

SHORT REPORT

Multiple microembolic borderzone brain infarctions and endomyocardial fibrosis in idiopathic hypereosinophilic syndrome and in *Schistosoma mansoni* infestation

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We report two cases of multiple distal borderzone ischaemic strokes associated with hypereosinophilia due to idiopathic hypereosinophilic syndrome in one patient and to acute *Schistosoma mansoni* infestation in the other. Endomyocardial fibrosis (EMF) was documented pathologically, in one case at autopsy and in the other after cardiac surgery; and by cardiac CT, with initially negative echocardiography, in one patient. These observations suggest that so called borderzone infarcts may be due to microembolisms and that, in the context of hypereosinophilia, EMF diagnosis warrants complete cardiac investigation including cardiac CT and repeat echocardiography.

In hypereosinophilic syndrome (HIS), three frequent patterns of neurological involvement can be found, including encephalopathy, sensory polyneuropathy, and brain infarction.¹ Brain infarcts are due to either thromboembolism from endomyocardial fibrosis (EMF) or to vascular endothelial toxicity of eosinophilic cells.² Although the association between endomyocardial fibrosis and stroke in hypereosinophilic syndrome has previously been documented, the extent, pattern, and mechanisms have not been described in detail. We report two patients with hypereosinophilic syndrome associated with distal microembolism in the brain and large scale endomyocardial fibrosis, one idiopathic and the other in the context of *Schistosoma mansoni* infestation.

CASE REPORTS

Patient 1

This 51 year old man, treated for IHS for two years with hydroxyurea, was admitted with a 10 day history of confusion and left hemiplegia, of progressive onset. On admission he was mute and bedridden. Brain CT scan and MRI showed multiple bilateral cerebellar and cerebral infarctions in distal vascular fields (fig 1A). Transoesophageal echocardiography and cardiac MRI revealed large scale EMF. The eosinophil count was 26 000/mm³. The patient received anticoagulation therapy and aspirin together with a high dose of intravenous prednisolone and short courses of VepesidTM perfusion; he recovered dramatically after lowering of the eosinophil count, and returned home with total independence. However, progressive sensory and motor loss in the left peroneal nerve and bilateral cubital nerve revealed polyneuropathy confirmed by EMG. Two years later he had progressive confusion, headaches, intellectual impairment, and behavioural disturbances including crying and agitation. Brain CT scan showed recurrent infarcts in the right centrum semiovale. The eosinophil count was 32 000/mm³. Despite receiving oral prednisolone, 1 mg/kg, and

VepesidTM perfusion, 150 mg/day, the patient eventually died. Post mortem examination showed recent and old ischaemic lesions in the cerebral and cerebellar borderzone areas on both sides, other without vascular lesions, as well as large scale EMF together with mural thrombi in the left ventricle (fig 1B).

Patient 2

This 25 year old woman, on return from a three month journey to Madagascar, complained of diarrhoea with abdominal pain and myalgia. A week later, she had clinical impairment with rapidly progressive headache, gait and limb ataxia, personality changes, loss of memory and attention, apathy, and lethargy, and she was finally admitted to hospital. Physical examination revealed a low grade fever (38°C) and subungueal haemorrhages, but neither meningeal syndrome nor focal deficit. There were no palpable lymph nodes or splenomegaly. Brain CT scan and MRI showed multiple ischaemic lesions in the borderzone area on both sides (fig 2A). The erythrocyte sedimentation rate was 72 mm and the eosinophil count was 3 900/mm³, with no past history of allergy. The CSF was normal and neck ultrasound and transcranial Doppler examinations were normal. ECG showed negative T waves at V4-V6-VF, D1-D2-D3, with a normal CPK-MB level. Transthoracic echocardiography (TTE) was normal, but ultrafast CT revealed non-calcified EMF within the left ventricle (fig 2B), which was found at follow up TTE two months later. Although initial serological testing for schistosomiasis and other parasitic or viral infection was negative, *S mansoni* was identified in a stool specimen three weeks after admission. At the same time, a seroconversion for schistosomiasis was documented. The patient received praziquantel orally and could return home on aspirin therapy. Although she had no neurological recurrence, the cardiomyopathy continued to progress, with dyspnoea increasing with effort. Although the eosinophil count returned to a normal range, a second course of praziquantel was given. Three months after her first admission, she had pericarditis treated with an increased dose of aspirin for 3 days. Dyspnoea progressively worsened and, 16 months after onset of the disease, TTE and ultrafast CT showed EMF progression with involvement of the whole left ventricle. The ejection fraction was 68%. Surgical removal of EMF was performed at month 16, under hypothermia. The surgeon found fibrosis filling the apex of the left ventricle up to the mitral annulus, covering the posterolateral as well as the anterior walls. The right ventricle was normal.

