Sri Lanka Journal of Medicine **SLJM**

Case Report

Citation: Alahakoon BD, Gowrishankar B & Weerasooriya N, et al.,2022. Hypereosinophilic Syndrome: a case of diagnostic and therapeutic difficulty. Sri Lanka Journal of Medicine, pp 92-96
DOI: http://doi.org/10.4038/sljm.v31i2.327

Hypereosinophilic syndrome: A case of diagnostic and therapeutic difficulty

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Abstract

Hypereosinophilic syndrome (HES) is a condition with a diverse clinical presentation and prognosis. Due to its rarity, it is often under-recognized. We present a 48-year-old female patient who presented with eosinophilic pneumonia and bullous pemphigoid; a rare skin manifestation of HES. It was considered as primary HES after a comprehensive evaluation excluded secondary causes. However, clinical picture and laboratory makers were inconclusive to categorize her as either myeloid or lymphoid HES. It was presumed to be of Lymphoid HES subtype since she responded well to a course of cyclosporin A. Due to heterogeneous clinical picture and multiple molecular and laboratory markers, evaluation of a patient with eosinophilia may be challenging, time consuming and costly. Expanding knowledge of disease endotyping and novel biomarkers have favorably modified the diagnosis and management of HES.

Keywords: *Hypereosinophilic syndrome, bullous pemphigoid, lymphoid HES, Cyclosporin A, Steroid therapy*

INTRODUCTION

Hypereosinophilia(HE) has been defined as a condition with a peripheral blood eosinophil count greater than 1500/mm^3 on two consecutive occasions, persistent for a minimum of 1 month with evidence of organ damage and/or dysfunction attributable to tissue eosinophil infiltration (1). Eosinophilic disorders can be single-organ diseases or multiple-organ diseases, accompanied by variable degree of blood eosinophilia. From an etiopathogenic point of view, eosinophilic disorders are classified as secondary/reactive to a broad range of causal factors, such as infections and allergens, or primary, when no causal factor can be identified. The term HE of undetermined significance is used to describe the subgroup of patients who have blood eosinophilia without end organ dysfunction. The classification criteria include other forms of HE, including idiopathic HE, overlap HE syndromes and associated HE disorders making the evaluation and diagnosis of this disorder complex and difficult (2).

CASE REPORT

We report a 48-year-old female patient who presented with a new onset rash and recent onset wheezing for 2 months' duration. She initially attributed the rash to the use of latex gloves, but it persisted even after she discontinued the practice.

Received: 2022-11-21 **Accepted revised version: 2022-10-27** **Published: 2022-01-08**

She was not any drugs and denied any allergies, but blood hyper eosinophilia with an absolute eosinophil count of 20,000 (200-500/mcL) was noted. She also developed new onset exertional dyspnoea and wheezing. 2 months into the course, she developed acute onset shortness of breath and desaturation which warranted hospital admission.

On admission she was afebrile and acutely dyspneic with a respiratory rate of 45/min. On respiratory examination, coarse crepitation and rhonchi were heard bilaterally in all zones. Healed vesicular and papular skin lesions were noted in bilateral arms, chest and torso.

Arterial blood gas revealed impending Type 1 respiratory failure for which she received noninvasive ventilation, successfully. The absolute eosinophilic count was 96,000 (200-500) with normal platelet and hemoglobin. The blood picture revealed marked eosinophilia with moderate rouleaux formation. CRP was 200mg/dl with an ESR of 79mmhr^{-1}. Liver, renal, and thyroid functions were normal. CXR-PA was suggestive of multilobar consolidation with predominant peripheral lung involvement. HRCT chest was reported as severe eosinophilic pneumonia (Figure 1). Bronchoalveolar lavage excluded active tuberculosis, bacterial and fungal infections. ECG and cardiac biomarkers were normal, transthoracic echo failed to demonstrate any systolic or diastolic dysfunction. Cardiac MRI was not performed. Subsequent analyses did not reveal any evidence of secondary HES including any autoimmune disease or parasitic infestation. She received 21 days of antihelminth treatment, despite which blood eosinophilia worsened. A bone marrow biopsy was performed, which demonstrated hyper cellular marrow with >80%, cellularity and markedly increased eosinophil lineage.

