Global Hypoperfusion: A New Explanation of Border Zone Strokes in Hypereosinophilia

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Received 10 April 2014; revision 11 May

2014; accepted 11 May 2014

doi: 10.1111/cns.12293

The neurological deficiencies due to hypereosinophilia were first systemically depicted in 1975 with a series of pathology results, including the finding of cerebral microthrombi [1]. The MRI imaging then demonstrated bilateral border zone infarction as a potential complication of hypereosinophilia [2]. The pathogenesis still remains controversial [3,4].

We report a case with border zone strokes in the settings of hypereosinophilia. Perfusion weighted imaging (PWI) showed global hypoperfusion and susceptibility weighted imaging (SWI) showed venous engorgement in the bilateral centrum semiovale and cortical area. With proper treatment, perfusion recovered as the symptoms alleviated. These findings possibly lead to a new explanation of border zone strokes in hypereosinophilia.

A 69-year-old right-handed male farmer with a 40 years history of cigarette-smoking was admitted complaining to have suffered with progressive limb weakness for the past 8 days. The patient also reported to have had diarrhea for 1 week about half a month prior to the onset. Prior medical history was negative. A general physical examination showed normal blood pressure (120/74 mmHg), pulse rate (66 beats/min), respiratory rate (18/min), and temperature (36.9°C). Neurological assessments demonstrated weakness of both lower extremities and the right upper extremity (3/5). The bilateral tendon reflex was reduced.

Brain MRI (3.0T) was performed on admission. Diffusion weighted imaging (DWI) revealed multiple ischemic lesions in the border zone (Figure 1A). Global hypoperfusion was displayed by delayed mean transit time (MTT; Figure 1D, F) and $T_{\max}$ (Figure 1E), especially in the bilateral watershed area, hemisphere cortical areas, and the cerebellum. However, the cerebral blood flow (CBF) and cerebral blood volume (CBV) did not show significant decrease. SWI revealed widespread venous engorgement in the bilateral centrum semiovale and cortical area (Figure 1C). Neither arterial narrowing nor a single fragile plaque was indicated

by cervical CT angiography or time-of-flight magnetic resonance angiography (TOF-MRA). Electrocardiography (ECG), transthoracic echocardiogram (TTE) and cardiac CT detected no myocardial fibrosis or thrombosis.

The peripheral blood eosinophil count was $5520/\text{mm}^3$ (normal range, $0\text{--}1000/\text{mm}^3$) with an extremely high IgE level above 2000 IU/mL (normal range, $<100\text{ IU/mL}$). Further tests revealed a mild microcytic anemia and a positive stool occult blood test. The erythrocyte sedimentation rate (ESR) was 22 mm/h (normal, $<20\text{ mm/h}$). Troponin I (normal, $<0.06\text{ ng/mL}$) was also increased to 0.31 ng/mL . As a result, an extensive investigation for the cause was conducted. A blood viscosity test was normal. Cerebrospinal fluid (CSF) analysis demonstrates only an increased IgG level of 65 mg/L (normal, $12\text{--}33\text{ mg/L}$). Bone marrow aspirate revealed no evidence of clonally abnormalities. Other diagnostic tests, including thyroid function tests, CMV tests, HSV tests, a serum lipid profile, coagulation studies and detection of self-immune antibodies were all unremarkable. Fluid supplementation, aspirin, and statin therapy were immediately provided with no significant improvement.

Finally, ancylostome eggs were detected in the patient's feces. After antiparasite therapy, the limb weakness abated dramatically. One month later, with a normal eosinophil count ($540/\text{mm}^3$) the muscle strength in all of his extremities were normalized. The brain MRI was repeated and displayed a complete perfusion recovery with shorter MTT (Figure 1G, I) and $T_{\max}$ (Figure 1H) compared with pretreatment images, but the old infarctions remained (Figure 1B). At the time of writing this report, the patient has not reported a recurrence of symptoms.

