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Idiopathic hypereosinophilic syndrome: a rare cause of erythroderma

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Abstract

Background: Idiopathic hypereosinophilic syndrome (HES) is a rare and potentially lethal disorder characterized by persistently elevated eosinophil counts without any underlying causes. Two variants, the myeloproliferative and lymphocytic hypereosinophilic syndrome, have been identified. The symptoms are variable and related to the organs involved (cardiovascular system, skin, central and peripheral nervous system, gastrointestinal tract, eyes). Skin lesions can be the dominating and/or presenting symptom in about 50% of patients.

Main observations: We describe a 54-year-old man with a 12-year history of skin lesions, clinically consistent with psoriasis and psoriatic erythroderma. The patient was treated with methotrexate with no response. He experienced intense pruritus, dry/coarse skin and palmoplantar hyperkeratosis. Histopathology showed spongiotic dermatitis with no epidermotropism. Inflammatory infiltrates in upper dermis consisted predominantly of lymphocytes and eosinophils. Peripheral and tissue eosinophilia, immunophenotyping, and results of FIP1L1-PDGFRA gene analysis were suggestive of lymphocytic HES. The patient was treated with hydroxycarbamide (1 g/day), prednisolone (40 mg/day) and antihistamines with improvement.

Conclusions: HES requires early treatment to prevent severe damage of targeted organs. The pleomorphic dermatological manifestations may delay the diagnosis. This case shows the importance of wide differential diagnosis of erythroderma. In this article we discuss the diagnostic criteria, the recommended work-up and management of idiopathic hypereosinophilic syndrome variants. (*J Dermatol Case Rep*. 2014; 8(4): 108-114)

Introduction

Hypereosinophilia is not an uncommon condition in clinical setting and can be cause by an underlying disease such as tissue helminth infection or other infestations, atopy or allergic reactions. Dermatological disorders (bullous pemphigoid, angiolymphoid hyperplasia, Kimura disease, eosinophilic cellulitis/panniculitis, eosinophilic folliculitis), haematological / myeloproliferative disorders, T-cell lymphoma, solid tumours, connective tissue diseases, systemic mastocytosis, vasculitis (Churg-Strauss vasculitis), and familial hypereosinophilia account for cases with a known cause. However, the cause of hypereosinophilia remains unknown despite thorough diagnostic evaluation in a subset of cases labelled as idiopathic hypereosinophilic syndrome (HES). It presents with persistent idiopathic hypereosinophilia and eosinophil-mediated complications and/or evident organ damage.[1] The diseases which are considered to occur because of toxic contents of directly accumulated eosinophils (Well's syndrome, Gleich's syndrome, eosinophilic gastroenteritis, eosinophilia-myalgia syndrome, Carrington's disease or chronic eosinophilic pneumonia) are well-defined organ-specific idiopathic hypereosinophilic syndromes.[1,2] However, the clinical presentation of idiopathic HES varies greatly from paucisymptomatic disease requiring no intervention and prolonged survival to rapid deterioration from sudden congestive cardiac failure with fatal outcome or occurrence of acute leukemic disease.[2] Based on the original diagnostic criteria by Chusid *et al*[3] (Table 1), complications occur in more than 50% patients with idiopathic HES involving

Table 1. Diagnostic criteria for idiopathic hypereosinophilic syndrome.

Sr No	Original diagnostic criteria of Chusid *et al*[3]	Modifications by Simon *et al*[5]	Comments
1	Blood eosinophilia exceeding 1500 eosinophils/ml[2] for more than six consecutive months	This arbitrary level of 1500 eosinophils/ml[2] is no longer necessary	The presence of marked eosinophilic tissue infiltration with tissue damage or organ dysfunction is more important than these levels
2	Absence of an underlying cause of hypereosinophilia despite extensive diagnostic evaluation	Blood eosinophilia must be confirmed but the 6-month duration of disease is no longer required	The marked eosinophilia in any symptomatic patient with organ involvement must be treated without delay to prevent organ damage, any duration is important
3	Presence of organ damage or dysfunction related to hypereosinophilia	Signs and/or symptoms of organ involvement are not mandatory	It is currently impossible to predict the outcome in an asymptomatic patient and all patients warrant follow up. As some patients may be asymptomatic at presentation and either remain so or develop symptoms related to tissue/organ involved.

