CASE REPORT

JIACM 2018; 19(3): 226-29

Fatal Eosinophilic Cardiomyopathy and Dysphonia: A Case Report From a Teaching Hospital in Nepal

RN Das, Rajesh Nepal**, Madhav Bista****

Abstract

***Background:** We report a rare case of Idiopathic hypereosinophilic (IHS) syndrome presenting as dilated cardiomyopathy with Ortner's syndrome, a diagnostic dilemma posed by it and a challenge in the treatment of this case.*

***Summary:** A 40-year-old non-smoker, teetotaler, non-diabetic Nepali farmer was admitted with persistent fever, cough, dyspnoea and refractory heart failure for 7 months. Clinical examination revealed fever (101° F), pulse 110/min, pressure 100/60 mmHg, distended jugular, pansystolic murmur and bibasal crackles. Earliest investigation revealed absolute eosinophil 68% and low haemoglobin. Echocardiography showed chamber dilatation and low ejection fraction (35%). Chest X-ray showed enlarged heart with bilateral pleural effusion. Conventional heart failure treatment with oxygen, frusemide and ramipril did little benefit. On subsequent hospital admission after a month, he developed atrial fibrillation and hoarse voice. Repeat peripheral eosinophil count was 65%. Serological, microbiological and stool tests were negative for ova, parasite and cysts. Echocardiography revealed more dilatation of chambers and thickened IVS. Laryngoscopy showed immobile left vocal cord. CT thorax confirmed pleural effusion, thickened alveolar septae and absence of mediastinal mass. Bone marrow showed hypercellularity with precursors of megakaryocytic and myeloid series and marked eosinophilia. Besides, warfarin and digoxin, empirically mebendazole and diethylcarbamazine (DEC) were added because of persistent eosinophilia. Trial dose of steroid in the face of heart failure dramatically reduced eosinophilia (68% to 8%) and relieved symptoms. The patient fulfilled criteria of IHS set by Michael Chusid. Patient had (i) infiltration of myocardium, pleurae, lungs and marrow, (ii) persistently raised peripheral eosinophilia and (iii) clonally expanding and reactive causes of eosinophilia were excluded.*

***Conclusion:** Present case of IHS infiltrating many organs posed a diagnostic dilemma and therapeutic challenge. High index of suspicion, meticulous investigations and judicious steroid administration resulting in dramatic relief and drastic reduction of eosinophilia confirmed IHS.*

***Key words:** Eosinophilia, cardiomyopathy, Ortner's syndrome.*

Introduction

Idiopathic hypereosinophilic syndrome (IHS) is so rare that in USA from 1971 to 1982 only 50 cases were reported with a prevalence of 1 - 2 per million people[1]. It manifests as persistently high peripheral eosinophilia causing infiltration and dysfunction of intestine, heart, lungs, pleurae, bone marrow and brain[2]. IHS is diagnosed after excluding clonal proliferation of eosinophils in myeloproliferative disorders and reactive eosinophilic expansion in acute or chronic infective or inflammatory diseases[3]. Though protective, eosinophils can damage vital organs by releasing cytotoxic granules such as eosinophilic major basic protein (MBP), cationic protein (ECP) and neurotoxin (EDN) leading to end-organ damage[4]. In tropics, parasitic infestation remains the chief cause of eosinophilia. IHS rarely involves the heart with significant morbidity and mortality. There are two eponymous hypereosinophilic heart diseases namely, 'Davies disease' or endomyocardial fibrosis, prevalent in the tropics and 'Loffler's syndrome' or eosinophilic endocarditis without any geographic predilection recorded in medical literature[5]. Present study reports a case of IHS with dilated cardiomyopathy which responded with steroids.

Case presentation

A 40-year-old non-smoker, teetotaler, non-diabetic normotensive patient from Eastern Nepal was admitted with fever (101° F), dry cough and progressive breathlessness for 7 months. Clinically he had anaemia, tachycardia, apical pansystolic murmur and bibasal crackles. There was no pruritic or vasculitic skin rash nor was any neurological deficit detected. Routine investigations revealed high peripheral eosinophilia (68%). Total WBC 17,250/cumm and absolute eosinophils were 11,212/cumm, respectively. Stool examination revealed no ova, parasite and cysts. Midnight microfilaria microscopy was negative. Aspergillus precipitin, rheumatoid factor and pANCA tests were negative. Echocardiography showed dilated chambers, thickened IVS and low ejection fraction (35%). Chest radiology confirmed

**Head, **Assistant Professor, ***Lecturer, Department of Medicine, Nobel Teaching Hospital, Biratnagar, Nepal.*
Corresponding Author: Dr RN Das, Head, Department of Medicine, Nobel Teaching Hospital, Biratnagar, Nepal. Phone: 977 9814301308, E-mail: das_drdeepak2004@yahoo.com.