In this case study, we first depict the PWI and SWI for a patient with hypereosinophilia-related strokes, affecting bilateral border zone areas. Historically, watershed infarcts have been related to hemodynamic-related disorders causing perfusion deficiency,

Figure 1 (A) Diffusion weighted imaging (DWI) revealing multiple ischemic lesions in the border zone on both sides, including MCA-ACA, MCA-PCA watershed territories. (B) Flair imaging showing bilateral border zone infarctions after 1 month. (C) Susceptibility weighted imaging demonstrating deep medullary and cortical venous engorgement. (D, E) perfusion weighted imaging showing severe perfusion deficiency marked as prolonged mean transit time (MTT) and T_{max} of the whole brain which was recovered 1 month following treatment (G, H). (F) Showing cerebellum hypoperfusion indicated by prolonged MTT compared with (I).

such as severe stenosis of extracranial or intracranial arteries, cardiac arrest and systemic hypotension. Without these disorders, however, our patient still demonstrated perfusion deficits of the whole brain. And these abnormality fully recovered consistent with the blood eosinophil count normalized. Taken together, the perfusion abnormality may be attributed to hypereosinophilia.

Other investigators have reported that cardiac embolism is the likely cause of hypereosinophilia-induced border zone infarctions [4]. The observation that eosinophils can damage the endocardium and myocardium by direct infiltration and secretion of cytotoxic proteins, renders the heart a potential source of emboli [3,5]. Indeed, hypereosinophilia frequently coexists with endomyocardial fibrosis and tropical endomyocardial thrombi [1]. However, this cardioembolic theory does not seem to apply in all instances. Some previous cases [6,7] showed the dementia and diffused slow-wave on the EEG, which were reversible after steroid therapy. This phenomenon cannot be explained by cardio-embolism.

According to our findings, we hypothesized that impairment of the microcirculation might be the key factor contributing to the perfusion deficiency. First, the global prolonged MTT indicated either hyperviscosity of blood constituent or the compromised patency of global small vessels. As no evidence of hyperviscosity or systemic hypotension was present, the latter one seems more reasonable. Second, the global venous engorgement can also be explained by slower microcirculation which cause accumulation of deoxygenated hemoglobin. Moreover, the cerebellar involvement displayed in PWI, which was first described as the “Gordon

phenomenon” [8] in hypereosinophilia, specifically argues that the neurotoxicity associated with eosinophil accumulation plays a vital role in hypoperfusion.

In fact, some studies have shown that eosinophils can cause inflammation and damage in small vessels [9]. The deposition of circulating eosinophil granule contents, including major basic protein (MBP), eosinophil cationic protein (ECP), and eosinophil peroxidase (EPO), can cause exfoliation of the endothelial layer [9], inhibit endothelial cell growth [10] and ultimately damage the integrity of the endothelium. Eosinophil degranulation can also result in smooth muscle contraction, with subsequent vasospasm [9]. Not surprisingly, damaged endothelium also results in coagulation when there is a disruption in thrombomodulin function [9]. Ultimately, the decrease in capillary perfusion can result in *in situ* microthrombi.

In conclusion, our case indicates that watershed infarction is a potential complication of hypereosinophilia. Evidence of global hypoperfusion involvement is also provided. We acknowledge the possibility that cardiogenic microembolism may also have occurred. However, in our opinion, the reversible blood flow restriction and *in situ* thrombi formation under impaired microcirculation also deserves attention, as cardiac complications may not be the actual cause, but the collateral victim to the brain.

Conflict of Interest

The authors declare no conflict of interest.

Sources of Funding

Dr. Lou is supported by grants from Zhejiang Provincial Natural Science Foundation of China [grant number LR12H09001]; the National Natural Science Foundation of China [grant number

81171095]; and the Health Bureau of Zhejiang Province [grant number WKJ2010-2-010]. Dr. Tong is supported by grants from Zhejiang Provincial Natural Science Foundation of China [grant number LQ13H090002].

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