nervous system, heart, or skin. The organ specific complications vary across studies, indication up to 58% for cardiovascular and 54% for neurologic involvement.[1] Neurological complications occur due to involvement of either central and peripheral nervous systems. Cardiac complications occur in three stages. The early asymptomatic stage of necrosis (necrotic stage) is followed by endocardium damage and intracavitary thrombus formation (thrombotic stage), and lastly endocardial fibrosis with atrioventricular valvular damage (fibrotic stage).[2,4] Angioedema and urticaria, erythematous papules and nodules, livedo reticularis, petechiae, Raynaud's phenomenon, pruritus, palmoplantar hyperkeratosis, and mucosal ulceration are common cutaneous manifestations.[2,4] Regular follow up, early diagnosis and timely intervention is highly desirable to prevent eosinophil-mediated complications in these patients. However, idiopathic HES is usually not included in the initial work up for erythroderma because of its rarity.

Case report

This HIV-negative 54-year-old man was hospitalized with the provisional diagnosis of generalized exfoliative dermatitis persisting for 2 months. History revealed that for the past 12 years he was having pruritic erythematous, mildly scaly skin lesions mainly over extremities. The disease had been persistent and he experienced frequent exacerbations without any apparent reasons. Although no records were available, he reported that he had received treatments on many occasions from different dermatologists, such as topical coal tar/salicylic ointment, systemic methotrexate, antihistamines, systemic and topical corticosteroids with no improvement. The disease progressed to erythroderma associated with intense generalized pruritus. He was afebrile and had feeling cold and shivering. His blood pressure was 150/96 to 160/100 mmHg on different occasions. Multiple axillary and inguinal lymph nodes were enlarged bilaterally. They were firm, mobile, non-tender and had normal overlying skin. Cutaneous examination (Fig. 1) showed generalized body involvement including of face and scalp with diffuse erythema, scaling/exfoliation, mild edema of extremities, dry coarse/thickened skin of hand and feet, and hyperkeratosis of palms and soles with honeycomb appearance. The scaling was more marked over back. The face also showed cutaneous infiltration with exaggerated skin creases resembling actinic reticuloid (Fig. 2). Mucous membranes and scalp hair were normal and nails had smooth shiny polished surface and loss of cuticle. There was no abdominal organomegaly and examination for central nervous, respiratory, cardiovascular and musculoskeletal systems was normal. He was investigated with the provisional diagnosis of erythrodermic psoriasis, mycosis fungoides and Sézary syndrome. Baseline hemogram showed normal hemoglobin (12.4 gm%), mild leukocytosis (11,500 cells/cm^3; normal range = 4000-11000 cells/cm^3), eosinophilia (18%,; 1-6%), and normal neutrophils (56%), lymphocytes (13%), monocytes (6%) counts. No Sézary/abnormal cells were observed in peripheral blood in two separate samples. Serum biochemistry including thyroid function tests, urinalysis and culture, stool for ova/cysts, and x-ray chest showed no abnormality. Echocardiogram showed tall T waves in chest leads suggestive of left ventricular hypertrophy but with normal function on echocardiography. A fine needle aspiration cytology (FNAC) from axillary lymph node showed reactive hyperplasia. A skin biopsy (Fig. 3) showed epidermal hyperplasia, acanthosis, papillomatosis, spongiosis, and papillary edema suggestive of chronic spongiotic dermatitis. There was no parakeratosis or epidermotropism. The inflammatory infiltrate in upper dermis comprised mainly lymphocytes, eosinophils, and few histiocytes and neutrophils around appendages and blood vessels. There was no evidence of vascultitis. The patient was treated empirically with two weekly doses of oral ivermectin (200 µg/kg bodyweight), albendazole (400 mg/d x 3 days) and azithromycin 500 mg/d x 7 days) for any occult infestation/infection. Amlodipine 5 mg/d was started for hypertension.

