

Case Study: Idiopathic Hypereosinophilic Syndrome Who Was Treated for 2 Times as Pulmonary Tuberculosis

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Abstract: *Idiopathic hypereosinophilic syndrome is a myeloproliferative disorder with unexplained prolonged eosinophilia and marked predilection for involving multiple organs, especially the heart. Respiratory symptoms often mimic other commoner pulmonary disease states, leading to a diagnostic dilemma and delay in treatment initiation. We report here a case of hypereosinophilic syndrome in a young male who presented with recurrent haemoptysis shortness of breath, weight loss, low grade fever and cough. Since tuberculosis is very common in India and presentation is nearly same, patient was misdiagnosed and treated as tuberculosis twice*

Keywords: Hypereosinophilic syndrome, tuberculosis.

1. Introduction

Hypereosinophilic syndrome (HES) is a rare and heterogeneous group of disorders defined as persistent marked blood eosinophilia ($>1.5 \times 10^9/L$ for more than six consecutive months) associated with evidence of eosinophil-induced organ damage, where other causes of hypereosinophilia such as allergic, parasitic, and malignant disorders have been excluded. The prevalence is unknown, younger to middle-aged patients are most frequently affected, with a male predominance (4-9:1 ratio).

HES is a disease of multifactorial genesis, from clonal tumorous proliferation to reactive changes. The myeloproliferative variant caused by interstitial deletion in chromosome 4q12 and the lymphoproliferative variant associated with clonal proliferation of phenotypically abnormal T cells have been differentiated. An autosomal dominant familial form that has been mapped to chromosome 5q31, episodic form (Gleich's syndrome) and a clinically silent or benign form have also been described. In patients with the myeloproliferative variant, well responding to imatinib therapy, FIP1L1/PDGFRA (F/P) has been identified, being deemed an imatinib responsive HES. The lymphoproliferative variant HES (L-HES) is characterized by a phenotypically distinct clonal T cell population in peripheral blood. Hypereosinophilia is a consequence of the increased production of the eosinophilopoietic cytokine, especially interleukin 5 (IL-5). Diagnosis is based on establishing a population of T cells with an aberrant phenotype, most often CD3-CD4+CD8- in peripheral blood. However, around 50% of patients with HES can be classified as neither myeloproliferative nor lymphoproliferative variant. HES is treated by steroids, cytotoxic agents, immunomodulatory therapies, tyrosine kinase inhibitors monoclonal antibody therapy and bone marrow transplantation. The organs affected by hypereosinophilia differ from case to case. Most commonly, these are the skin, heart, lungs, central and peripheral nervous systems. Frequent manifestations are also hepato and/or splenomegaly, eosinophilic gastroenteritis, coagulation disorders, etc.

The lung may be affected usually presenting as eosinophilic pneumonia or may masquerade pulmonary tuberculosis clinically and radiologically. We report here a case of hypereosinophilic syndrome presenting in a young male with fever, cough, chest pain haemoptysis and dyspnoea, weight loss with radiological b/l infiltrates that was treated as pulmonary tuberculosis twice.

2. Case report

A 35-year-old male presented with cough, shortness of breath, and recurrent mild haemoptysis for 9 months. There was no haematemesis, melaena, jaundice, or fever. Over the past two weeks, his dyspnoea had progressively increased

He was diagnosed with pulmonary tuberculosis four years ago on the basis of low-grade fever, cough, streaky recurrent haemoptysis, significant weight loss and radiological pulmonary infiltrates, although repeated sputum examination did not show acid-fast bacilli. She had received anti-tubercular treatment (ATT) for 9 months. This time again he was prescribed ATT and took ATT for 6 months as he presented with same symptoms with no relief with the ATT. There were no other significant past illnesses. On physical examination, the patient was pale, was tachypnoeic and had a pulse rate of 120/minute. The blood pressure was normal. There was no lymphadenopathy, sternal tenderness, peripheral signs of embolism or infective endocarditis. On cardiac examination, the apical beat was normally situated. There were bilateral upper and midzone crepitations

Rest of the examination was normal. Investigations revealed microcytic hypochromic anaemia and leucocytosis (P26L12E60M2). The total eosinophil count was $11,500/mm^3$. The platelet count was normal and the ESR (Westergren) was 65 mm in the first hour. The hepatic and renal functions were normal. Review of past medical records revealed persistently elevated eosinophil counts. Stool examination did not show any ova or cysts. Peripheral smear did not reveal microfilaria. serological tests for suspected parasitic infections like schistosomiasis, filariasis, toxocariasis etc The total IgE levels were normal and serum precipitins to aspergillus were negative. Skin prick tests and

allergen specific IgE tests were negative. The tuberculin test was not reactive and sputum was repeatedly negative for acid-fast bacilli. Antinuclear and antineutrophil cytoplasmic (ANC) antibodies were not detected in blood. The coagulation profile was normal. Lupus anticoagulant and IgM and IgG anticardiolipin antibodies were absent.

Cytogenetic analysis on bone marrow aspirate and Molecular analysis on peripheral blood cells for *PDGFRA*, *PDGFRB* and *FGFR1* gene rearrangements were not done. Serum erythropoietin levels were normal, serum vitamin B12 were also normal. Imaging studies (CT scan, ultrasound) of chest and abdomen for underlying lymphoma or non-haematological malignancy were negative. Serum troponin and ECG / echocardiogram were normal. Pulmonary function tests were also done which were normal.

