Idiopathic Hypereosinophilic Syndrome Presenting with Recalcitrant Oral and Genital Ulcers Responding Well to Thalidomide

Abstract

Hypereosinophilic syndrome is a myeloproliferative disorder characterized by abnormal accumulation of eosinophils in the blood or peripheral tissues. It is uncommonly seen in children. We describe a 14-year-old girl diagnosed with idiopathic hypereosinophilic syndrome presenting with recurrent, painful oral and genital ulcers, hepatosplenomegaly along with consistently high eosinophil count and leucocytosis. Genetic studies showed negative for *FIPIL-PDGFRA* fusion gene. Mucosal ulcers were recalcitrant to conventional therapy and responded well to thalidomide.

Keywords: *Hypereosinophilic syndrome, idiopathic, mucosal ulcers, recurrent*

Sahana M. Srinivas, Pooja G. Chebbi[1], Sanjay K. Shivappa

Departments of Pediatric Dermatology and [1]Pediatric Medicine, Indira Gandhi Institute of Child Health, Bengaluru, Karnataka, India

Introduction

Hypereosinophilic syndrome (HES) is a heterogeneous group of rare disorders characterized by eosinophilia (>1.5 × 10^9/l) for at least six months, absence of a secondary cause, and the presence of organ dysfunction.[1] There are six proposed clinical variants: myeloproliferative, lymphoproliferative, overlapping, idiopathic, associated, and familial variant with the most common variants being myeloproliferative and lymphoproliferative.[1] Cutaneous manifestations are observed in 27–69% of HES and range from pruritic erythematous macules, urticaria, nodules, angioedema, bullous lesions, and rarely erythroderma, erythema annulare centrifugum, vasculitis, livedoreticularis, splinter hemorrhages, and mucosal erosions.[2]

Case Report

A 14-year-old girl presented with recurrent, painful, oral and genital ulcers of one-year duration associated with intermittent abdominal pain. There was no history of red eyes, photosensitivity, weight loss, cough, vomiting, diarrhea, or dyspnea. She had recurrent episodes of fever and joint pains in the past three years for which she was evaluated at different hospitals. Cutaneous examination showed multiple, variably sized, discrete, and coalescing ulcers with irregular borders on the buccal mucosa, labia, inguinal folds, and perianal region [Figures 1 and 2]. Inguinal lymphadenopathy and hepatosplenomegaly were present. Histopathology showed a neutrophilic infiltrate with few eosinophils in the dermis [Figure 3a and b]. Her investigations done at various points of time in the past revealed persistent leucocytosis (85 × 10^3/µl to 109 × 103/µl), eosinophil count of 71–82%, and hepatosplenomegaly. She had been treated earlier with oral hydroxyurea 500 mg/day, five days per week for six months without improvement. Her current investigations showed leucocytosis (22.37 × 10^3/µl) and eosinophilia (1.93 × 10^3/µl). The following investigations were normal: hemoglobin, platelet count, blood glucose, HIV, HbsAg, HCV, ANA profile, serum tryptase, mantoux test, chest X-ray, serum tryptase, serum electrolytes, serum LDH, immunoglobulin levels, vitamin B12 levels, ECG, 2d-Echo and urine microscopy. Stool examination for parasites was negative. Bone marrow examination showed hypercellular marrow with eosinophilia (80%) with no evidence of malignancy. Her genetic workup for *FIPIL-PDGFRA* fusion gene was done by fluorescence *in situ* hybridization, *JAK 2 (V617F)* and *BCR-ABL?* major (p210) and minor (p190) fusion transcripts were negative. The leukemia genetic panel and T-cell receptor gene rearrangement studies were normal.

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Address for correspondence:
Dr. Sahana M. Srinivas, Department of Pediatric Dermatology, Indira Gandhi Institute of Child Health, Bengaluru - 560 001, Karnataka, India.
E-mail: sahana.bmc@gmail.com

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Because of the history, evolution of clinical features, mucosal ulcerations and persistent eosinophilia and negative genetic studies, she was diagnosed with idiopathic HES. Oral prednisolone, colchicine, and cyclosporine were given with minimal improvement of mucosal ulcers. She had numerous flares with progressive and necrotic ulcers. Due to the recalcitrant ulceration, we started her on oral thalidomide 100 mg once per day for six months with regular monitoring. There was a complete resolution of the ulcers [Figure 4]. At present, she has been in remission for more than one year without flares or side effects to thalidomide, along with a normal leucocyte and eosinophil count.