Abbreviations: EMF, endomyocardial fibrosis; IHS, idiopathic hypereosinophilic syndrome; TTE, transthoracic echocardiography

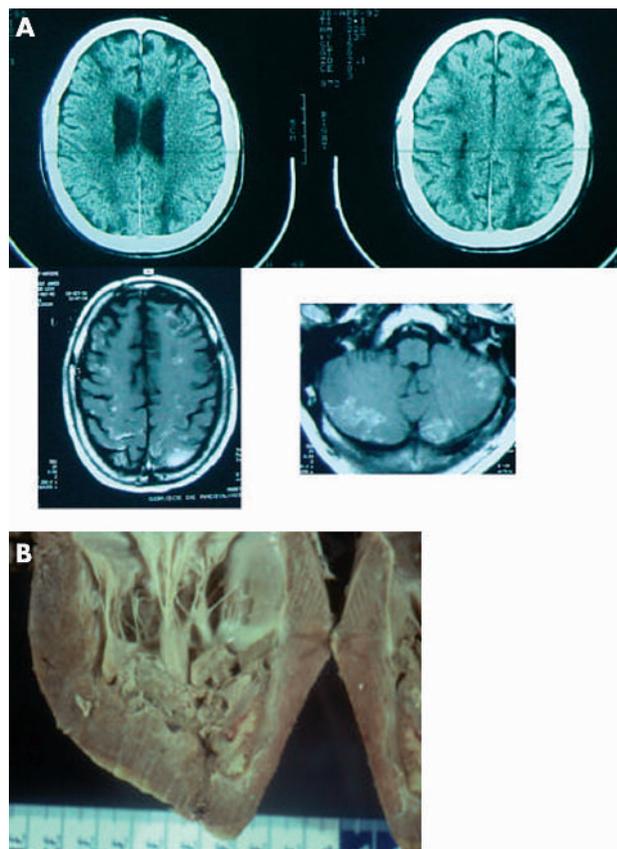


Figure 1 Patient 1. (A) T-2 weighted MRI showing multiple distal field infarcts in the borderzone area. (B) Endomyocardial fibrosis at pathological examination.

DISCUSSION

These two cases illustrate that bilateral borderzone infarcts may present as progressive encephalopathy and may be due to multiple microemboli. Microembolism in our cases was the result of large scale endomyocardial fibrosis, which is a common finding in hypereosinophilic syndrome, although it is an extremely rare cause of brain infarction. In patient 2, we would have missed the diagnosis if we had performed an echocardiogram only. Cardiac ultrafast CT confirmed the clinical diagnosis. Patient 2 had EMF secondary to *S mansoni* infestation; this is, to our knowledge, the first reported case of EMF due to parasitic infection and revealed by multiple brain infarcts. It is worth noting that EMF developed despite eradication of the schistosomiasis.

In the literature, although patients with either reactive or idiopathic IHS have a high incidence of CNS involvement,¹ and particularly brain infarction, most reports omit to detail neurological examination or cerebral or cardiac imaging, giving no idea of the potential mechanisms of the brain artery occlusions.

In 52 patients with IHS,² peripheral neuropathy was the most frequently documented neurological abnormality, followed by CNS dysfunction and encephalopathy. In the four cases of encephalopathy, CT scan had either shown decreased density of white matter or was reported normal; neither MRI nor TTE was performed. Cerebrovascular thromboembolic disease affected six other patients and was associated with heart involvement in five. Unfortunately, neither clinical symptoms nor cerebral imaging (CT scan or MRI) nor follow up of myocardial lesions was reported.

