Idiopathic Hypereosinophilia Syndrome with Loeffler Endocarditis, Embolic Cerebral Infarction, and Left Hydranencephaly: A Case Report

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Abstract-

Purpose: Idiopathic hypereosinophilia syndrome (iHES) is classically defined as prolonged peripheral eosinophilia and multiple organ involvement. The involvement of the heart can lead to intraventricular thrombus because of infiltration of the endomyocardium by eosinophils. Cerebral infarction has been ascribed to thromboembolic events originating from intraventricular thrombus.

Case report: A 67 year-old woman with hypereosinophilia for 6 months presented acute weakness of the right limbs. Left hydranencephaly and absence of the left internal carotid artery were found on brain computed tomography. Brain magnetic resonance imaging (MRI) showed multiple infarctions at bilateral hemispheres. An intraventricular thrombus was detected both in transesophageal echocardiography and in heart MRI. Hypereosinophilia responded well to steroid use and warfarin was used for stroke prevention.

Conclusions: Complete evaluation of systemic involvement in iHES is mandatory and early intervention may prevent deterioration of this disease. Both cardiogenic embolism and endothelial damage related to circulating eosinophils may contribute to the occurrence of stroke in this patient.

Key Words: Hypereosinophilia, Cardiac thrombus, Embolic stroke, Hydranencephaly

Acta Neurol Taiwan 2009;18:207-212

INTRODUCTION

Idiopathic hypereosinophilia syndrome (iHES) is a complex disorder defined by; (1) sustained elevation of eosinophils (eosinophils >1500 /mm³) without identifiable secondary cause (such as parasitic or allergic dis-
ease) for at least six months, and (2) evidence of multiple organ involvement\(^{(1)}\). The second criterion excludes patients that are clinically benign and may remain asymptomatic for decades. When both clinical and laboratory evaluations do not clearly identify a secondary or a clonal cause, a working diagnosis of idiopathic eosinophilia is plausible\(^{(2)}\).

Loeffler endocarditis is a restrictive cardiomyopathy characterized by hypereosinophilia and fibrotic thickening of portions of the heart, commonly with large mural thrombi\(^{(3)}\). Cardiovascular complications cause the majority of morbidity and mortality in iHES. In a large series of 52 iHES patients, peripheral neuropathy was the most frequently documented neurological abnormality\(^{(4)}\). Cerebral infarctions are mostly due to either thromboembolism from endomyocardial fibrosis or vascular endothelial damage related to hypereosinophilia\(^{(4)}\).

Hydranencephaly is a rare neurologic condition in which most of the cerebral hemispheres are absent and the brain tissue is replaced with fluid. An occlusion of the carotid artery is thought to be the underlying mechanism\(^{(5)}\). Here we report a case of iHES with left hydranencephaly and bilateral hemispheric thromboembolism secondary to Loeffler endocarditis with mural thrombus.

**CASE REPORT**

A 67 year-old left-handed woman was brought to our emergency department with the chief complaint of a confusional state and weakness of the right limbs of acute onset for two days. On examination, the patient was awake and was able to respond to simple questions, but her articulation was slightly slurred. Her Glasgow Coma Scale was E4V4M6. Her muscle power was graded as one and four (MRC grade) for the right upper and lower limbs, respectively. Hoffmann and Babinski signs were present on the right side. Under the impression of stroke, computed tomography was performed and revealed focal encephalomalacia corresponding to the territory of left middle cerebral artery (Fig. 1A). Bone window from the petrous portion of the temporal region showed an absence of left internal carotid canal (Fig. 1B), implicating occlusion of the left internal carotid artery (ICA) and consequent hydranencephaly. No hypodensity of a possible recent onset was found on this CT scan.

The woman had been born uneventfully at term. She was the first daughter among four otherwise healthy siblings from nonconsanguineous healthy parents. The parents noticed that she was “a bit clumsy” at ~4 years of age. Walking was interfered by right hemiparesis with an equine deformity at the ankle. At the age of 10, the patient experienced convulsions, but has remained seizure free after taking diphenylhydantoin. She reported difficulties in fine motor tasks of her affected right hand but had no major disabilities in daily activities.
She experienced nonproductive cough six months prior to this visit. Hypereosinophilia was found during blood testing. The leukocyte count was 9950 mm⁻³, with 19.8% eosinophils. She denied using any medication except diphenylhydantoin in the past two years. Since the cause of hypereosinophilia was still under investigation, she did not receive any treatment before this admission.