Discussion

The exact prevalence of HES in children is not known. In a retrospective study of the evaluation of hypereosinophilia in children and adults, idiopathic HES was the most common clinical subtype comprising 47% and 46% cases of HES in adults and children respectively.[3] Mucosal ulcerations are commonly associated with a myeloproliferative variant with an increased risk of developing myeloid malignancies.[4] They usually manifest as chronic, recurrent ulcers, erosions, pemphigus-like lesions or aphthae involving the oral, genital, and conjunctival mucosa. Mucosal ulceration is seen late in the course of the disease, which was also seen in our case.[5] One of the major complications of the hypereosinophilic syndrome is endomyocardial fibrosis.[2] Based on the literature review of pediatric hypereosinophilic syndrome, Katz *et al*., reported fever, arthralgia, and rash as

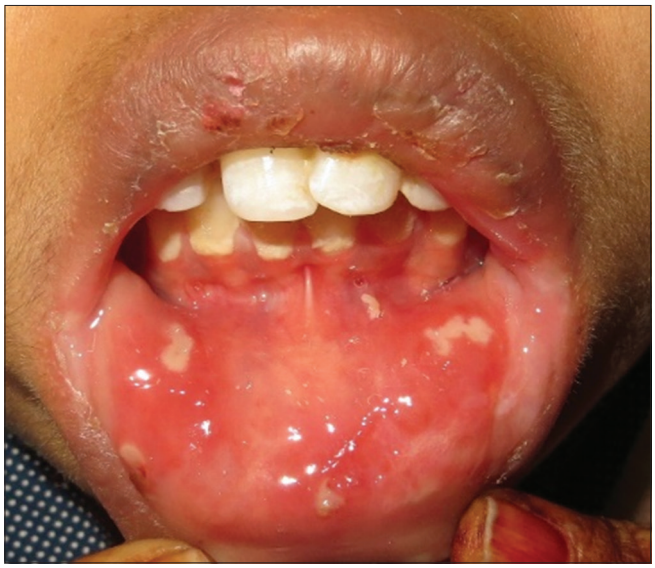

Figure 1: Multiple well-defined necrotic ulcers with erythematous border on the lower lip

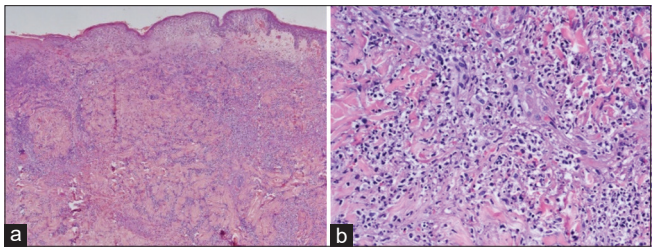

Figure 3: (a) Neutrophilic infiltrate with few eosinophils in the dermis [H and E x40] (b) Higher magnification showing neutrophilic infiltrate and few eosinophils in the dermis [H and E x400]

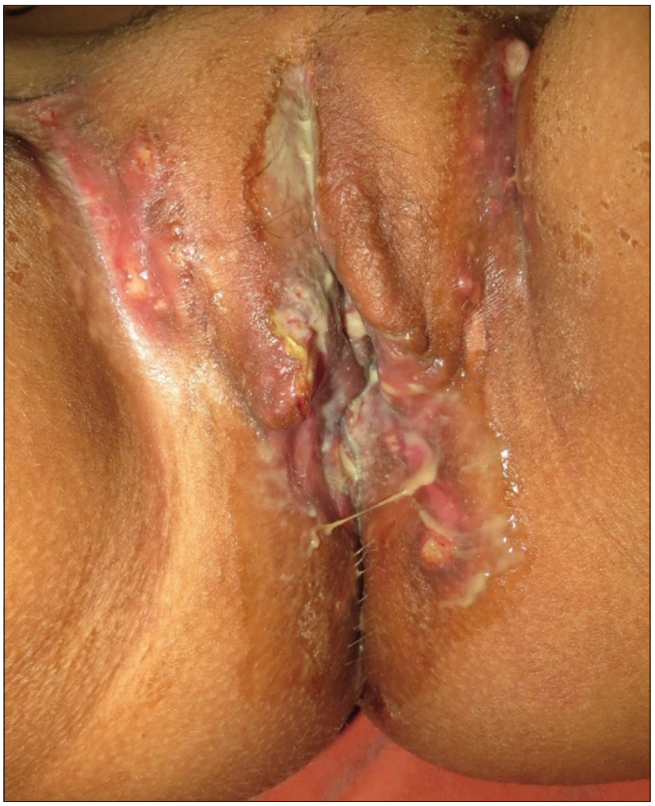

Figure 2: Multiple small to deep necrotic ulcers with irregular and erythematous border on the labia, inguinal region and perineum

