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*RESEARCH ARTICLE*

# MYELOPROLIFERATIVE HYPEREOSINOPHILIC SYNDROME; A RARE CAUSE OF DILATED CARDIOMYOPATHY WITH A REVIEW

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## Abstract

Hypereosinophilic syndrome (HES) is aheterogenous group of rare haematological disorders, the majority of which are idiopathic. Cardiac manifestations of HES are rare and the myeloproliferative HES (M-HES) is very rare. Eosinophilic myocarditis and endomyocardial fibrosis are a typical course of morbidity and mortality in hypereosinophilic syndrome. We present a case of idiopathic eosinophilia who presented with dyspnea, abdominal distention and edema with peripheral eosinophilia (82%) in a complete blood count test done before presentation to us. Echocardiography showed enlarged cardiac chambers, global hypokinesia,moderate to severe tricuspid regurgitation, with reduced left ventricular ejection fraction <40% suggestive of dilated cardiomyopathy (DCM). Parasitic disease, autoimmune disease and drug induced cardiomyopathy were excluded as possibilities. He was treated with steroids, imatinib, and anti failure therapy. Cardiac function improved with therapy and the eosinophilic count reduced. Monitoring chest radiography and electrocardiogram and echocardiography according to fluctuations in eosinophils may enable early detection and treatment of cardiac involvement in patients with HES.



## Introduction:-

Hypereosinophilic syndrome (HES) is a rare and heterogenous group of haematological group of disorders characterized by blood and tissue eosinophilia and eosinophilia driven tissue damage and dysfunction.[1-4] Tissue damage results from eosinophilic infiltration,eosinophil induced fibrosis, allergic mechanism or eosinophilic promotion of hypercoagulability.[5] Clinically HES manifestations can be extremely varied[3]. Cardiac dysfunction is reported in fewer than 5% of the patients at the time of diagnosis. [3,6,7]Skin,lung and gastrointestinal involvement is most common manifestation and affects about 14-37% patients.[3]

Here we report a case of hypereosinophilia who presented with congestive cardiac failure. The patient exhibited cardiomegaly on chest radiography and a low voltage ECG. Echocardiography showed a dilated cardiomyopathy which is very very rare in HES.

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**Casereport**

A 15 year old male patient was admitted to the hospital for dyspnea,abdominal distention and edema of two week duration. Initially he had exertional dyspnea progressing to dyspnea on ordinary work. He also noticed abdominal distention which was progressive and developed bilateral shin and pedal edema. His medical history was insignificant and was on no medication. He had no history of any drug intake or parasitic infection. Examination revealed a poorly nourished lean built, dyspneic patient. His jugular venous pressure (JVP) was raised. He had tachycardia, bilateral shin and pedal edema. Cardiovascular examination revealed cardiomegaly, diffuse apical impulse and a thrill in mitral and tricuspid area. He had loud S1 with a mitral and tricuspid systolic murmur. Chest examination revealed bilateral inspiratory crepts. Abdominal examination showed hepatomegaly with shifting dullness.

Laboratory findings on admission showed marked leukocytosis 72,100 with 80 % eosinophils. Haemoglobin was 7.6 gm/dl with raised ESR (30 mm), elevated CRP concentration 24mg/dl (Normal level < 0.4 mg) and increased brain natriuretic peptide concentration of >2000pg/ml (Normal range: < 18.4 pg/ml) suggesting inflammation and myocardial damage. Liver function test showed transaminitis AST>265, ALT >220, elevated vitamin B12 levels.

A chest x-ray revealed cardiomegaly with bilateral pleural effusion (fig 1), and electrocardiogram showed low voltage, abnormal Q waves and sinus tachycardia(fig II). An abnormal USG showed hepatomegaly, splenomegaly with moderate ascites. HRCT thorax revealed Cardiomegaly, Pulmonary edema with bilateral pleural effusion. Echocardiography showed enlarged and dilated (RA/RV/LA/LV) cardiac chambers with severe eccentric mitral regurgitation, moderate to severe tricuspid regurgitation, global hypokinesia and systolic dysfunction with an ejection fraction of <40%. There was no thickening of ventricular wall (hypertrophy), apical thrombus or vegetation. A diagnosis of dilated cardiomyopathy was made.

In view of very high leukocytosis with marked eosinophilia (fig 3), a bone marrow aspiration was done. The bone marrow examination revealed myeloid hyperplasia with minimal increase in eosinophilic precursors. No blast cells were seen. After this patient was diagnosed as myeloproliferativehypereosinophilic syndrome (M-HES) with resultant dilated cardiomyopathy.