After admission, she was still confused but could follow orders without much difficulty. Neurological examination revealed slurred speech and mild dysphagia. Her muscle power remained the same compared with the records from the emergency room. Hoffmann and Babinski signs were present in the right limb. There were no signs of cerebellar or extrapyramidal dysfunction. Laboratory test results were as the following: haemoglobin, 11.8 g/dL; hematocrit, 34.2%; leukocyte count 21300 mm⁻³ with 45% eosinophils, and platelets, 232K/mm³. Chemistry panel results were normal both in renal and liver function tests. Elevated IgE (1350 IU/mL) was found but IgG, IgA and IgM were within normal limits. The erythrocyte sedimentation rate was 59 mm/h and C-reactive protein level 24.8 mg/L. Autoimmune profiles of antinuclear antibody, anti-α streptolysin O titer, rheumatic factor, serum protein electrophoresis, C3, C4, double strand DNA, P- and C- anti-neutrophil cytoplasmic antibodies, anti-ENA screening, anti-beta 2 glycoprotein, anti-cardiolipin IgG and IgM, lupus anticoagulants were all negative. The survey for possible allergens by the specific IgE in vitro test (MAST) was negative. Stool examinations revealed no parasite ova. Blood smear showed eosinophilia with normal WBC morphol-

The chest radiograms revealed bilateral pleural effusion and mild cardiomegaly. The diffusion weighted images (DWI) of the brain performed two days after ictus revealed multiple high signal intensity lesions in both hemispheres (Figs. 2A-B). Magnetic resonance angiography (MRA) showed the absence of left ICA and middle cerebral artery (MCA) (Fig. 2C). The distribution of ischemic lesions and clinical presentation were highly suggestive of embolic events.

There was no significant arrhythmia on 24-hour holter monitoring. Two-dimensional echocardiography revealed thickening of the left ventricular (LV) endocardium, reduction of LV cavity, and a ~7.8-cm², flat, immobile thrombus extending from the apical to the posterobasal portion (Fig. 3A). Cardiac MRI showed high signal intensity on T2 weighted image (T2WI) (Fig. 4A).
and low signal intensity on T1WI (Fig. 4B), compatible with an intraventricular thrombus. Extracranial duplex Doppler study revealed no difference of peak systolic or diastolic flow velocity between bilateral external and common carotid arteries (CCA). However, markedly reduced ICA flow was noted. The peak systolic flow velocities were 48 cm/s and 7 cm/s, and diastolic flow velocities 20 cm/s and 1 cm/s, for the right and left ICA, respectively. The caliber of the right and left extracranial ICA was 0.75 and 0.57 cm, respectively. Transcranial Doppler study could clearly identify the right anterior, middle, and posterior cerebral arteries (ACA, MCA, and PCA) and the left posterior cerebral artery, but failed to show the left anterior and middle cerebral arteries, suggesting occlusion of the left ICA.

Hydrocortisone 100 mg Q12H infusion was given after the diagnosis of iHES. The eosinophil count declined to 1.5% three days later. Hydrocortisone had been used for six days before it was shifted to prednisolone, which was started at 30 mg per day and then tapered to a maintenance dose of 10 mg per day for seven months. Heparin followed by warfarin was given.

Figure 3. (A) Two-dimensional echocardiogram of the left ventricular (LV) apical two chamber view shows endocardial thickening, reduced size LV cavity, and a large flat LV apical thrombus; (B) Echocardiogram performed two months later shows reduced size of the thrombus.

Figure 4. Cardiac MRI reveals one intraventricular mass-like lesion (2.7 × 2.3 cm²) in the left ventricle apical region with slight hypointensity on T2WI (A, arrow) and hyperintensity on T1WI (B, arrow).
for stroke prevention. Surgical intervention for cardiac thrombi removal was suggested but was declined by the patient. After nine months of follow-up at outpatient clinic, the neurological condition improved but the self-care of daily living was not totally independent. There was still dysarthria during the conversation, although she was able to communicate with others without difficulty. The follow-up cardiac echo showed that the cardiac thrombus was smaller, measuring 5.87 cm$^2$ (Fig. 3B), and the left ventricular ejection fraction had returned to 81%.

