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Case report: Open Access

Idiopathic Hypereosinophilic Syndrome Presenting With Meningoencephalitis; An Uncommon Presentation: A Case Report

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Abstract

Introduction: Hypereosinophilic syndrome is a rare heterogeneous disorder characterized by persistent eosinophilia with eosinophil mediated tissue infiltration and organ dysfunction in the absence of a secondary cause. Clinical presentations involving nervous system vary markedly causing encephalopathy, thromboembolic disease or peripheral neuropathy. Eosinophilic infiltration of meninges and central nervous system causing meningo-encephalitis is a rare presentation in hypereosinophilic syndrome and is infrequently published in scientific literature.

Case presentation: A previously healthy 19-year-old Sri Lankan male presented with mild fever, headache and photophobia with abnormal behavior. On examination, he was drowsy with neck stiffness, positive Kernig's sign, hypertonia and quadri-hyperreflexia. Cerebrospinal fluid analysis revealed heavy eosinophilic infiltration with sterile cultures. Peripheral blood smear showed persistent absolute eosinophilia and bone marrow revealed hyper-cellularity with eosinophil predominance. Other organ involvement was also noted with global hypokinesia of myocardium on echocardiogram and moderate restrictive lung disease. Secondary causes for hyper-eosinophilia were excluded and he made a remarkable recovery following treatment with steroids for idiopathic hypereosinophilic syndrome.

Conclusion: Although rare, eosinophilic infiltration of cerebrospinal fluid (with sterile cultures) and peripheral blood absolute eosinophilia should prompt the physician towards the diagnosis of idiopathic hypereosinophilic syndrome in the absence of secondary causes, as early treatment can be lifesaving.

Keywords

Idiopathic hypereosinophilic syndrome, Encephalopathy, Thromboembolic disease, Meningo-encephalitis, Cerebrospinal fluid, Leucoproliferative disorder.

List of Abbreviations

ANCA: Anti-Neutrophil Cytoplasmic Antibodies, CNS: Central Nervous System, CSF: Cerebro-Spinal Fluid, ECG: Electrocardiogram, FEV1: Forced Expiratory Volume during the 1st second, FVC: Forced Vital Capacity, GCS: Glasgow Coma Scale, HES: Hypereosinophilic Syndrome, NAP: Neutrophil Alkaline Phosphatase, TPPA: Treponema Pallidum Particle Agglutination, VDRL: Venereal Disease Research Laboratory.

Background

Hypereosinophilic Syndrome (HES) is a rare heterogeneous group of leucoproliferative disorders. It is characterized by persistent blood absolute eosinophilia (1500/microliter or more) with signs and/or symptoms of eosinophil mediated organ dysfunction in the absence of secondary causes for eosinophilia [1-5]. It is recognized as a spectrum of diseases with variable organ involvement, clinical manifestations, and response to treatment as well as prognosis [1]. Although any organ system may get involved, cardiac (58%), dermatological (56%) neurological (54%), and pulmonary (49%) involvement had been observed in more than 50% of cases [6-8]. Patients with HES develop a variety of neurological abnormalities involving central and peripheral nervous systems, with the commonest being strokes, encephalopathy, fits and peripheral neuropathy [9]. Eosinophilic meningitis is a rare presentation of idiopathic HES which is infrequently noted in medical literature [8,10,11].

Case Report

A previously healthy 19-year-old unmarried Sri Lankan army soldier was transferred from a regional hospital to Teaching Hospital, Kandy, Sri Lanka for specialized neurological management.

The patient had experienced mild fever, headache and photophobia for 4 days followed by abnormal and aggressive behavior for 1 day. This was not associated with a history of head trauma, convulsions or focal neurological symptoms. There were no preceding upper respiratory tract or ear infections. On detailed history, he had not experienced any dyspnea, cough, wheezing, joint pains, skin rashes, oral ulcers, night sweats, significant loss of weight or loss of appetite. Systemic review, travel history and drug history were nil of note. He was a non-smoker and denied any usage of alcohol or substance abuse.

