fraction but no evidence of fibrosis or thrombosis. Bone marrow biopsy showed 70% cellularity with increased eosinophil precursors but no abnormal cell populations. The patient was diagnosed with hypereosinophilic syndrome (HES), and treatment with oral steroids was started. The eosinophilia responded well, and the absolute eosinophil count normalized within 3 days. The patient was discharged from the hospital, rendering the heart a potential source of emboli.5 If eosinophilia persists, larger cortical and subcortical areas are involved. Cardiac embolism is the likely cause. Eosinophils 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 endomycardium and in the endothelium of coronary vessels.8 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,6 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 detecting endomyocardial fibrosis in HES.9

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 endomycardium and in the endothelium of coronary vessels.8 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,6 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 detecting endomyocardial fibrosis in HES.9

CASE 3

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.

Figure 1. Diffusion-weighted magnetic resonance image of patients 1 (A) and 2 (B) showing border zone infarcts.

Figure 2. Diffusion-weighted magnetic resonance image showing multiple embolic strokes in patient 3.
tecting 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 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. It presents, 4301 W Markham St, Slot 500, Little Rock, AR 72205 (drhartejsingh@gmail.com).

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REFERENCES