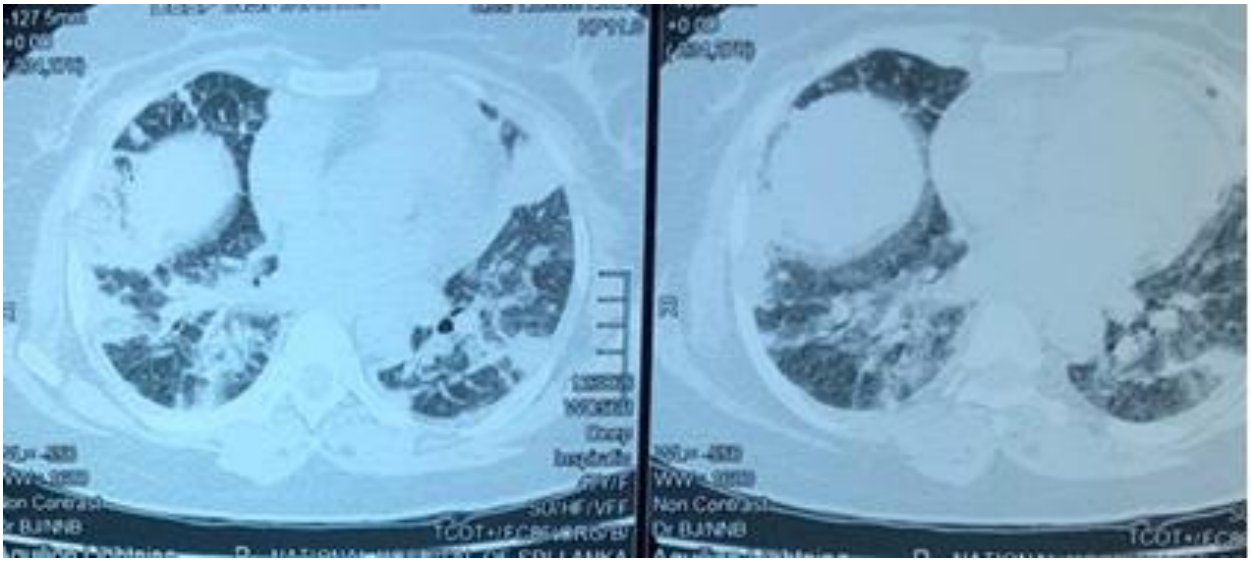

Figure 1 – High Resolution Computed Tomography of the Chest - Ground Glass pattern with predominant peripheral lung involvement

There was no evidence of myelofibrosis. T cell clonality was normal, therefore, T cell phenotypes and T cell receptor (TCR) gene rearrangement were not checked. FIP1L1-PDGFRA, JAK2 V617F, MPL, KITPD816U, CALR47 or BCR-ABL rearrangements were not detected by reverse transcription polymerase chain reaction technique done on peripheral blood. Serum tryptase was 6ng/l (3-15). IgE 399.0 (87) and vitamin B12 levels 1216 (187-883) were elevated. P-ANCA and C-ANCA were negative. USS abdomen failed to demonstrate hepatosplenomegaly. Skin biopsy from active lesions showed sub epidermal blister formation with eosinophils and superficial dermal oedema. Direct immunofluorescence (DIF) detected linear IgG and complement deposits at the basement membrane zone. These findings were compatible with bullous pemphigoid.

A diagnosis of hypereosinophilic syndrome with lung and skin involvement was made. She was pulsed with intravenous methylprednisolone for 3

days under broad antibiotic cover, before she was started on Imatinib 100mg daily, hydroxyurea 1g daily and high dose prednisolone (1mg/kg). At the end of the 2nd week a leukopheresis was offered. As the clinical and biochemical improvement was poor Imatinib was gradually increased to 400mg daily dose with minimal response. During the third week oral Ciclosporin 100 twice daily was introduced while tailing off steroids. 1 week into treatment patient demonstrated a favourable clinical response. A week after, the eosinophilic count dropped to the normal range (Figure 2).