The patient was diagnosed with dilated cardiomyopathy with congestive cardiac failure with anaemia. He was treated with diuretics, oral prednisolone and imatinib (tyrosine kinase inhibitor).The patient improved over a period of two weeks. After discharge he was monitored as an outpatient by tracking his eosinophil count.He is doing well on follow up.

## Discussion:-

The aim of this review is to improve the overall knowledge of different HES variants with respect to patient data at diagnosis, signs and symptoms, organ involvement, treatment and outcomes. Results are based on 350 individual case reports with support from 19 publications containing aggregate data.

Hypereosinophilic syndrome was coined by Hardy and Anderson in 1968[8]. Hypereosinophilia is characterized by an elevated eosinophil count ($>1.5\times10^9$/L) observed on two separate occasion more than one month apart. HES is a rare[1,2]group of haematological disorders that result in peripheral hypereosinophilia and organ damage directly attributed to tissue hypereosiniphilia. HES is usually diagnosed in the age group of 20 to 50 years.[9] The HES is more common in males as compared to females[3,9,10]. It is currently understood that M-HES is more common in males but other HES variants occur more equally across sexes[3,9-11].

The distribution of HES variants among patients with HES is not well characterized[9]; indeed the 188 included publications give a representative data on the distribution, which collectively showed a distribution of 43% I-HES, 11- 14% M-HES and 16% to 22% L-HES[3,10,11]

The distribution recorded depends wholly on the definitions and diagnostic techniques used which varies between studies because consensus criteria for all HES variants have not been established. Newer detection methods may detect chronic eosinophilicleukemias not on steroids(CEL-NOS) cases that may otherwise have been classified as I-HES cases[12] and RT-PCR/genomic PCR can detect the FIPILI-PDGFRA fusion where others do not[13].

The diagnostic criteria for HES includes a blood eosinophilic count of more than 1500 cells/μL[14,15]. A multicenter retrospective study of patients with HES (n=188) reported absolute blood eosinophil counts of 1500- to 400,000 cells/μL with a peak mean eosinophilic count of 6600 cells/μL[3]. Our patients had M-HES with a blood eosinophilic count of 57,680 cells/μL

HES patients commonly present with dermatological,respiratory and gastrointestinal symptoms but less than 5% demonstrate cardiac symptoms at the time of diagnosis[3,16,17]. HES has previously been associated with early deaths[9] particularly in patients with PDGRA associated M-HES[18]. Many reports of HES with respiratory symptoms have been reported[3]. Patients of M-HES/CEL-NOS more frequently presented with splenomegaly (40-67%) and patients with L-HES more frequently with skin conditions (upto 34%)[11].

The heart involvement is more common in M-HES as also to the present report. Cardiac manifestations particularly eosinophilic myocarditis and endomyocardial fibrosis are common causes of morbidity and mortality in HES[3,4,19]. Loeffler first reported the association between eosinophilia and heart disease in his observation of fibroplastic parietal endocarditis and peripheral eosinophilia.[20]The cardiac pathology of HES can be classified into three stages; an acutenecrotic stage, a thrombotic necrotic stage and a late fibrotic stage[4]. The pathogenic mechanism of acute necrotizing eosinophilic myocarditis has not been defined, extensive infiltration of eosinophils into the myocardium and activated eosinophils may cause tissue damage through release of toxic granules, cytokines or recruitment of inflammatory cells[19].

During initial stages of cardiac manifestation echocardiography is typically normal although wall thickening may be identified if there is myocardial edema because of inflammatory process. In the thrombotic stage, thrombi can be identified in the apices of ventricles. In the later stage echocardiography can reveal endomyocardial and valvular tissue fibrosis which may lead mitral regurgitation and restrictive cardiomyopathy[4,21-23]there were no thrombi or restrictive cardiomyopathy in our case.

Cardiac magnetic resonance imaging can detect endocardial fibrosis with wall thickness due to inflammatory edema within the myocardium. As patient refused to undergo endomyocardial biopsy which is gold standard for definitive diagnosis of eosinophilicendomyocardial disease[8,24]. Some cases of eosinophilic myocarditis without peripheral eosinophilia were diagnosed by endomyocardial biopsy[8,24].

In our case patient had severe peripheral eosinophilia, with myeloid hyperplasia with marked increase in eosinophilic precursors, congestive heart failures and echocardiography showing features of dilated cardiomyopathy with an ejection fraction of <40%, a diagnosis of M-HES with dilated CMP was made.

The treatment of HES for all variants include corticosteroids. Patients with M-HES and among them also with rearrangements of PDGFRB or PDGFRA variants may also be prescribed imatinib at dose of 100 to 400mg daily[9,25]. Additional options for those with L-HESor CEL-NOS include hydroxyurea and interferon alpha[11]. Several trials have used imatinib in different HESvariants, showing some response in patients with L-HES, I-HES or CEL-NOS. our patient received imatinib and improved along with corticosteroids.