cardiomegaly, pulmonary infiltrates and pleural effusion. Routine blood sugar, electrolyte, renal, thyroid and liver function tests were normal. He was diagnosed as Idiopathic dilated cardiomyopathy. He was given anti-heart failure treatment with oxygen, frusemide and ramipril with little benefit. On second hospital admission he developed fast atrial fibrillation, low BP, distended jugular veins, hoarse voice and enlarged tender liver. He had no lymphadenopathy, sternal tenderness or hepatosplenomegaly. Repeat tests showed WBC 16,400/cumm and absolute eosinophil counts 11,152/cumm, respectively (Table I). Bone marrow showed hypercellularity with megakaryocytic and myeloid series and predominance of eosinophilic precursors. No immature cells were found (Fig. 3). The serial investigations have been shown below in Table I.

Table I: Serial investigations.

Date	WBC	Eosinophils (%)	CXR	ECHO	ECG	CT thorax	Laryngoscopy	Bone marrow
12.12.14	16,400	11,152 (68)	Cardiomegaly		ST			
10.06.15	17,250	11,212 (65)	Cardiomegaly, pleural effusion,	LA (4.8) IVS (11)	ST			
12.07.15	13,440	7,526 (56)	Cardiomegaly, pleural effusion, pulmonary infiltrates	LA (5.2) IVS (12)	AF	Septal thickening	Left vocal cord palsy	Myeloid hypercellular marrow; high eosinophil count (> 60%)
13.07.15	9,850	2,758 (28)	No pleural effusion; pulmonary infiltrate: reduced	LA (5.2) IVS (12)	AF	Septal thickening		
05.08.15	7,600	608 (8)	No pulmonary infiltrates	LA (5.2) IVS (12)	AF (slow)			

NB: ST: Sinus tachycardia, AF: Atrial fibrillation, IVS: Interventricular septum, LA: Left atrium.

CT thorax confirmed pleural effusion, bilateral alveolar septal thickening and no mediastinal mass. Pleural fluid aspirate showed protein 5.2 gm% and eosinophils 32%. He was initially treated for congestive heart failure due to idiopathic dilated cardiomyopathy and was given conventional heart failure treatment. On second admission after a month, he had persistent eosinophilia (65%), atrial fibrillation and hoarse voice. Empirically he was treated with mebendazole and DEC for unidentified parasites producing persistent eosinophilia but there was little improvement. After excluding all secondary causes of eosinophilia, a trial dose of corticosteroid (1 mg/kg) was given in the face of heart failure along with diuretics, digoxin, warfarin and ramipril. Eosinophilia reduced significantly from 68% to 65% then 28% and finally 8% within 3 weeks. Patient was improved symptomatically but dysphonia persisted. The patient was discharged with relevant medications and advised for follow-up.

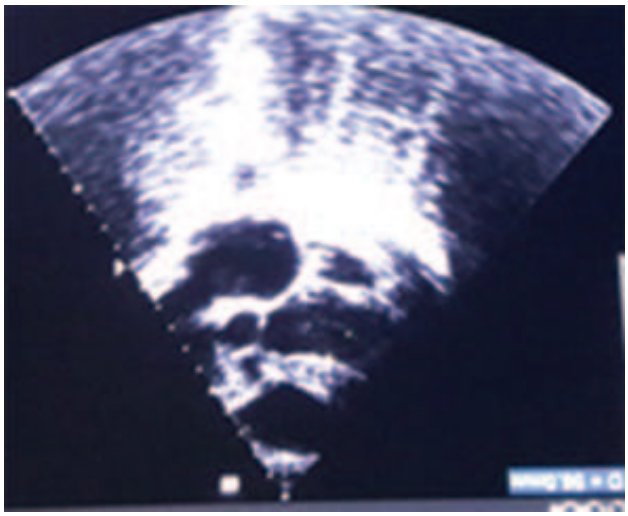

Fig. 1: *Dilated cardiomyopathy with thickened IVS.*

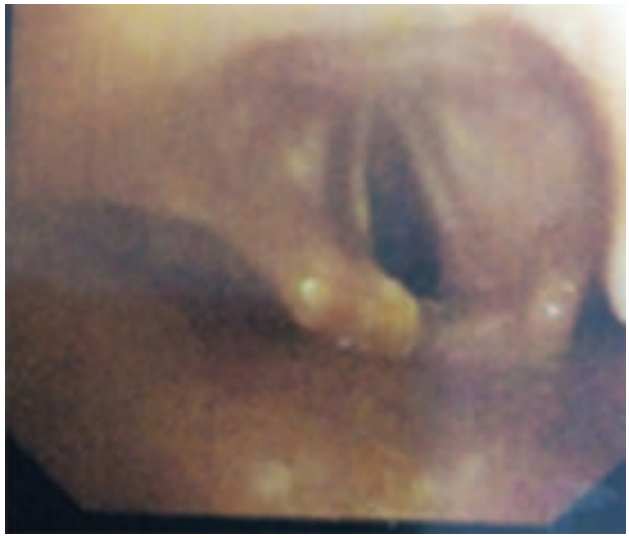

Fig. 2: *Laryngoscopy: Impaired movement of left vocal cord. No mass or ulcer seen.*

Discussion

Eosinophilia in a tropical country like Nepal is a common finding in routine blood test for many medical disorders.