On examination, the patient was drowsy with a Glasgow Coma Scale (GCS) of 10/15 with equally reacting pupils (3mm in diameter). Fundi were normal. Neck stiffness was demonstrable with a positive Kernig's sign. There were no cranial nerve palsies. Quadri-hypertonia

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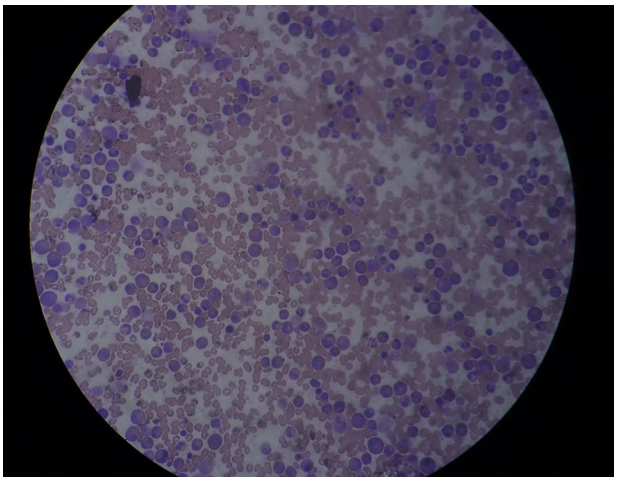

Figure 1: Bone marrow showing absolute eosinophilia with mature forms.

was noted with a power of 5/5. Deep tendon reflexes were brisk in all four limbs with equivocal plantar response. Cerebellar signs were difficult to elicit as the patient was drowsy on admission. General examination was normal with a temperature of 98.6 F on admission. Pulse rate was 88 beats per minute with a blood pressure of 100/70mmHg. Respiratory and abdominal system examination was clinically normal.

Investigations revealed a hemoglobin of 12g/dl, white cell count of 32200x10^3 /µL (neutrophils – 46.9%, eosinophils – 47.4% & lymphocytes – 2.9%) and a platelet count of 172x10^3/µL. Blood picture showed polymorphonuclear leukocytosis with an absolute eosinophilia more than 50% without blast cells. Red blood cell and platelet morphology was normal. Erythrocyte sedimentation rate was 88mm in 1st hour (normal<20). C-reactive protein was 48U/L (0-5). Creatinine phosphokinase value was 32.9U/L (38-174). Electrolytes, renal function tests and liver profile and serum immunoglobulin E level were normal. Both contrast and non contrast enhanced computed tomography of the brain did not reveal any abnormalities. Electro-encephalogram showed generalized slow waves suggestive of encephalopathy or encephalitis. Cerebrospinal Fluid (CSF) analysis revealed a protein concentration of 80mg/dl with a white cells count of 16/mm^3 (eosinophils-80% & lymphocytes-20%). CSF for gram stain, bacterial and fungal cultures, staining for cryptococcus, bacterial antigens (*Streptococcus spp.*, *Haemophilus influenza B, Neisseria meningitides* ACYW 135 and *B/E coli K1*) and acid fast staining for *Mycobacterium tuberculosis* were all negative.

Bone marrow aspirate showed absolute eosinophilia (55%) with mainly mature forms predominating including bi and tri-lobed eosinophils (Figure 1). Blast cells were less than 2%. Trephine biopsy revealed hypercellular marrow with a cellularity of 85%, in which severe eosinophilia and normal erythropoiesis and megakaryopoiesis were noted. No atypical cells were identified in the bone marrow. Genetic studies for the mutant gene *FIP1L1-PDGFR* was negative. Possibility of eosinophilic leukemia was excluded by blood picture, bone marrow, normal Neutrophil Alkaline Phosphatase (NAP) score and negative genetic studies.

On further evaluation for a secondary cause for absolute eosinophilia, stool full report for parasitic ova/cysts, *Wuchereria bancrofti* antigen, Anti-Nuclear Antibodies (ANA), Anti-Neutrophil Cytoplasmic Antibodies (ANCA), retroviral studies, *Treponema pallidum* Particle Agglutination Assay (TPPA) and Venereal Disease Research Laboratory test (VDRL) were all negative. Ultrasound scan and contrast enhanced computed tomogram of the abdomen and pelvis was normal.

Following the admission, serial Electrocardiograms (ECG) showed dynamicity with biphasic T inversions in LI-III and V2-V6 leads in the subsequent electrocardiograms. 2-dimentional echocardiogram showed mild global hypokinesia with an ejection fraction of 45%. Troponin I titre was 1.21ng/ml (0-1). Chest roentgenogram showed prominent alveolar markings throughout the lung fields. X ray of the paranasal sinuses was normal. Lung function tests indicated moderately restrictive lung disease with FEV1/FVC -115%. Trans-bronchial lung biopsy revealed eosinophilic infiltrates without features of necrotizing vasculitis or necrotizing granuloma. Nerve conduction studies were normal. Upper gastrointestinal endoscopy was normal with normal histology in gastric and duodenal mucosa.