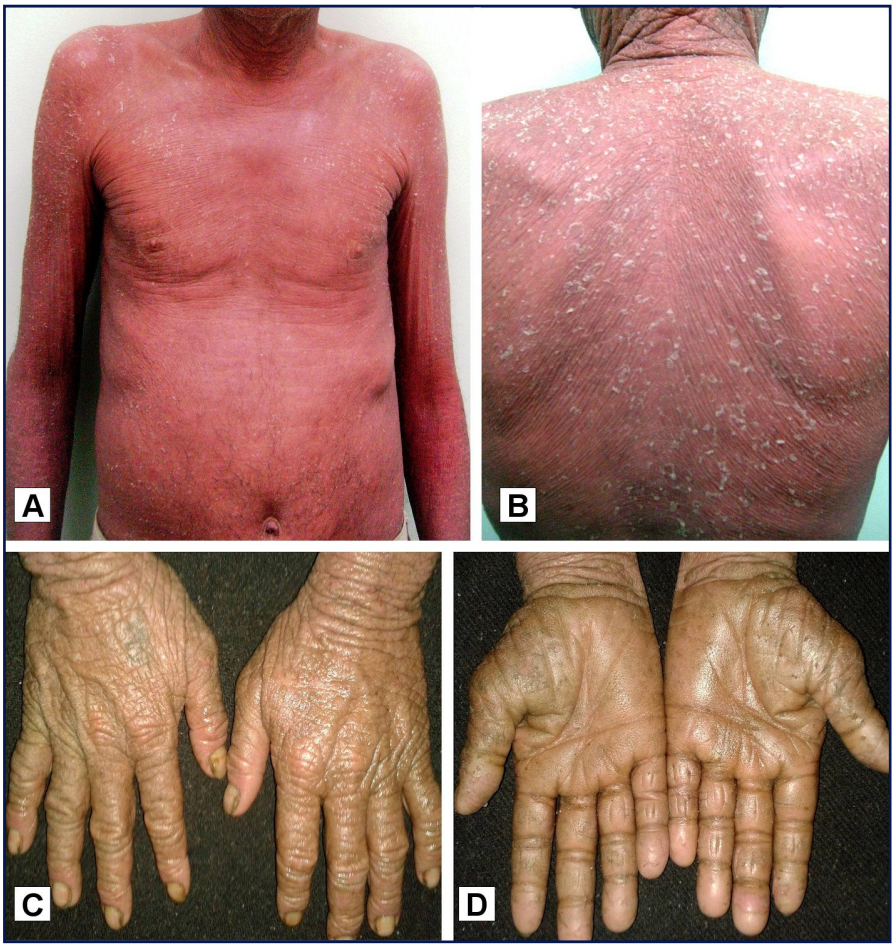

Figure 1

Generalized body involvement with diffuse erythema and exfoliation (A, B). The scaling is more marked over the back. Dry coarse and thickened skin of dorsal hands (C) and palms (D) (Note: these images were photographed 12 weeks after methotrexate therapy).