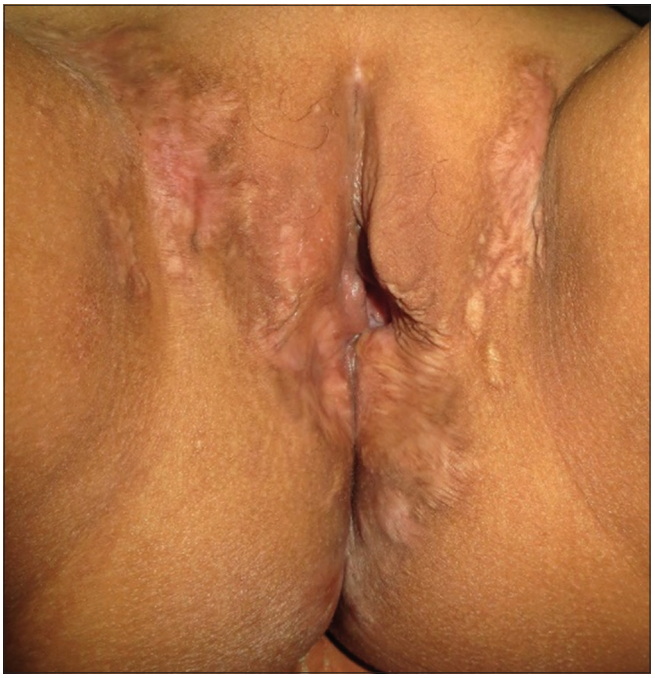

Figure 4: Post treatment: healed genital ulcers with scarring

the most common presenting symptoms. Skin involvement was seen in 34.2% of cases.[6] We were unable to find any reported cases of idiopathic hypereosinophilic syndrome with mucosal ulcers in children.

Differential diagnosis considered in our case were recurrent aphthous stomatitis (RAS), Behcet disease, and inflammatory bowel disease. RAS is characterized clinically by round to oval, small-deep ulcers with grey-white pseudomembranous membrane surrounded by an erythematous halo that heals without scarring. In our case, the presence of systemic involvement with scarring ulcers on the genital area ruled out RAS. Behcet disease, which presents as painful, recurrent, small-large oral and genital ulcers, healing with minimal scarring. Other features include ocular involvement and other cutaneous features like acne-like papules, pustules, pseudofolliculitis, and erythema nodosum-like lesions.[7] The presence of persistent eosinophilia, leucocytosis, and the absence of ocular and other cutaneous features in a long-standing case ruled out the possibility of Behcet disease. Enteropathy, oral ulcers, and, in rare cases, genital ulcers are clinical features of ulcerative colitis. Skin involvement is the most common extra-intestinal manifestation of Crohn's disease. Crohn's disease ulcers are deep and linear, referred to as "knife-cut ulcers." Histopathology shows non-caseating granulomas.[8] There are few reports of hypereosinophilia with Bechet disease, but the exact pathogenesis of this coexistence is still elusive, probably depicted as a coincidental finding.[9]

The mucosal ulcers are usually refractory to conventional treatment. Imitanib mesylate, a tyrosine kinase inhibitor is very effective in patients with *FIPIL-PDGFRA* mutation with mucosal ulcers than in those without the mutation. We did not attempt this treatment in our case due to negative *FIPIL-PDGFRA*. Oral steroid is the first line of management, but due to the toxicities, prolonged treatment is not feasible in children. Other treatment modalities that have been tried with minimum success are hydroxyurea, azathioprine, cyclosporine, IFN–α, anti-IL-5 antibody, dapsone, methotrexate, intravenous immunoglobulin, mycophenolate mofetil, thalidomide, cladribine, efalizumab, and alemtuzumab.[10] One reported 10-year-old boy with idiopathic hypereosinophilic syndrome responded to prednisolone and thalidomide.[11] Our case showed complete resolution of the ulcers after initiation of thalidomide.

Persistent and recurrent severe mucosal ulcerations, though commonly seen in the myeloproliferative variant can be a presenting feature in idiopathic HES and pose a diagnostic and therapeutic challenge. Persistent high eosinophil count with leucocytosis in a patient with recurrent oral and genital ulcers should raise suspicion of HES. Thalidomide can be a useful option for recalcitrant mucosal ulcers in patients with a negative *FIPIL-PDGFRA* gene.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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