CASE REPORT

JIACM 2019; 20(2): 131-33

Idiopathic Hypereosinophilic Syndrome Presenting as Cerebral Infarct

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Abstract

Hypereosinophilic syndrome (HES) is a rare multisystem disorder associated with significant morbidity and mortality. Most common manifestation of hyper eosinophilic syndrome includes-gastrointestinal abnormalities, pulmonary fibrosis, cardiac involvement and neurological deficit. Idiopathic hypereosinophilic syndrome is a leukoproliferative disorder subset of HES causing multiorgan damage and diagnosis requires marked peripheral eosinophilia and exclusion of infection, vasculitis and haematological malignancy. However, neurological deficit in the form of acute stroke is a rare presentation and cause of diagnostic dilemma. Here by, we present a case of a 29-year-old young male with hypereosinophilic syndrome complicated with stroke.

Key words: Hypereosinophilic syndrome, peripheral eosinophilia, cerebral infarct.

Introduction

Hypereosinophilic syndrome (HES) first described by Hardy and Anderson in 1968, is characterised by sustained overproduction of eosinophils. The term Idiopathic Hypereosinophilic syndrome as defined by Chusid *et al* is characterised by 3 criteria- eosinophil count greater than 1,500 cells/ml persisting longer than 6 months and single or multiple organ system dysfunction attributable to cytotoxic injury by eosinophils, without an identifiable aetiology to explain the eosinophilia[1]. The mortality in untreated patients 3 years after diagnosis, can be as high as 75%[2]. Cardiac involvement is the most common cause of increased morbidity and mortality[3]. Early identification and aggressive therapy is of paramount importance in decreasing the morbidity and mortality associated with this condition. Neurological complications include peripheral neuropathies, CNS dysfunction like meningitis, encephalopathy, memory impairment, ataxia, behavioural changes and thromboembolic stroke. Cerebral infarction as a complication of Idiopathic hypereosinophilic syndrome (IHES) is rarely documented. We describe a case of a patient of IHES with cerebral infarcts.

Case report

A 29-year-old male, smoker, nonalcoholic presented to emergency department with a history of intermittent fever since 6 months which was low grade, mostly in evening hours, partially relieved with medication. Patient complained of weakness of right side of body for 5 days and altered sensorium since 1 day. There was no history of headache, seizure, trauma or loss of consciousness. There was no history of cough, expectoration, difficulty in breathing, skin rash, nausea, vomiting, pain abdomen, allergy and no recent travel history. On examination, patient was haemodynamically stable and with normal general physical examination. His blood pressure was 100/70 mmHg in right arm, pulse rate of 78 bpm and respiratory rate was 14/min. He was conscious but not oriented to time, place and person. Motor power was 3/5 in right upper and lower limb with weak hand grip. Left side motor power was 5/5. Babinski sign was positive with brisk deep tendon reflexes on right side. Patient had no features suggestive of raised intracranial pressure. Meningeal signs were absent. Examination of respiratory system, cardiovascular system and abdomen systems were normal. Based on history and examination provisional diagnosis of stroke in young patient was made.

His blood investigations revealed Hb: 14.3 gm%, TLC: 15,000/cumm (N - 25%, L - 25%, E - 44%) with absolute eosinophil count of 6,600/cumm. His blood sugar, liver function, kidney function and thyroid profile were within normal limits. NCCT of head revealed nonenhancing hypodensity in left caudate nucleus, left parietotemporal region and periventricular region. MRI brain confirmed the findings of left middle cerebral artery infarct (Fig. 1). Patient had repeatedly raised eosinophil count on serial investigations with AEC of 5,200, 3,800 and 2,552/cumm on day 2, 4 and 6, respectively. Aetiology workup for stroke, including lipid profile, electrocardiogram, carotid duplex ultrasound, transcranial Doppler ultrasound, transthoracic echocardiogram (TTE), MR angiography brain (Fig. 2) and tests for disseminated intravascular coagulation was non-revealing. Chest X-ray, ESR, CRP, urine examination, CSF study were also normal. Stool for ova and cyst and stool culture was normal. Total Ig E was > 30,000 k UA/L. Pulmonary function test was normal. CECT abdomen and thorax was done to rule-out neoplastic