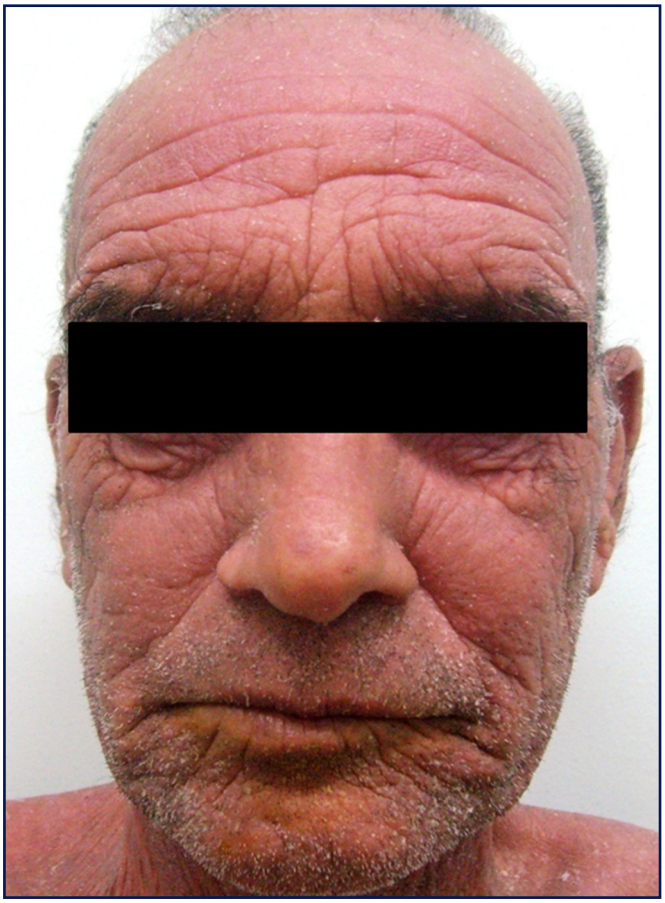

Figure 2

Diffuse erythema and mild exfoliation of facial skin.

With the possibility of psoriatic erythroderma, he was put on treatment with oral methotrexate (20 mg/week), desloratidine (5 mg twice/d) and hydroxyzine (25 mg at bedtime), and frequent application of emollients (coconut oil, vaseline). Twelve weeks later, he was re-hospitalized with no improvement. Repeated examinations revealed leukocytosis (13,300 cells/cm^3), eosinophilia (25%) and normal blood biochemistry. He was re-investigated. A repeated fine needle aspiration cytology from axillary lymph node and a skin biopsy showed features as earlier. His serum IgE level was elevated (289 IU/ml reference range = 20-80 IU/ml) and other immunoglobulin profile was normal (IgG =1039.00 mg/dL, IgM = 75 mg/dL, IgA = 367 mg/dL). Immunohistochemical staining was positive for CD3 and CD4 and negative for CD7 and CD8 (Fig. 4). Serum vitamin B12, tryptase, and troponin T were normal. Computed tomography (CT) of the chest and ultrasonography (USG) of abdomen were normal. Bone marrow examination showed myelopoiesis with 11% eosinophils, normal erythropoiesis and megakaryopoiesis, and no abnormal cells/parasites. FIP1L1--

PDGFRα (F/P) gene rearrangement was not detected. With diagnosis of lymphocytic HES (L-HES), he was treated with hydroxycarbamide (500 mg, twice/day), oral prednisolone 40 mg/day tapered off to 40 mg on alternate days, antihistamines and emollients. After 12 weeks, his pruritus had subsided and a significant improvement of erythroderma was noted.

Discussion

Idiopathic hypereosinophilic syndrome (HES) is a rare disorder characterized by marked peripheral blood eosinophilia in association with eosinophilic tissue infiltrate and ensuing damage and/or dysfunction in a setting where