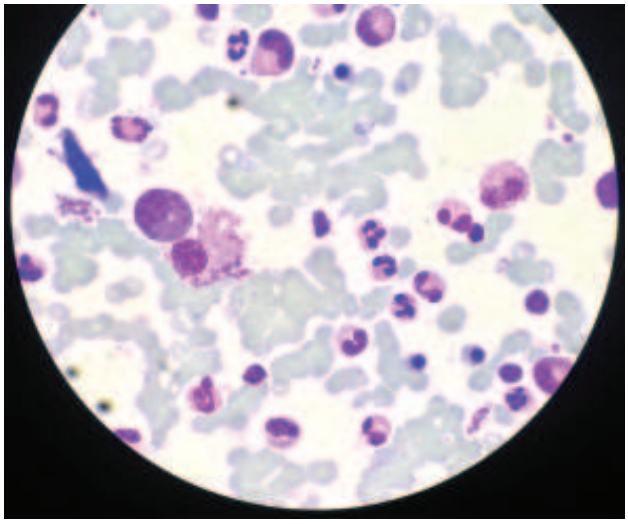

Fig. 3: *Bone marrow showed hypereosinophilia.*

Eosinophilia occurs in allergy, autoimmune, bacterial, fungal and parasitic infestation as a protective immune reaction. Eosinophilia is seen infrequently in blood dyscrasias and malignancies. All common causes of peripheral eosinophilia were excluded in the present case (Table II).

Table II: Common causes of eosinophilia in the tropics.

Causes	Pathogenic agents
infection	1. Helminths: nematodes, cystodes, trematodes (also scabies) 2. Bacteria: rebound post-sepsis, Lyme's disease 3. Fungus: aspergillosis
Neoplasia	1. Lymphoma: Hodgkin's or T-cell non-Hodgkin's (secretes IL-5) 2. AML-eosinophilic leukaemia 3. CML-hypereosinophilic syndrome
Autoimmune	1. Atopy: food or drug allergy, asthma, eczema 2. Vasculitis: esp., PAN, rheumatoid arthritis, Chürg-Strauss syndrome 3. Addison's disease

In this study, patient had persistent eosinophilia which infiltrated: (i) bone marrow causing anaemia and eosinophilia, (ii) invaded pleura causing effusion, and (iii) lungs causing parenchymatous infiltrate besides (iv) myocardium causing dilated cardiomyopathy with unusually thickened intraventricular septum. The enlarged left atrium had impinged on left recurrent laryngeal nerve causing Ortner's syndrome. There was no evidence of eosinophilic leukaemia or lymphoma from physical examination and laboratory tests. In 1957 Bousser *et al* reviewed 29 cases of hypereosinophilia with various types of clinical manifestations[6]. In 1961 Bentley reviewed a case of "hyper" eosinophilia and thought it to be an eosinophilic leukaemia. He also laid down a set of criteria to differentiate 'blastic' form of leukaemia from 'mature' form of hypereosinophilic syndrome[7]. In 1968 Hardy and Anderson first reported IHS[8]. In 1971, similarly Rickles *et al* reviewed 16 cases of hypereosinophilic syndrome, most of which came out to be doubtful eosinophilic leukaemia[9]. After that many isolated cases with various manifestations were reported across the globe. In 1975 Chusid *et al* analysed 14 cases of idiopathic hyperesonophilic syndrome (IHS) with review of literature and published a review article giving a set of criteria for the diagnosis of IHS as opposed to eosinophilic leukaemia. He laid down three criteria, (i) peripheral eosinophilia more than 1,500 cells/cu mm for at least six months duration, (ii) signs, symptoms of end-organ (heart, lungs, gastrointestinal tract, skin, bone-marrow, brain damage with eosinophilic tissue infiltration/injury and (iii) exclusion of known secondary causes of eosinophilia[10].