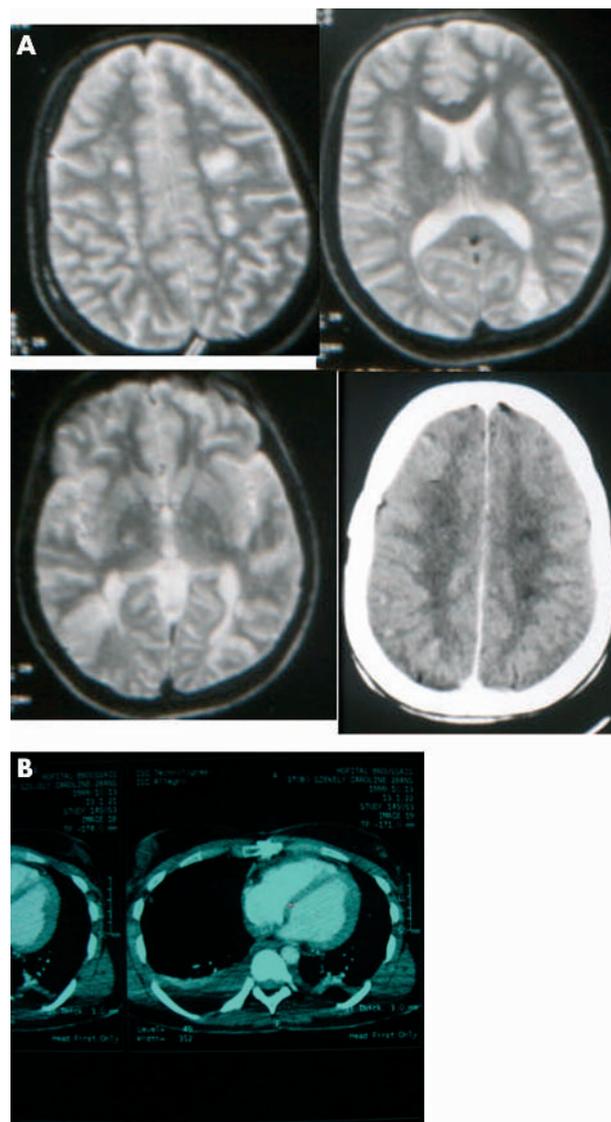


Figure 2 Patient 2. (A) Multiple distal hemispheric infarcts in the borderzone area. (B) Endomyocardial fibrosis at ultrafast CT.

Thromboemboli in IHS usually occur throughout the course of the disease in conjunction with cardiac involvement.² Cardiac endothelial injury is often extensive and results in fibrosis and thrombosis of endocardial surfaces (fig 1B). Restrictive endomyocardiomyopathy may follow.³ However, it is worth noting that, at an early stage of the disease, cardiac involvement may be clinically silent, as in our patient 2. Minor ventricular myocardial degeneration may only be associated with electric disturbances.⁴ When performed, endomyocardial biopsies always show significant changes.⁴

CNS involvement may be seen at any stage of schistosomiasis, but is far more common in the later stages of the disease in association with the chronic hepatosplenic and cardiopulmonary forms or with severe urinary schistosomiasis.³ In the course of the acute invasive stage of schistosomiasis due to *S japonicum*, the prevalence of neurological complications has been estimated at 2.3%: during World War II, 27/1200 soldiers with acute schistosomiasis developed neurological complications. These included headache, obtundation, focal visual impairment,

convulsions, dysarthria, ataxia, urinary incontinence, and motor deficit.⁶ Since 1948, just one case of focal CNS lesions in an individual with acute schistosomiasis due to *S japonicum* has been reported: cerebral CT scan showed multiple lucencies and severe oedema in the left frontal, parietal, and occipital lobes.⁷

Similarly, CNS involvement has been described in other helminthic diseases with hypereosinophilia, such as trichinosis and filariasis. In one study of neurotrichinosis, CT scanning and MRI showed multifocal CNS involvement in two subjects, suggesting infarction.⁸ Seshadri *et al* reported a patient in India who presented with an infarction in the left frontal lobe, demonstrated by CT scan, and a hypereosinophilia (3600/mm³) reactive to microfilarial infection. Although cardiovascular testing was negative, focal myocarditis was diagnosed by endomyocardial biopsy.⁹

As to areas where schistosomiasis is endemic, EMF has been reported in Egypt in 15/10 000 infected persons,¹⁰ although this ratio was not supported in Brazil.¹¹ No stroke has been described. Therefore the borderzone ischaemic syndrome of the brain in our two patients, and the context of *S mansoni* infestation we report in one patient, are unique in the literature.

The cardioneurological complex found in our cases was similar to that described in a study of nine persons with neurotrichinosis infestation¹²: 8/9 had both diffuse and focal neurological signs associated with myocardial injury.¹² The CT scan pattern showed many small distal ischaemic areas in the cortex and white matter. Neuropathological examination revealed multiple arteriolar fibrinocruoric thrombi without inflammatory changes. Eosinophilic toxicity to endothelial cells was thought to be the main mechanism, through the production of TNF- α mediated by an eosinophil cationic granule protein.¹³

Another explanation for the neurological abnormalities found in hypereosinophilia could be a direct or indirect neurotoxicity of eosinophils, as these have been found in the CSF of a demented patient who dramatically improved after steroid therapy, with disappearance of eosinophils from the CSF.¹⁴ The CSF in our patients was normal.

We suggest that, in persons with distal field brain infarctions in the context of hypereosinophilia, and in view of the high incidence of potentially silent but lethal cardiac involvement due to EMF, complete cardiac investigations should be performed. These should include ultrafast CT or MRI, even if echocardiography is normal.

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