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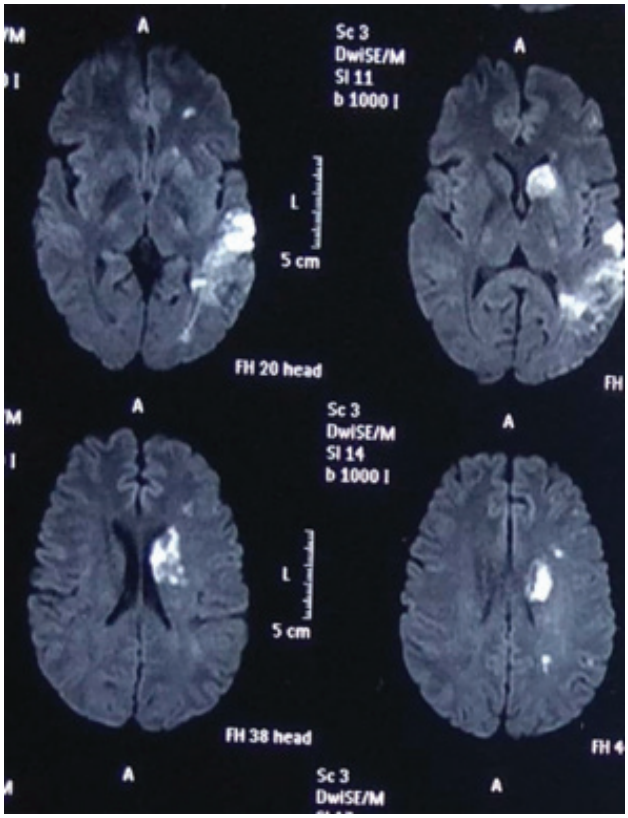

Fig. 1: *Showing MRI brain axial view, diffusion weighted images which confirmed presence of acute infarct in left caudate, left parietotemporal and periventricular infarct.*

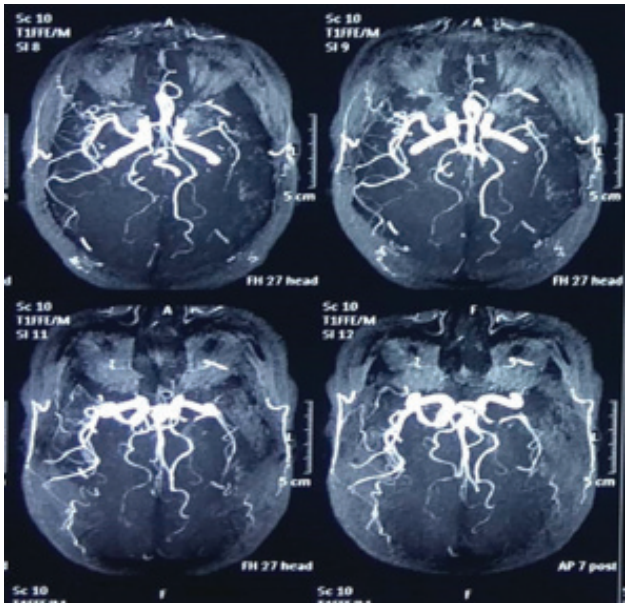

Fig. 2: *Showing MR angiogram of cerebral vessels.*

cause of hypereosinophilia, which came out to be normal. Bone marrow aspiration and biopsy was suggestive of eosinophilic myeloid reaction and blast cells less than 5% (Fig. 3). Patient was advised cytogenetics to rule-out clonal disorder, i.e., PDGFA, PDGFB and FGFR1, which were negative. After which, patient was diagnosed as idiopathic HES with stroke in left MCA.

Initially on presentation, patient was started on ecosprin 150 mg, atorvastatin 40 mg, albendazole 400 mg and ivermectin 12 mg stat dose was given. After ruling-out other causes of hypereosinophilia, he was started on prednisolone 60 mg daily. Patient responded drastically clinical and biochemically with reduction in eosinophil count to 2% (150/cumm) within 1 month. At present,patient is on tapering dose of steroid and has no neurological deficit.