Present case of a middle-aged male fulfilled all those criteria and designated as IHS, first to be reported from Nepal having dilated cardiomyopathy and heart failure. IHS can occur from 5 - 80 years though middle-aged patients (45 to 55 years) predominate[11] and a literature review showed that more than 90% of cases occurred in males[12]. Though 78% cases of IHS were documented in Caucasians, no study revealed true prevalence in Asian population. Present case showed persistent eosinophilia over 7 months with cough and dyspnoea and was attributed to heart failure.

The eosinophilic pleuro-parenchymal infiltrates were demonstrated on chest imaging and pleural aspirate revealed 32% eosinophils with raised protein (5.2 gm%) reflecting eosinophilic infiltration. The pericardium and myocardium were also infiltrated as evidenced by effusion, chamber dilatation and thickened septum demonstrated by echocardiogram. Laryngoscope revealed immobile left vocal cord. The dramatic reduction of eosinophilia from 68% to 65%, then 56% to 28% and finally 8% along with symptomatic improvement by steroid administration proved this case to be a rare example of IHS. His hoarse voice persisted. CT neck and thorax did not reveal any mass infiltrating the recruitment lamynged nerve. His marrow also showed hypercellularity of megakaryocytes and myeloid series with predominance of eosinophilic precursors. Literature showed that a small proportion of patients with IHS had mutation of PDGFRA and FIP1L1 genes involving tyrosine kinase fusion protein dysfunction[13]. Though testing for this mutation is now a routine practice in Europe, as its presence indicates response to tyrosine kinase inhibitor 'imatinib', we had no facility to do this type of cytogenetic investigation in Nepal.

Conclusion

A Nepali farmer had persistent eosinophilia infiltrating

myocardium, pleurae, lung-parenchyma and bone marrow. His conventional heart failure treatment did not give him any relief. Though eosinophilia in Nepal is a common laboratory finding but high index of suspicion of IHS must be considered in multi-organ dysfunction with persistent eosinophilia. Subsequent hospital admissions confirmed IHS after marrow examination, dramatic response of steroid in reducing eosinophilia and relieving patient's symptoms. Mebendazole and DEC had no effect on eosinophilia. The patient was discharged with conventional treatment and advised follow-up. The awareness of IHS among attending physicians in the tropics will avoid misdiagnosis of multi-organ dysfunction and early detection and institution of proper treatment will save patients.

Aknowledgement: The authors are grateful to Dr. Biswanath Adhikari, Dy. CEO, Nobel Teaching Hospital, Biratnagar, Nepal for giving permission to study the medical records of the patient.

References

1. Seifert M, Gerth J, Gajda M *et al*. Eosinophilia - a challenging differential diagnosis (German). *Med Klin (Munich)* 2008;103 (8): 591-7.
2. Bain B. The idiopathic hypereosinophilic syndrome and eosinophilic leukaemias. *Haematologica* 2004; 89 (2): 133-7.
3. O'Connell EM, Nutman TB. Eosinophilia in Infectious Diseases. *Immunol Allergy Clin North Am* 2015; 35 (3): 493-522.
4. Liao W, Long H, Chang CC *et al*. The Eosinophil in Health and Disease: from Bench to Bedside and Back. *Clin Rev Allergy Immunol* 2015.
5. Gotlib J. World Health Organisation-defined eosinophilic disorders: 2014 update on diagnosis, risk stratification, and management. *Am J Hematol* 2014; 89 (3): 325-37.
6. Simon HU, Rothenberg ME, Bochner BS *et al*. Refining the definition of hypereosinophilic syndrome. *J Allergy ClinImmunol* 2010; 126 (1): 45-9.
7. Bentley HP, Reardon AE, Knoedler JP. Eosinophilic leukaemia. *Am J Med* 1961; 30: 310.
8. Hardy WR, Anderson RE. The hypereosinophilic syndromes. *Ann Intern Med* 1968; 68 (6): 1220-9.
9. Fazel R, Dhaliwal G, Saint S *et al*. Clinical problem-solving. A red flag. *N Engl J Med* 2009; 360 (19): 2005-10.
10. Chusid MJ, Dale DC, West BC *et al*. The hypereosinophilic syndrome: analysis of fourteen cases with review of the literature. *Medicine (Baltimore)* 1975; 54 (1): 1-27.
11. Curtis C, Ogbogu PU. Evaluation and Differential Diagnosis of Persistent Marked Eosinophilia. *Immunol Allergy Clin North Am* 2015; 35 (3): 387-402.
12. Simon HU, Rothenberg ME, Bochner BS *et al*. Refining the definition of hypereosinophilic syndrome. *J Allergy ClinImmunol* 2010; 126 (1): 45-9.
13. Metzgeroth G, Walz C, Reiter A *et al*. Safety and efficacy of imatinib in chronic eosinophilic leukaemia and hypereosinophilic syndrome – A phase-II study. *Br J Haematol* 2008; 143 (5): 707-15.