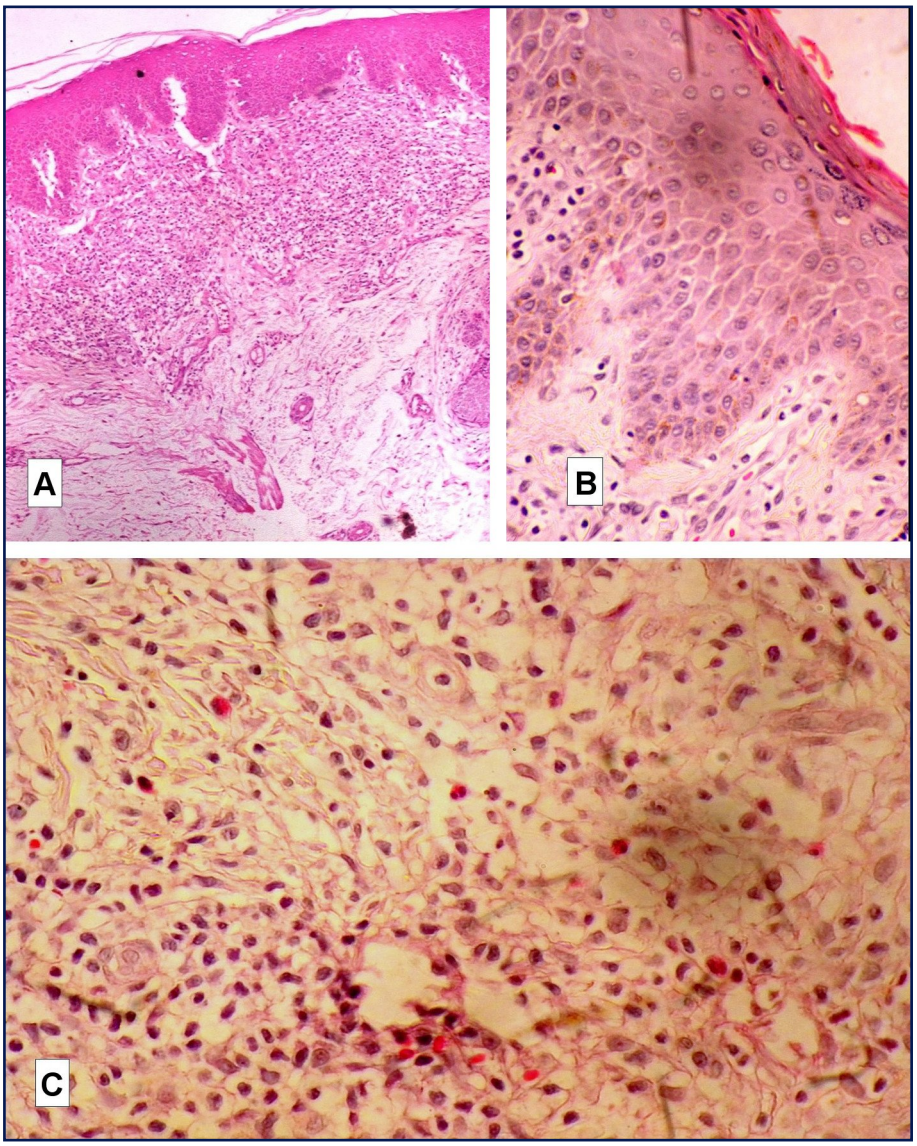

Figure 3

Histopathology showed epidermal hyperplasia, acanthosis, paillomatosus and intense inflammatory infiltrate (H&E, x10) (A). Spongiosis and papillary edema in absence of parakeratosis and epidermotropism (H&E, x40) (B).The inflammatory infiltrate in upper dermis predominantly comprises lymphocytes and eosinophils, few histiocytes and neutrophils around blood vessels (H&E, x40) (C).

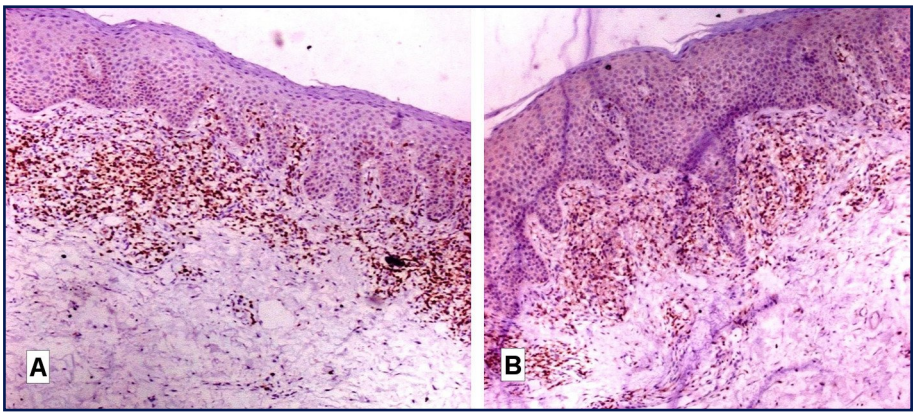

Figure 4

Immunophenotyping. A majority of the infiltrating cells in the upper dermis and deep dermis are CD3+ and CD4+ (x 10).