Mepolizumab has only recently been approved for HES without an identifiable non haematological cause[26] and other anti IL-5/IL-5 receptor antibodies (including reslizumab and benalizumab) and anti-cd 52 antibodies (alemtuzumab) are still under clinical investigation[9].

## Conclusion:-

Hypereosinophilic syndrome (HES) is rare and cardiac involvement confers a poor prognosis[27,28]. M-HES is even more rare among HES. Cardiac involvement causes myocarditis, inflammation, necrosis and fibrosis leading to restrictive cardiomyopathy. Our case is rarer one. M-HES presenting as dilated cardiomyopathy has been rarely reported. Response to imatinib[25,29-31] was excellent.

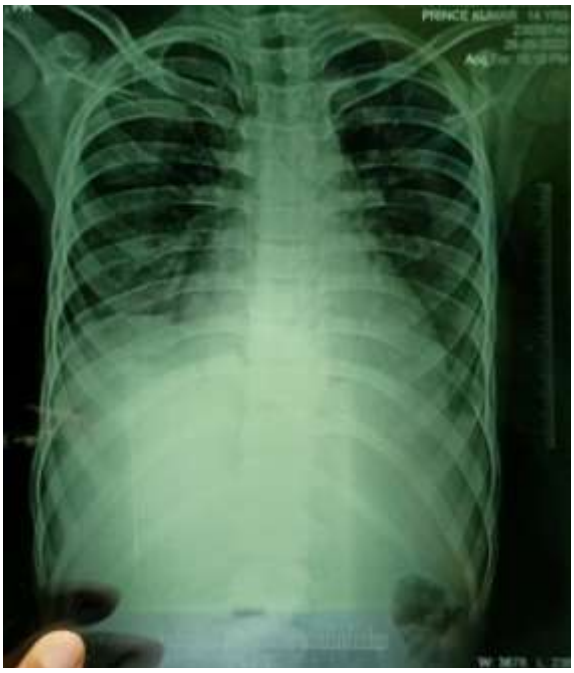

**Fig1:-**

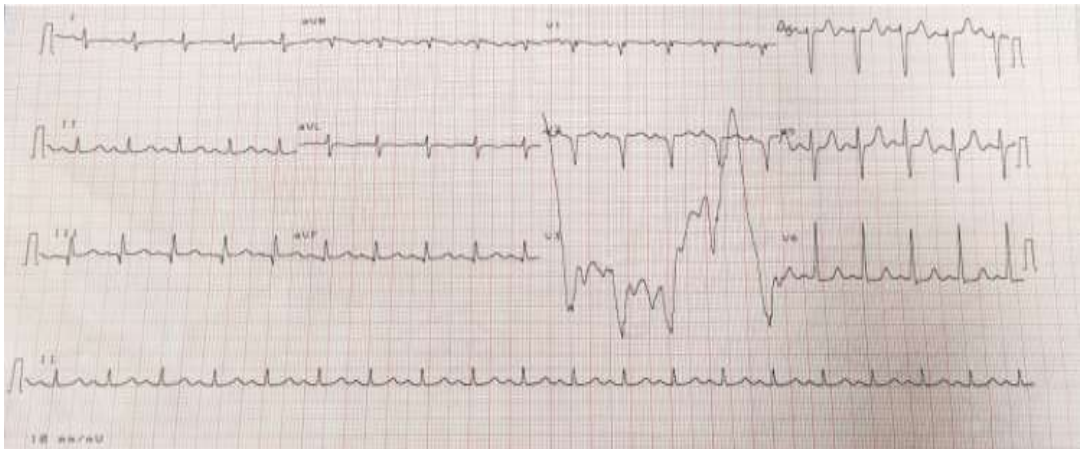

**Fig 2:-**

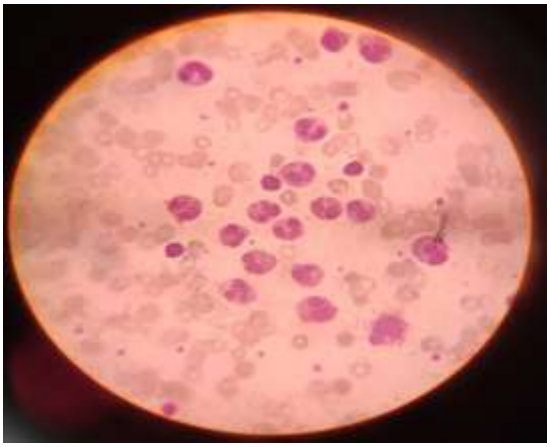

**Fig 3:-**

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