INTRODUCTION

Idiopathic hypereosinophilic syndrome (HES) refers to a group of leukoproliferative disorders characterized by an overproduction of eosinophils that results in organ damage. Peripheral eosinophilia with tissue damage has been noted for over 80 years, but Hardy and Anderson first described the specific syndrome in 1968. (defined in 1975 by Chisid et al). It has a triad of eosinophilia (greater than 1500/cumm) for more than 6 months with no other etiology to account for the eosinophilia and, signs and symptoms of end-organ involvement. The end organ disease is caused by distant thromboembolic events originating from the HES cardiopathy or due to chronic disseminated intravascular coagulation, activated eosinophils release oxidative products i.e. various cationic proteins, cytokines, they enhances urokinase-induced plasminogen activation and enhance factor XII dependent reactions.

We report a young patient with HES who developed stroke and was managed in our hospital.

CASE REPORT

A 33 years male, non diabetic, normotensive, smoker (10 cigarette/day for 15 years) and chronic alcoholic about 180ml/day for 12-13 years was admitted to our hospital with a history of weakness in the left half of body for 4 days. The patient had a sudden onset weakness in the left half of body and facial asymmetry when he fell down while walking. He gave no history of head injury, ENT bleed, seizure, difficulty in swallowing; hoarseness of voice, audiovisual complaints or neck weakness. He had no other constitutional symptoms like fever, cough, dyspnoea, and dysuria. The patient was apparently well 2 months prior to admission when he developed a painful swelling of right side of neck and upper arm. MRI of right arm showed axillary lymphadenopathy with diffuse ill defined heterogeneous signal intensities in the intermuscular spaces (Fig. 1). Blood picture showed leucocytosis with predominant eosinophilia (AEC 7000). The patient was...
treated with analgesics, antibiotics and antihelminthics albendazole 400mg single dose, diethylcarbamazine and was symptomatically better.

On examination at our hospital, he was conscious, oriented, and afebrile. There were no skin lesions. CNS examination revealed normal higher mental functions with residual left hemiplegia and left upper motor neuron facial palsy. The sensory examination was normal with no peripheral neuropathy. Rest of the systemic examination including CVS was normal.

On investigations the total white blood counts were 22100/cumm with N23 E60 L16 B1 and absolute eosinophil count (AEC) of 13000. ESR was 10 mm/1st hr. Chest X-ray, urine and stool examinations were normal. Renal and liver function tests, lipid profile, prothrombin time, APTT, CPK, and CPK-MB were within normal limits. Rheumatoid factor and CRP, ANA, anti dsDNA and p-ANCA were negative. Serum IgA was 169 mg/dl and IgE levels were 94.3 IU/ml. The karyotype was normal. Bone marrow showed eosinophilia with occasional eosinophilic precursors. Carotid Doppler study was normal and 2D echo showed anterior mitral leaflet prolapse into the left atrium in systole. CT scan showed an infarct in right temporoparietal region (Fig. 2).

CT angiography revealed a sudden cut off of right M1 at its trifurcation with non visualization of the M2 and M3 segments with minimal narrowing of right internal carotid artery (Fig. 3).

The patient was managed conservatively with low molecular weight heparin for the cerebral infarct and with corticosteroids for the HES. He showed consistent improvement in the neurological signs but eosinophilia persisted. Hydroxyurea was added but the AEC persisted between 30000-40000. He was then started on imatinib mesylate (400mg/day) and showed regression of eosinophilia and imatinib was tapered off to 100mg/day.

**DISCUSSION**

Eosinophilia of a marked degree is found in various pathological conditions – allergy, parasitic infections, various neoplasms, vasculitis and some autoimmune diseases (Table 1).

In addition a distinct hypereosinophilic syndrome characterized by sustained overproduction of eosinophils in the bone marrow, eosinophilia, tissue infiltration, and organ damage has been described. The diagnosis is based

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**Table 1: Diseases associated with eosinophilia**

<table>
<thead>
<tr>
<th>Type of disease</th>
<th>Eosinophilia</th>
<th>Examples of causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
<td>Present</td>
<td>Infections with especially invasive helminths</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Present or absent</td>
<td>Eosinophilic pneumonitis, asthma</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Present or absent</td>
<td>Inflammatory bowel disease, eosinophilic gastroenteritis, allergic colitis</td>
</tr>
<tr>
<td>Allergic</td>
<td>Present or absent</td>
<td>Allergic rhinoconjunctivitis, asthma, eczema</td>
</tr>
<tr>
<td>Systemic</td>
<td>Present</td>
<td>Idiopathic hypereosinophilic syndrome, vasculitis</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>Present</td>
<td>Drug reaction, cytokine infusions (e.g. granulocyte-macrophage colony-stimulating factor)</td>
</tr>
<tr>
<td>Malignant</td>
<td>Present or absent</td>
<td>Lymphoma, colonic carcinoma</td>
</tr>
</tbody>
</table>
on the criteria of Chusid et al: sustained eosinophilia (more than 1500 eosinophils per cubic millimeter) for more than six months; the absence of other causes of eosinophilia, including parasitic infections and allergies; and signs and symptoms of organ involvement, most frequently the heart, the central and peripheral nervous system, the lungs, and the skin (urticaria and itchy nodules). The syndrome is more common in men than women (ratio, 9:1) and occurs predominantly between the ages of 20 and 50 years.