underlying diseases known to cause hypereosinophilia have been excluded adequately.[1,2] As initiation of prompt medical treatment is recommended in the presence of life-threatening organ damage, it was observed that the hypereosinophilia gets stabilized to normal before the defined 6-month interval is completed. Thus, the arbitrary level of 1500 eosinophils/ml[2], duration of 6 months, signs and symptoms of organ involvement have been removed in the revised diagnostic criteria by Simon *et al*[5] (Table 1). Similarly, prior requirement that the trigger for eosinophilia be unknown is no longer required with the identification of HES variants with known pathogenic mechanisms as separate entities. Two variants, myeloproliferative HES (M-HES) and lymphocytic HES (L-HES), have been identified in view of great clinical and pathologic heterogeneity among these patients.[2] Both, as primitive hematological disorders, involve either myeloid or lymphoid cells that accounts for hypereosinophilia in patients fulfilling the diagnostic criteria for idiopathic HES. The myeloproliferative variant is characterized by clonal expansion of myeloid lineage, dysplastic eosinophils in peripheral blood smear and normal IgE levels attributable to chromosomal abnormalities.[2] The chromosomal abnormalities consist of translocation creating fusion genes; t(5;12)(q33;p13) and t(8;13)(p11;p12) with associated ETV6-PDGFRβ and ZNF198-FGFR1 fusion genes respectively with oncogenic potential.[6] The fusion of FIP1L1 and PDGFRα (F/P) genes mapped to chromosome 4q12 has been demonstrated in few idiopathic HES cases.[7] Most affected patients are men and may have associated anemia and/or thrombocytopenia, increased serum B12 levels, endomyocardial fibrosis, splenomegaly or mucosal ulcerations with cutaneous symptoms being less common.[2,8] However, its independent status remains debatable and labelling of these patients as 'chronic eosinophilic leukemia' is perhaps more apt especially when associated with F/P mutations.[6,7,9] This is particularly true for those patients in whom eosinophil clonality, clonal cytogenetic abnormalities within cells of eosinophilic lineage, and/or increased blasts can be demonstrated. Contrarily, non-malignant clonal T-cell proliferation bearing CD3- and CD4+ surface phenotype (less commonly CD3+ CD4- CD8- or CD3+ CD4+ CD7-) with ability to produce eosinophilopoietic cytokines (interleukin (IL)-5 and IL-4) and hypereosinophilia occurs in patients with L-HES variant.[10,11] Furthermore, CD3- and CD4+ cells also produce Th2 cytokines, IL-4, IL-2, and IL-13.[12] Clinically, both men and women are affected equally and the patients often have increased levels of serum IgE in accordance with Th2 cytokine profile and polyclonal hypergammaglobulinemia occurs mainly from increased IgM and IgG levels.[10,13,14] There is relative paucity of associated organopathy and endomyocardial fibrosis is rare despite high eosinophil levels. Complications of hypereosinophilia occur more commonly in the skin, lungs and gastrointestinal system.[10] However, cutaneous involvement is most common and seen in the form of non-specific itchy maculopapular eruptions, urticaria, angioedema, pruritus, eczema, and eruptions resembling atopic dermatitis or erythroderma in majority.[10,12,14,15] The histopathology of a skin lesion is usually nonspecific with variable eosinophilic infiltration. The perivascular inflammatory cell infiltrate consists of lymphocytes without cell atypia and eosinophils in the dermis reaching up to the subcutis.[4] These lymphocytic cells are polyclonal type and stain positive for CD4, negative for CD3 and CD8, and lack surface CD7 antigen, a characteristic of skin homing T-cells, on immunohistochemical staining in most cases.[10,11]

An early diagnosis of idiopathic HES and distinguishing the two variants is important from long-term prognosis and therapeutic perspective. However, majority of these cases remain under diagnosed for want of clinical suspicion as was in our patient. He was managed as psoriatic erythroderma initially without benefit. Intense pruritus, dry/coarse skin of hand and palmoplantar hyperkeratosis was characterisitc of Sézary syndrome but non-specific histopathologic features and peripheral and tissue eosinophilia were suggestive of L-HES despite few features overlapping with M-HES. Identification of L-HES is mainly based on clinical suspicion and analysis of circulating T-cells/T-cell cytokine profile. The recent PCR techniques with enhanced sensitivity despite limitations of low specificity, and monoclonal rearrangement of T cell receptor (TCR)-gene or immunohistochemical analysis of TCRs are recommended but not considered useful especially when the abnormality is very discrete or aberrant cells represent a small proportion of total lymphocytes.[13,14] Moreover, T-cell clonality may not be detected in all patients with aberrant lymphocyte subset.[13] Hence, the absence of clonality or negative immunohistochemical results is generally not construed to exclude the diagnosis in such cases. Moreover, these modern diagnostic techniques are expensive, complex, and have limited availability in routine clinical settings. Nevertheless, these patients require extensive investigative workup for making a diagnosis (Table 2).