A diagnosis of idiopathic hypereosinophilic syndrome was made on clinical and hematological evidences. Patient was treated with high dose intravenous methyl prednisolone followed by oral prednisolone 1mg/kg/day. Marked clinical and biochemical improvement was observed within a week of treatment. On discharge he showed a good clinical recovery (GCS-15/15) with a white cell count of 10.6x10^3/µL; eosinophils – 6% (absolute eosinophil count – 636/µL).Oral steroids were gradually tailed off with close monitoring of the peripheral eosinophil counts.

Six months later, repeat two-dimentional echocardiogram showed good left ventricular systolic function with an ejection fraction of 65%. Lung functions had improved (FEV1/FVC 70%). The white cell count was 12.4x10^3µ/L (eosinophils – 15%, absolute count- 1860/µL) while on prednisolone 10mg daily. Hydroxyurea was added as the second drug for further management of his high eosinophil count and there was a good biochemical response with absolute eosinophil count dropping to less than 1000/µL during treatment.

Discussion

Hypereosinophilic Syndrome (HES) is a rare but fatal condition that occurs with male predominance of 4-9:1 [8-14]. Hardy and Anderson in 1968 reported 3 cases of this syndrome and described the disease as Hypereosinophilic syndrome [8,12]. Definition of idiopathic HES was originally presented in 1975 and was subsequently modified to include three criteria, with all being required for the diagnosis of HES.

1. Blood eosinophilia of ≥1500/microliter, present for more than six months

2. No other apparent etiologies for eosinophilia, such as parasitic infection, allergic disease, autoimmune process or malignancy

3. Signs and/or symptoms of eosinophil-mediated organ dysfunction

Main drawback of above definition is the need for fulfillment of six months duration, where patients presenting with end organ damage with severe eosinophilia could not be classified as HES at the onset, thus delaying the treatment. Therefore, above definition was recently extended to include patients with idiopathic HES with an end organ damage in whom treatment had to be initiated irrespective of the fulfillment of the time duration of 6 months [7]. This was practiced in the cited case where treatment had to be initiated immediately with a diagnosis made on available clinico-laboratory evidence without waiting for 6 months in-order to prevent further end organ compromise and mortality.

Exact pathogenesis of the diseases under the umbrella term HES is unknown but, several mechanisms suggested in the literature are overproduction of eosinophilopoetic cytokines (IL-3, IL-5, GM-CSF), functional abnormalities in above cytokines causing enhanced and prolonged action, defects in the normal regulation of eosinophilopoetic pathways and primary molecular defects of haemopoetic stem cells (stem cell mutations leading to FIP1L1-PDGFRA fusion gene) resulting in clonal proliferation of the eosinophil lineage [7,14]. In whom the underlying pathogenesis is unknown, the term idiopathic HES is used. The mechanism by which the HES causes organ damage is of two ways (1) direct eosinophil infiltration of the organs (2) via the mediators released from the granules of eosinophils (examples - basic protein, cationic protein, peroxidase, neurotoxin) [7,14]. The degree

of end organ damage is heterogeneous and there there is only little relationship with the magnitude and the duration of the eosinophilia against the severity of organ damage [8].

Any organ system is vulnerable to get affected by HES. Commonest organ to affect is heart with a frequency of 58% of all documented cases. Other systems are: cutaneous 56%, nervous system 54%, pulmonary 46%, splenic 43%, hepatic 30% and gastrointestinal 23%.

Nervous system related signs and symptoms are noted in 30% - 60% of the reported cases [10]. Common manifestations of the neurological involvement are; (a) thromboembolic disease with transient ischemic attacks or strokes (originating from the left ventricle or rarely from right ventricle through patent foramen ovale [8,16], (b) encephlalopathy and (c) Peripheral neuropathy, with sensory predominant symmetrical or asymmetrical involvement [8,15].

Eosinophilic meningitis accounts of less than 3% of all the meningitis cases [10]. Diagnosis of eosinophilic meningitis is based on clinical manifestations, detection of CSF eosinophilia on microscopy or autopsy findings of eosinophilic infiltration of the meninges. CSF eosinophilia identified by microscopic examination is defined as counts higher than 10 eosinophils per milliliter or 10% of the total CSF leukocyte count [17]. Since routine CSF examination and cell counts are usually done with fresh, unstained samples, eosinophils are difficult to identify and this under-detection of eosinophils in CSF contributes to the underestimation of the prevalence of eosinophilic meningitis [17]. Therefore it is important to specifically look for eosinophils in CSF with relevant staining methods even though the prevalence of eosinophilic meningitis is low, as it is important to make a crucial decision in management. Amongst the other causes for eosinophilic meningitis are helminthic infections (*Angiostrongylus cantonensis, Gnathostoma spinigerum, Taenia solium)*, neoplastic diseases including Hodgkin's disease, drug use and prosthetic reactions.