**DISCUSSION**

The differential diagnosis of the reported case may include the other established causes of ventricular mural thrombus and peripheral blood eosinophilia. Inasmuch as possible causes of both clonal and nonclonal hypereosinophilia had been ruled out, iHES with endomyocardial disease was considered$^{49}$. Although a disease duration of six months is required to establish the diagnosis of HES, a recent review has advised that iHES be suspected if two of the three criteria are fulfilled with a chronic and unremitting clinical course$^{49}$.

The patient’s hydranencephaly is most likely ascribable to a vascular lesion of the brain, such as occlusion or congenital agenesis of the ICA$^{10-12}$. The clinical history of an acute event of right limb clumsiness during childhood indeed implicated an old stroke for this patient. This childhood-onset stroke might cause left ICA hypoplasia$^{13}$, fibromuscular dysplasia or carotid dissection. From the extracranial duplex, the patient’s ICA was smaller in lumen with trifle flow. Because there was no image studies such as neck MRA or carotid angiogram, it is difficult to make a differential diagnosis between congenital hypoplasia or carotid dissection$^{14}$.

According to the literature, intramural thrombi of the heart often develop in iHES in a later stage when thromboembolic events tend to prevail. If left untreated, our patient might have evolved into the last or the fibrotic stage, and intramural fibrosis might start to jeopardize cardiac function. Sarazin et al.$^{15}$ reported two cases which, just like the reported case here, demonstrated the association between hypereosinophilia and bilateral cerebral borderzone infarcts. One of the two cases had cardiac thrombus formation similar to that in our case, whereas the other went through an initial stage of acute endomyocardial necrosis. A possible mechanism underlying the association is eosinophilic infiltration of the myocardium with release of toxic cationic proteins from the degranulating eosinophils$^{16,17}$. This could break down the endothelial lining, initiating the cascade of fibrin thrombus formation$^{18,19}$. The thrombus is subsequently replaced by fibrosis and scarring of the chordae tendineae and endocardium, leading to restrictive or dilated cardiomyopathy$^{20}$. The chronic cough of this reported case might well be one of the consequences of pulmonary involvement, which most commonly causes chronic, nonproductive cough with a normal chest radiogram.

Although the association between Loeffler endocarditis and stroke in HES has been noted$^{21}$, the coexistence of embolic stroke in the vascular territory of ICA and hydranencephaly has not been documented before. Most of the previous reports emphasized that the cytotoxic effect of the proteins released by circulating eosinophils and the subsequent endothelial damage as well as thrombus formation are responsible for brain infarction$^{21}$. The ischemic pattern on MRI in this patient suggested that in addition to cardiac emboli passing through the right MCA and collateral circulation of the left MCA, sequestration of eosinophils in the cerebral circulation may also play a role in the thromboembolic event of the left hemisphere. In this regard, it is interesting to note the previous case report by Chang et al.$^{22}$, where a patient with HES suffered from two strokes in less than three weeks. These cases clearly illustrate the adverse events caused by elevated eosinophils and the necessity of emergent management.

In terms of treatment, a meta-analysis$^{23}$ in 1993 concluded that anticoagulation could reduce the risk of embolization, although that study was designed with more emphasis on the reduction of myocardial infarction. Controversy exists because embolic events still occurred despite adequate anticoagulation$^{24}$. Surgical removal of the thrombus may be the other option. Schneider et al.$^{25}$ observed that surgical intervention reduced incidences of endomyocardial fibrosis related to HES. The 10-year survival rate was approximately 70%.
This reported case should be monitored for a longer period of time as she has refused surgical intervention.

In conclusion, the manifestations of iHES are not uniform and this reported case illustrates the difficulties in the diagnosis and treatment of iHES. iHES may cause embolic stroke if intramural thrombi are present. Early diagnosis is thus crucial for the timely therapy that may prevent the progression of systemic involvement.

REFERENCES