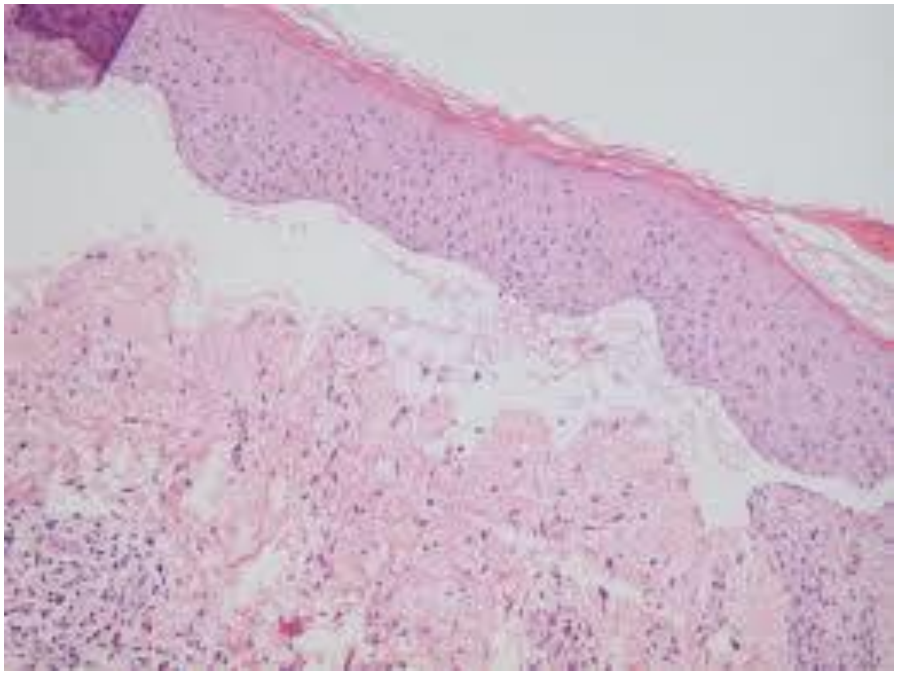

Figure 2 – Bullous pemphigoid lesion of upper arm

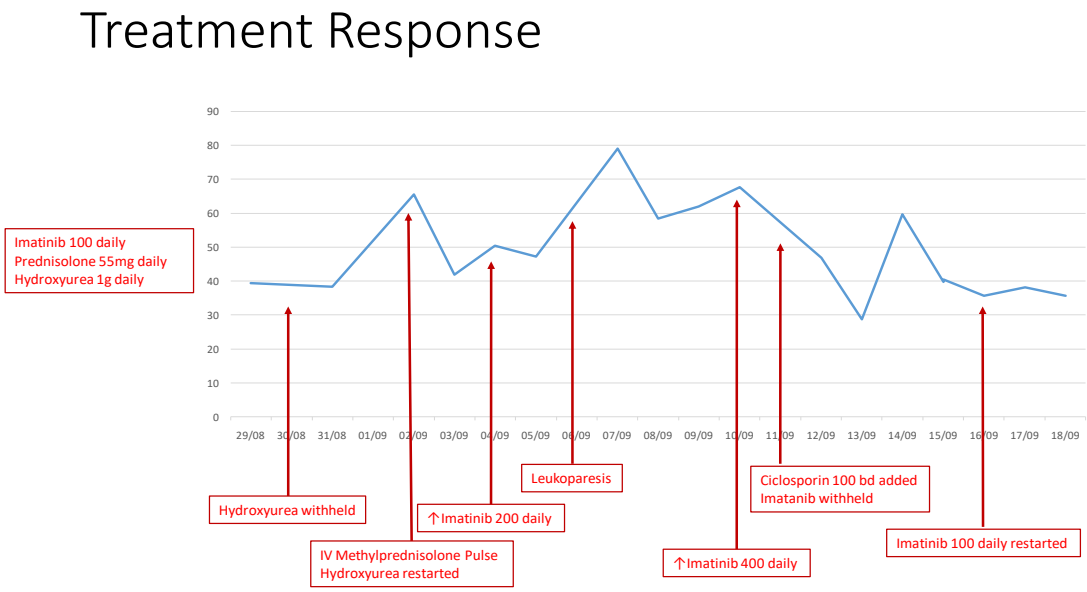

Figure 3 – Treatment Response Curve

DISCUSSION

HES is a condition with a diverse clinical presentation and pathophysiology, hence different treatment options, clinical outcomes and prognosis. It is considered as primary when comprehensive evaluation excludes secondary causes of eosinophilia; allergic, infective, autoimmune, endocrine and immunodeficiency (4). The two major categories of primary HES are myeloproliferative HES (M-HES) and lymphocytic HES (L-HES) with other overlap syndromes.

