Hyper-Immunoglobulin E Syndrome: Case Series of 6 Children from India

Abstract

Hyper-immunoglobulin E syndrome is a rare primary immunodeficiency syndrome characterized by severe atopic dermatitis, recurrent pulmonary and staphylococcal skin infections. Its diagnosis requires a high degree of suspicion, typical clinical features, and not mere rise in serum IgE levels. Genetic studies are not always possible in a resource poor setting in developing countries. In this case series, all children had recurrent eczematoid rash, secondary infections, multiple episodes of hospitalization for pulmonary infection and raised serum IgE levels. Diagnostic genetic study was feasible in only one of the cases which revealed pathogenic homozygous deletions of exons 15 to 18 (Transcript: NM_203447) in *DOCK8* gene. The main goal of management of hyper-immunoglobulin E syndrome is aggressive treatment of infections and optimum skin care. Our case series highlights various characteristic, presentations, and management of this rare syndrome childhood cases. Awareness of these manifestations may facilitate early identification and contribute to optimal care of patients as representative data on the same is limited in literature.

Keywords: *Atopic dermatitis, eczematous rash, hyper-immunoglobulin E syndrome, pulmonary infection, serum IgE*

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Introduction

Hyper-immunoglobulin E syndrome (HIES) is a multisystem immunodeficiency disorder characterized by recurrent eczematoid rash, pulmonary and skin infections, and markedly elevated serum-IgE levels. The inherited form is uncommon and is classified into two types. Type-1 HIES (Job syndrome) is autosomal dominant (AD-HIES) and includes immune system abnormalities along with vascular, skeletal, and connective tissue abnormalities. Type-2 HIES is autosomal recessive (AR-HIES). In addition to immune system abnormalities, it involves recurrent skin (viral, bacterial) and lung infections more commonly but lacks musculoskeletal abnormalities.[1,2] Elevated serum-IgE levels may be seen in various conditions; hence, its diagnosis requires a high degree of suspicion and typical clinical features.[3] This case series of six children highlights various presentations and management of HIES in children.

Report

Case 1

A 2-year-old male child, born out of consanguineous marriage, had a history of recurrent generalized erythematous rash with occasional pustules over the body since 10 months of age. He had a history of hospitalization twice for pneumonia and erythroderma, which were managed with injectable antibiotics. There was involvement of ~60% body surface area (BSA) involving face, trunk, and extremities with multiple erythematous, hyperpigmented papules and plaques with mild scaling. Lips showed hyperpigmentation, scaling, and crusted erosions. He had mild dysmorphic features with prominent forehead, broadened nasal bridge, and slightly thick skin [Figure 1a and b]. Palms and soles showed diffuse scaling, crusting, and erosions [Figure 1c and d]. On evaluation, he had leukocytosis (34,070 cells/mm^3) with absolute eosinophil count (AEC) of 20,101 cells/mm^3 and raised serum-IgE levels (16,000 IU/mL). Histopathology was suggestive of eczematous dermatosis.

The child was managed as severe atopic dermatitis (AD) with wet-wrap therapy, emollients, topical corticosteroids (TCS), and cyclosporine to which he responded

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poorly. A possibility of immunodeficiency syndrome was considered. Genetic studies revealed pathogenic homozygous deletions of exons 15 to 18 (Transcript: NM_203447) in *DOCK8* gene which confirmed type-2 AR-HIES, and bone marrow transplant (BMT) was done successfully. However, he developed lower respiratory tract infection and died two months after BMT. Both the parents were found to be carriers of *DOCK8*-gene deletion mutation.

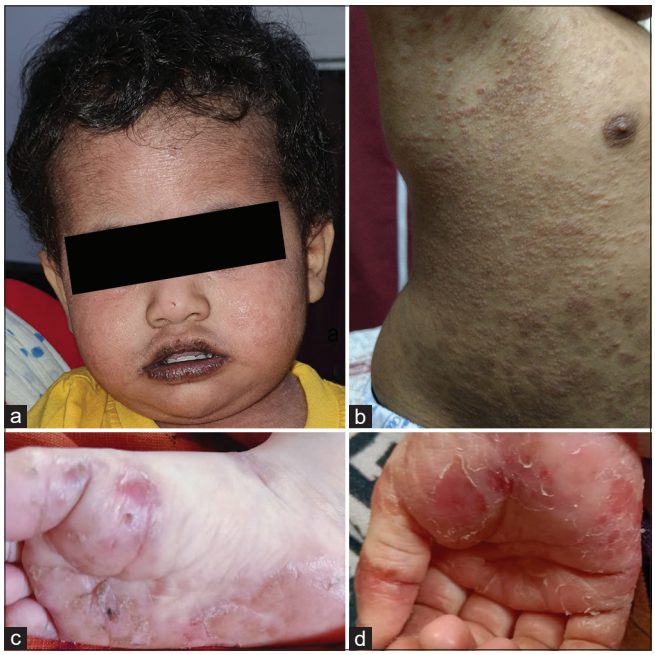

Figure 1: (a) Face showing mild dysmorphic features (prominent forehead, broadened nasal bridge and slightly thick skin), diffuse scaling, erythema, and lip hyperpigmentation with few crusted erosions (b) Trunk showing multiple erythematous and hyperpigmented papules coalescing to form plaques (c) Sole showing diffuse scaling, crusting and few erosions (d) Palm showing diffuse scaling, crusting and few erosions