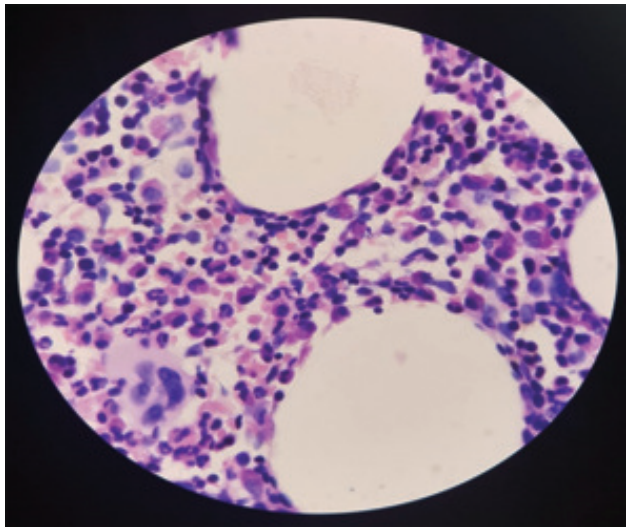

Fig. 3: *Bone marrow biopsy slide shows eosinophilic myeloid reaction.*

Discussion

Eosinophilia is a common disorder with count more than 500/ul[4]. It can be due to primary (clonal), idiopathic and secondary (reactive) causes. Secondary eosinophilia includes parasitic infection, toxins, medications, allergic disorders, autoimmune diseases, endocrine disorders, malignancies. Primary and idiopathic disorders are rare and probably underdiagnosed. Idiopathic HE and HES are diagnoses of exclusion in patients who have been appropriately assessed with a detailed history, physical examination and thorough investigation, without any cause being found.

Clinically, HES is a heterogenous disease with varied manifestations. Patient may present with nonspecific symptoms like fatigue, low grade fever, rash, cough, myalgia, dyspnoea. Organ systems involved include heart, lungs, skin, peripheral and central nervous system and gastrointestinal tract. Cardiovascular system involvement can lead to myocarditis, endocarditis, fibrosis, intracardiac clot formation, heart failure and this is the most common cause of mortality[5].

CNS can be involved in three different ways. First is cerebral infarct, which is due to either thromboembolism from endomyocardial fibrosis or vascular endothelial toxicity of eosinophils. An eosinophilic cationic protein has been reported to have a profound effect on coagulation system and this protein has also been shown to be responsible for thromboembolic phenomena[6]. Patients can experience embolic strokes or transient ischaemic attack, either single or multiple, which is the only presenting feature. Initially small arterial border zone infarct can occur, later on large cortical and subcortical area can be involved. Our patient had multiple small infarcts as the initial presentation. Second neurologic manifestation in HES is peripheral neuropathies, which occurs in nearly 50% patients. Symmetric and asymmetric sensory polyneuropathies or mixed sensory or motor deficit is common. The aetiology of peripheral neuropathy is largely undefined. Monaco *et al* have suggested that damage to endothelial cell leads to capillary leakage and increased endoneural pressure causing axonal damage. The third type of HES associated neuropathy is primary central nervous system dysfunction. Patients exhibit changes caused by distinct encephalopathy, including changes in behaviour, confusion, ataxia, and memory loss and exhibit upper motor neuron signs with increased muscle tone, deep tendon reflexes and a positive Babinski. The exact pathogenesis of encephalopathy is not known but changes are due to markedly elevated AEC. Some studies revealed that cerebral infarctions in arterial watershed zone lead to encephalopathy[7].

The mechanism of eosinophil-related tissue damage is not fully known; eosinophil accumulation appears to have pathological consequences. Eosinophils have direct cytotoxicity through the local release of toxic substances including cationic proteins, enzymes, reactive oxygen species, pro-inflammatory cytokines, and arachidonic acid derived factors[8].The degree of end-organ damage is diverse, and there is often no correlation between the level or duration of eosinophilia and the severity of organ damage.

However the definition, as described in the introduction, has some inherent problems. For example, as in our case, some patients may report and require therapeutic intervention well before the six months period specified in the first criterion. Once secondary causes of hypereosinophilia have been excluded, a diagnosis of 'idiopathic HES' can be entertained and there is no reason to withhold treatment in a patient with sustained and potentially life-threatening hypereosinophilia[9].

Steroids are recommended as initial treatment for patients with IHES. Patients who do not respond to corticosteroids or require prolong therapy, can be considered for short trial of immunomodulatory agents (interferon alpha, ciclosporin, azathioprine) or newer monoclonal antibody therapy with mepolizumab (anti interleukin 5). Alemtuzumab (anti CD52 monoclonal antibody) can be used in severe IHES and in patients with cardiac and cerebral involvement.

In conclusion, IHES is not that rare as we think; rather it is ignored. Every physician must consider a diagnosis of IHES in a young patient with stroke with eosinophilia, and start treatment with steroids without waiting for 6 months.

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