The main clinical features of M-HES are: male predominance, hepato-splenomegaly, anaemia, thrombocytopenia, severe organ involvement, and poor prognosis. The molecular defect responsible for this distinct phenotype is a gene fusion of FIP1-like 1 (FIPL1) and platelet-derived growth factor receptor alpha (PDGFRA) (F/P mutation) which is the fusion gene resulting in constitutive activation of tyrosine kinase leading to eosinophilic clonal expansion from stem cells. The incidence of FIPL1-PDGRFA is estimated to be 11%, and the rest may harbour other mutations; PDGFRB or FGFR1. These too lead to clonal eosinophilia, and progression to myeloproliferative diseases. Diagnosis of M-HES with negative F/P mutation may be confirmed based on at least four of the following criteria: dysplastic eosinophils in the blood, high serum level of tryptase and vitamin B12, anaemia and/or thrombocytopenia, hepato-splenomegaly, bone marrow cellularity >80%, myelofibrosis or spindle-shaped mast cell (5).

L-HES is a less well-defined entity where an overproduction of eosinophilopoietic cytokines, IL-5, IL-4 and IL-13, by a clonal population of activated T-lymphocytes (T-cells) results in eosinophilia. L-HES is characterized by cutaneous signs, rheumatologic, gastrointestinal, pulmonary, neurologic and cardiovascular involvement (6). The respiratory clinical manifestations may be: severe asthma, infiltrative pulmonary disease, pleural effusions, pulmonary embolism or fibrosis. Hoffman et al described a case of Bullous pemphigoid and systemic hypereosinophilia, as in our patient (8). The diagnostic markers; CD3−CD4+TCRab−, CD3+CD4+CD7−, and CD3+CD 4−CD8−TCRab+ T cell subsets and clonal TCR rearrangement can be detected by flow cytometry in peripheral blood and marrow. Several other biological biomarkers such as IL-5, CCL-17/ TARC and IgE also support the diagnosis of L-HES (7).

Understanding the pathophysiology of HES helps optimise treatment. Imatinib, an inhibitor of tyrosine kinase, has an important role in the treatment of the FIPL1-PDGRFA positive M-HES variant. Corticosteroids combined with hydroxyurea remain first-line therapy for patients with HES, regardless of the subtype as steroids are known to interfere with the transcription of pro-inflammatory genes necessary for eosinophil maturation. However, in recent trials, treatment failure and steroid toxicity have confined its use to F/P negative M-HES and L-HES (9) as steroids decrease absolute numbers of CD3- CD4+ T cells in L-HES patients. Second-line options in L-HES include interferon-alpha (IFN-α) which induces partial regression of pathogenic CD3– CD4+ T cells; Cyclosporin A, a calcineurin inhibitor, which inhibits IL-2; Alemtuzumab which targets the CD52 antigen and Mepolizumab, a monoclonal anti-IL-5 antibody (10). Successful use of oral Cyclosporin A in the treatment of non-M-HES is described in the literature, but further studies are required to elucidate the mechanism of action, efficacy and risk benefit with side effect profile (11).

Our patient presented with a relatively indolent clinical course with skin manifestations which later progressed to pulmonary involvement with severe organ dysfunction. She had high serum B12 and IgE levels without any specific biomarker positivity in serum or bone marrow. Unfortunately, we could not perform T cell subtyping in the bone marrow. She did not respond to initial corticosteroid and hydroxyurea therapy. Subsequent Imatinib therapy also failed. She demonstrated a favourable response 1 week after administration of low dose oral Cyclosporin A (4mg/kg/day). The disease was successfully maintained in remission with Cyclosporin A. Even though the initial assessment could not categorize her into any subtype based on the clinical picture, it was presumed that response to Cyclosporin A increases the likelihood of the L-HES subtype.

CONCLUSION

Due to heterogeneous clinical picture and multiple molecular and laboratory markers, evaluation of a patient with eosinophilia may be challenging, time consuming and costly. With expanding knowledge of disease endotyping and novel biomarkers, specific therapeutic targets have been identified. In conclusion, an improved understanding of pathophysiology in different subgroups has favourably modified the diagnosis and management of HES.

Author declaration
Authors' contributions:
All authors disclose

Funding sources
None

Conflicts of interest
No competing interests

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