Meningeal involvement with eosinophilic infiltration due to idiopathic HES is noted uncommonly [8]. The first case of well-documented eosinophilic meningitis secondary to hypereosinophilic syndrome was reported by Weingarten et al. in 1985 [10]. A 56-year-old male with idiopathic HES presented with confusion and CSF evidence of eosinophilic pleocytosis (leucocyte count 53/μL with eosinophils 74%, prteins 113mg/dL). Other causes of CSF eosinophilia were ruled out and his autopsy following cardiopulmonary arrest had shown marked eosinophilic infiltration of multiple organ systems [10]. Choi H-Y et al. described a 36-year-old patient with idiopathic hypereosinophilic syndrome presenting with headache, in whom CSF showed leucocytes 43/μL, out of which 59% were eosinophils. He also had pleural effusion and multiple liver nodules as a part of systemic infiltration by the eosinophils. His symptoms and CSF eosinophilia had shown a good response to steroid therapy [11]. Chou CW described a patient with idiopathic HES with eosinophilic meningeal infiltration leading to subdural effusion and death despite adequate medical therapy and surgical drainage, emphasizing the poor prognosis of meningeal infiltration [19]. Kaplan et al. reported a 66-year-old lady with idiopathic HES presenting with dementia and CSF eosinophilia and following treatment showing complete resolution of symptoms and CSF findings following steroid therapy [20]. The limited numbers of other case reports to-date describe meningeal involvement in patients with idiopathic HES which were detected on autopsy findings. Thus the importance is highlighted in having a high degree of suspicion to diagnose HES causing CNS manifestations in the appropriate clinical background and to initiate treatment. Our patient presented with clinical features of meningo-encephalitis which was later confirmed with electroencephalogram and CSF findings. Other causes of CSF eosinophilia such as helminthic infestations, neoplasms like lymphoma and drugs were excluded in the cited case. Eosinophilic vasculitis was excluded as criteria for Churg-Strauss syndrome were not fulfilled and the lung biopsy findings were not favoring eosinophilic vasculitis. Meningeal biopsy was not performed due to high risk. Our patient did not have evidence of peripheral neuropathy, which is usually the commoner form of nervous system involvement in HES.

This index case also showed multisystem involvement with regard to hematological, central nervous system, cardiac and pulmonary systems. Although well recognized and common, cutaneous and gastrointestinal involvement were not observed in our patient. All these manifestations resolved with steroid therapy, strengthening the diagnosis of idiopathic HES in absence of a secondary cause.

With the development of molecular genetics, better understanding of the HES varients (myeloproliferative, T-lymphocytic, familial, undefined, overlap and idiopathic) and their pathogenesis lead to the development of new therapies for management. Current treatment options include imatinib (monoclonal antibodies inhibiting tyrosin kinase) [1] for *FIP1L1/PDGFRA* gene positive patients who show thyrosin kinase activity while glucocorticoid remains as the initial treatment for *FIP1L1/PDGFRA* gene negative patients. In the event of persisting disease or steroid intolerance, hydroxyurea, interfeon alfa, cyclosporine or anti-CD52 treatment is recommended [1]. But till now, most effective single treatment is prednisolone. Refractory patients are candidates for allogenic stem cell transplant [7]. Our patient showed a marked clinical response to steroids and hydroxyuria was subsequently added to low dose maintenance steroids to cover the persistent peripheral blood eosinophilia despite the patient being asymptomatic. He showed a good response to combined therapy.

Prognosis of HES has markedly improved since it was first described (3 year mortality 75-88%[13]) due to improved diagnostic methods, better understanding of pathogenesis, improved therapeutic measures and surgical interventions for cardiac involvement. Nowadays, prognosis depends on the extent of cardiac involvement and the likelihood of development of haematological malignancies.

Conclusion

Hypereosinophilic syndrome is a rare heterogenous disease with multisystem involvement. It may manifest with maningo-encephalitis as a presenting feature. It is important to have a high index of suspicion by the physicians in the background of persistent peripheral eosinophilia (after exclusion of secondary causes for eosinophilia) to diagnose and commence the appropriate treatment. The mortality of the condition is high with multi-organ involvement and early treatment can save lives.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-chief of this journal.

Authors' Contribution

HW made the clinical diagnosis and supervised the manuscript drafting. SSCG reviewed the literature and drafted the first manuscript. SBA contributed diagnosis by performing bone marrow biopsy. HW, SBA, SB, SBow, SSCG and SUJ were involved in direct management of the patient. All authors read and approved the final manuscript.

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