Chest radiograph revealed a normal-sized heart with bilateral upper- and middle-zone fibro-parenchymal infiltrates. The bone marrow biopsy examination showed increased eosinophils and its precursors (30%) with no appreciable increase in immature cells or evidence of fibrosis in the marrow. Fiberoptic bronchoscopy (FOB) showed an inflamed apical segment of the right upper lobe. Bronchoalveolar lavage fluid recovered a large number of eosinophils with acute inflammatory exudate. Transthoracic echocardiography was normal. The contrast-enhanced computed tomogram (CECT) of the chest showed patchy fibrosis predominantly involving the peripheral and subpleural areas of the middle and upper lobes of both lungs. A Doppler scan did not show any thrombus in the inferior vena cava, hepatic veins, or veins of both lower limbs. A course of diethylcarbamazine citrate failed to revert the eosinophilia. An upper gastrointestinal endoscopy revealed eosinophilic gastropathy. In view of the persistently elevated eosinophil count with multiorgan involvement, a diagnosis of hypereosinophilic syndrome was considered and oral prednisolone initiated at 1 mg/kg/day. Within 1 week, the eosinophil count normalised.

The eosinophil count remained normal. The patient improved symptomatically and was discharged on and prednisolone after 6 weeks of hospitalisation. He is on our regular follow up and doing fine.

3. Discussion

Idiopathic hypereosinophilic syndrome (HES) is a myeloproliferative disorder with unexplained prolonged eosinophilia and marked propensity for damaging specific organs like the heart. The diagnosis is based on the following criteria:

- 1) sustained eosinophilia > 1,500 eosinophils /mm³ for more than six months;
- 2) the absence of any other cause of eosinophilia including parasitic infections and allergic disorders, and 3) signs and symptoms of organ involvement, most frequently the heart, gastrointestinal tract, central and peripheral nervous systems, lungs and skin¹.

Hypereosinophilic syndrome is predominantly a disease of middle-aged males (male: female ratio of 9:1). The onset is insidious with symptoms such as lethargy (26%), cough

(24%), dyspnoea (16%), muscle pains and angioedema (14%), rash or fever (12%) and retinal lesions (10%), weight loss and cachexia. Although cardiac involvement is a common manifestation of HES, recurrent pulmonary thromboembolism is rarely observed.

Approximately 40 - 60% of patients have pulmonary involvement, usually presenting with a chronic, persistent, non-productive cough². Pulmonary involvement in HES may be secondary to congestive heart failure, infiltration and sequestration of eosinophils in lung tissues, or pulmonary emboli originating from ventricular thrombi. In contrast to the pulmonary infiltrates in chronic eosinophilic pneumonia, HES may show diffuse or focal infiltrates without any lobar preference (seen in 14 - 28% of patients)^{3,4}. These infiltrates may or may not clear with prednisolone treatment, and pulmonary fibrosis can develop in patients with EMF⁵. Adult respiratory distress syndrome is an occasional complication of HES and may be associated with poor prognosis⁶. Recurrent pulmonary thromboembolism is rare and may lead to chronic pulmonary hypertension⁷.

Cardiac involvement in HES begins with either acute myocarditis or endocardial damage by circulating eosinophil proteins. This is followed by formation of a mural thrombus, typically at the apex of one or both ventricles and propagating toward the ventricular inflow tracts, often causing atrio-ventricular valve incompetence.

Finally, the thrombus gets organised and fibrosed, giving a typical echocardiographic finding of an echodense mass that obliterates one or both ventricular cavities⁶. Although survival for up to 12 years has been observed, EMF is usually relentlessly progressive. Death is due to progressive myocardial failure often associated with pulmonary congestion, infection, infarction, or sudden unexpected cardiovascular collapse, presumably arrhythmic in origin.

However, the risk of developing cardiac disease is not necessarily related to the extent or duration of eosinophilia⁶. HES patients who do not develop heart disease tend to be females with angioedema, hypergammaglobulinaemia, and increased serum levels of IgE and immune complexes. The patient's haemoptysis and pulmonary infiltrates in the last few years could be due to recurrent episodes of eosinophilic pneumonia. However, with a marked similarity of these symptoms with pulmonary tuberculosis, she was probably misdiagnosed and treated with anti-tubercular therapy, thus leading to valuable time being lost and progression to irreversible multisystem involvement. Patients with haemoptysis and eosinophilia may be seen in other diseases such as parasitic infections, allergic bronchopulmonary aspergillosis, etc; however, HES must be ruled-out as well in these circumstances.

The prognosis of HES is good, with 80% survival at 5 years, provided the cardiac damage can be managed. No therapy is indicated if there is no evidence of any target organ damage, or if there is isolated eosinophilia. Corticosteroids are the first-line agents, generally administered as a short course of oral prednisolone in the dose of 1 mg/kg/day that is tapered when peripheral eosinophilia resolves. Hydroxyurea and Vincristine may be used in selected steroid unresponsive

patients. Leukapheresis and plasma exchanges have been tried in severe eosinophilia, but their use should be restricted for emergency purposes only. Recently, imatinib mesylate, a tyrosine kinase inhibitor has been tried in HES with good response⁷. Antiplatelet and anticoagulant therapy is indicated wherever thromboembolism is documented. Cardiac surgery is necessary in patients with marked valvular compromise and endomyocardial thrombosis or fibrosis.

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