Case 2

A 2-year-old male child was brought with recurrent red painful rash over body since seven months of age and history of hospital admissions thrice for respiratory illnesses which were treated with antibiotics. He had multiple ill-defined scaly erythematous plaques with oozing, crusting, and pustules over body [Figure 2a and b], AEC of 1,872 cells/mm^3, and raised serum-IgE levels (8,700 IU/mL). Skin biopsy was suggestive of chronic eczematous dermatosis [Figure 2c]. He was treated with syrup prednisolone, oral antibiotics, antihistamines, emollients, and bleach-bath to which he responded poorly. He was clinically diagnosed as likely a case of AR-HIES and was started on trimethoprim–sulfamethoxazole prophylaxis for recurrent infections at 10 mg/kg/day, topical emollients, and TCS. This significantly reduced the severity of cutaneous lesions and frequency of respiratory infection.

Case 3

A 2-month-old infant admitted for acute pneumonia had history of recurrent episodes of itchy erythematous scaly plaques, occasional pustules, vesicles, and bullae over extremities since day five of life [Figure 3a and b]. She had leukocytosis (23,000 cells/mm^3), elevated AEC (9,400 cells/mm^3), and serum-IgE levels (2,600 IU/mL). Pus culture isolated methicillin-resistant coagulase-negative *Staphylococcus*. Blood culture isolated *Klebsiella pneumonia*. He was treated with parenteral antibiotics, emollients, and short-course oral steroids. The skin lesions responded well with post-inflammatory hyperpigmentation and minimal scarring at few sites.

A total of six cases, including the above-mentioned, are summarized in Table 1. All had recurrent eczematoid rash

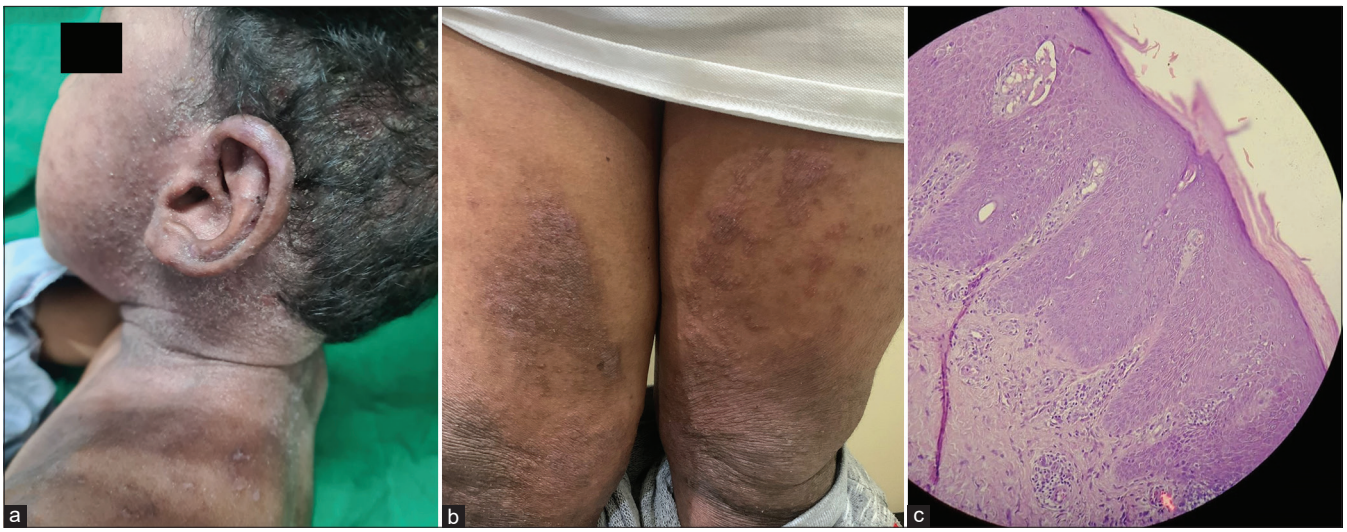

Figure 2: (a) Multiple ill-defined scaly erythematous crusted plaques, papules and pustules over scalp, face, ear, neck, and trunk (b) Well-defined scaly lichenified plaques and papules over lower limbs (c) Histopathology showing hyperkeratosis, acanthosis, mild spongiosis with lymphocyte exocytosis, and perivascular and periadnexal lympho-histiocytic infiltrate with eosinophils in the dermis corroborating to chronic eczematoid dermatosis (H and E, 400x)