Therapeutically, M-HES patients respond poorly to systemic corticosteroids and more likely to respond to hydroxycarbamide, interferon (IFN)-α, and other chemotherapeutic agents like busulfan, chlorambucil, and vincristine.[2] Imatinib mesylte is found highly effective in F/P mutation-positive patients and is first-line choice in this subset of idiopathic HES.[16] However, endomyocardial fibrosis manifestations remain irreversible.[17] In contrast, the clinical manifestations of L-HES are generally well controlled by systemic corticosteroids given alone or in combination with other drugs (cyclosporine A, hydroxycarbamide, IFN-α).[10] Chemotherapy using cyclophosphamide, doxorubicin, vincristine, teniposide, bleomycin, fludarbine and 2-chlorodeoxyadenosine is recommended in non-responders and in patients with malignant transformation.[2] Anti-IL-5 mAb (mepolizumab), developed to treat eosinophilia in allergic disorders, appears effective for F/P-negative HES patients but remains unstudied for treatment of L-HES.[2] Extracorporeal photochemotherapy is another potential therapeutic modality owing to its suppressive effect on circulating pathogenic T-cell clones.[2] Bone marrow or allogeneic stem cell transplantation may be needed in the presence of malignant transformation.[2] The prognosis has improved from initial 3-year survival of 12% to 10-year survival of 70% after the realization of the necessity of lowering eosinophil levels to prevent target organ damage, especially of cardiac complications.[2]

Adequate remission could be maintained with combination of hydroxycarbamide and prednisolone in our patient. However, ultimate benefit cannot be comprehended at the moment as prolonged survival depends upon the severity of end-organ damage, especially cardiac involvement, and development of malignancy in M-HES variant. On the other hand, L-HES usually remains a benign clonal disorder with indolent clinical course and occasional development of lymphoma.[18]

Conclusions

As ultimate prognosis of HES depends on severity of damaged targeted organ system, the disorder requires early diagnosis and treatment. However, the diagnosis is often delayed due to pleomorphic dermatological manifestations and for want of clinical suspicion. In every case of erythroderma HES should be considered as differential diagnosis.

Table 2. Recommended investigative work-up for idiopathic hypereosinophilic syndrome variants.

First line investigative work up	Specialized investigations when indicated
Complete blood counts with differential leukocyte count	Serum tryptase
Microscopy for peripheral blood film	Serum TARC
Serum IgE, IgG, IgA, IgM	FIP1L1-PDGFRα fusion- – RT-PCR, FISH – CHIC2 deletion as a surrogate marker
Serum B12	Lymphocyte phenotyping for CD2, CD3, CD4, CD5, CD6, CD7, CD8, CD25, CD27, CD45RO, TCRα/β, TCRγ/δ, HLA-DR, CD95
Leukocyte alkaline phosphatase score	TCR gene rearrangement analysis-on a FACS-sorted phenotypically aberrant population
Bone marrow biopsy and smear (microscopy, tryptase and reticulin stain)	Conventional cytogenetic analysis -in the presence of rIL-2 in addition to usual mitogens
Lymphocyte phenotyping	Cytokine profile of T-cell populations- – IL-4, IL-5, IL-13, IL-3, GM-CSF, IL-2, IFN-α – Intracellular cytokines at the single cell level by flow cytometery – Cytokines in culture supernatants of phenotypically suspect T-cell population
TCR gene rearrangement analysis (Southern blot, PCR)	
Ultrasonography of abdomen for organomegaly	
Echocardiogram and cardiac MRI (when possible) for function, valvular lesions, and intracavitary thrombus	

Modified after Roufosse F, et al[2]

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