End-organ disease is caused by distant thromboembolic events originating from HES cardiopathy or due to chronic disseminated intravascular coagulation. Eosinophils circulating in the blood of HES patients exhibit a number of functional and biochemical measures, indicating that they are “activated.” These changes include increased metabolic activity, diminished density (hypodense), enhanced antibody mediated cytotoxicity, enhanced leukotriene C4 formation and morphological alterations, including cytoplasmic vacuolization, alterations in granule numbers and size. Specific granules contain four cationic proteins, eosinophil peroxidase, major basic protein (MBP), eosinophil cationic protein (ECP), and eosinophil derived neurotoxin (EDN). Each exerts toxicities on the host cells. The eosinophil can undergo a respiratory burst to generate oxidative products that alone or in concert with eosinophil peroxidase cause further oxidant-mediated damage. A number of cytokines are elaborated that contribute to inflammation and fibrosis, including transforming growth factor (TGF), TGF, tumor necrosis factor (TNF), interleukin 1 (IL-1), macrophage inflammatory protein, IL-6, IL-8, as well as the hematopoietic cytokines, IL-5, IL-3, and GM-CSF.

The most striking organ damage in HES is to the heart, culminating in thrombosis and fibrosis. With regard to thrombus formation, the eosinophil cationic protein (ECP) enhances urokinase-induced plasminogen activation and enhance factor XII-dependant reactions. The oxygen radicals and potent lipid mediators are toxic to endocardial and myocardial cells leading to platelet and mural thrombi, valvular insufficiency and peripheral embolization. High serum levels of cationic protein released by eosinophilic granules leads to a hypercoagulable state and thromboembolic phenomena.

Eosinophilic myositis is another manifestation of hypereosinophilic syndrome. Muscle involvement is by perivascular eosinophilic infiltration and intravascular leucocytic infiltration of capillaries and medium-sized muscular vessels. This leads to degeneration of muscle fibers and bands of fibrosis.

Historically, HES has carried an extremely poor prognosis with high morbidity and mortality. The major thrust of therapy has been aimed at lowering the eosinophil count and alleviating the clinical manifestations. Patients without progressive organ dysfunction are not treated and are followed closely at 3 to 6 months intervals. If patients show organ system dysfunction, they are treated initially with prednisolone, 1 mg/kg body weight on a daily basis followed by an alternate day regime.

These patients are followed on a 3 monthly basis with careful evaluation. If the disease stabilizes or improves, the corticosteroid is continued and ultimately tapered to the lowest possible dosage that will control the disease. In progressive disease, a cytotoxic agent, specifically hydroxyurea (0.5 to 1.5 g/d) is added to the regimen with the aim of maintaining the eosinophil count at less than 1900/cumm. Leucopheresis may be required for an occasional patient with extremely high levels of eosinophils (100000/cumm or greater) encountered during the induction period with hydroxyurea. Alpha interferon has showed sustained remission in some patients.

Imatinib mesylate is effective in the treatment of hematological malignancies that are characterized by either abl- or PDGFR beta (Platelet derived growth factor receptor) activating mutations. The drug is also active in a subset of patients with eosinophilic disorders. Recently, a novel tyrosine kinase that is generated from fusion of the fip 1-like 1 (FIP1L1) and PDGFR alpha (PDGFRA) genes has been identified as a therapeutic target for imatinib mesylate in HES. The prescribed dose is 100 – 400 mg/day. It is hypothesized that the higher doses of imatinib mesylate for chronic myeloid leukemia may not be necessary for HES. Some reports suggest even 75 mg/day to be effective in maintaining normal eosinophil levels. The lowest effective dose for HES is unknown.

Antithrombotic and antiplatelet agents, viz. warfarin and aspirin are used to prevent thrombosis.

In our patient, the CNS manifestations of stroke were managed conservatively along with prednisolone with which he showed consistent improvement in clinical signs. As the eosinophilia persisted, he was started on imatinib mesylate (400mg/day) with significant improvement. Thereafter the patient was discharged and remained asymptomatic. Three months after starting Imatinib, his CBC revealed Hb12g%, TLC 9600 with a normal DLC and normal eosinophils. To the best of our knowledge this is the first reported case of HES being managed with imatinib mesylate in India.

REFERENCES


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