Table 1: Summary of patients with hyper-immunoglobulin E syndrome

Case	Age	Sex	Consanguinity	Onset Eczematoid rash	Skin infection	Pulmonary infections	Allergy	S. IgE (IU/mL)	AEC (cells/mm^3)	Musculoskeletal involvement	Genetics	Treatment
1.	2 years	M	Yes	10 months Yes	Yes	Yes	Yes	16000	20,101	Prominent forehead, broadened nasal bridge and slightly thick skin	Pathogenic homozygous deletions of exons 15 to 18 (Transcript: NM_203447) in *DOCK8* gene	Wet wrap therapy, emollients, TCS[†], syrup cyclosporine followed by BMT[‡],
2.	2 years	M	No	7 months Yes	Yes	Yes	No	8700	1872	Normal	-	Syrup prednisolone, oral antibiotics, antihistamines, emollients, bleach bath followed by TMP-SMX[§] prophylaxis at 10 mg/kg/day
3.	2 months	F	Yes	Birth Yes	Yes	Yes	No	2600	9400	Normal	-	Parenteral and topical antibiotics, emollients, TCS and short course oral steroids intermittently
4.	5 years	M	No	1 year Yes	Yes	Yes	No	28350	2100	Normal	-	Same as case 3
5.	3 years	M	No	6 months Yes	Yes	Yes	Yes	4800	1500	Normal	-	oral cyclosporine, emollients and TCS intermittently
6.	10 years	M	No	2 years Yes	Yes	Yes	Yes	5530	2320	Fracture humerus twice	-	Same as case 5

[†]TCS=Topical corticosteroids, [‡]BMT=Bone marrow transplant, [§]TMP-SMX=Trimethoprim-Sulfamethoxazole

Figure 3: (a) Multiple erythematous and hyperpigmented to brownish-blue scaly crusted plaques over lower limbs predominantly the extensors (b) Multiple erythematous and hyperpigmented to brownish-blue scaly crusted plaques over upper limbs mainly over the extensors

responding poorly to conventional treatment, secondary infection, multiple hospitalizations, and raised serum-IgE levels.

Discussion

Hyper-immunoglobulin E syndrome is a rare primary immunodeficiency syndrome. Majority of cases occur sporadically; however, it may be inherited too. AD-HIES usually involves mutation in *STAT3*, whereas AR-HIES commonly involves *DOCK8* gene.[3,4] Due to unavailability and financial constraints, we could carry out genetic studies in only one case who had *DOCK8* gene mutation. However, clinically most of our cases had features favoring type-2 AR-HIES in view of recurrent skin (viral, bacterial) and lung infections.

It commonly involves scalp and face and usually present early in life or even at birth.[5,6] Our case series had six childhood cases of HIES with age ranging from two months to ten years. All had onset in first ten months of life except case 6 with late onset at two years. All children had almost similar presentation with variable severity of recurrent eczematoid rash with secondary infection that progressed to erythroderma in two cases requiring hospitalization. One case had occasional vesicles, bullae, and crusted plaques over extremities. Two had prominent involvement of scalp and face, in addition to trunk and extremities which was the predominant pattern seen in rest of the cases.

Sinopulmonary infections like recurrent pneumonia are common and >50% may have ≥3 episodes, and

Staphylococcus aureus, *Haemophilus* influenzae, *Streptococcus pneumonia,* and occasionally fungus are implicated.[7-9] All our cases had history of 1–3 episodes of hospitalization for pulmonary infection treated with antibiotics. One had food allergy, whereas two had history of bronchial asthma.

Characteristic musculoskeletal abnormalities and facial features may be seen usually during late childhood involving prominent forehead, wide-set eyes, broadened nasal bridge, high-arched palate, coarse skin, and delayed shedding of primary dentition. Only one child had mild dysmorphic features here. Case 6 had fracture humerus twice at the age of three and five years, respectively, following insignificant trauma in the form of fall while walking.

Serum-IgE levels are usually >2000 IU/mL and elevated AEC may be seen in ~90%; however, the specificity of IgE is uncertain and eosinophilia too does not correlate with rise in serum-IgE.[9] All six cases in our series had significantly raised serum-IgE levels and AEC.

Atopic dermatitis is the commonest differential diagnosis and may be distinguished based on the presence of various immunological and non-immunological features.[10] The main goal of management in HIES is aggressive treatment of infections and optimum skin care. Staphylococcal infection is thought to be the main driver of dermatitis. Almost all our patients received multiple courses of antibiotics, oral, and TCS intermittently. Hematopoietic stem cell transplantation (HSCT) has been tried in both dominant and recessive forms; however, its role is more favored in recessive form with significant reduction in cutaneous lesions, recurrent infections, and elevated IgE.[1] Case 1 underwent BMT but succumbed to lower respiratory tract infection after two months.

Our case series highlights various characteristics, presentation, and management of this rare syndrome in childhood cases. AR-HIES subtype may be more common in skin-of-color; however, large-scale studies are required to establish the same. Awareness of these manifestations may facilitate early identification and contribute to optimal care of patients as representative data on the same is limited in literature.

Declaration of patient consent

The parents/caretakers of patients in this manuscript have given written informed consent to the publication of their case details and photographs.

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Conflicts of interest

There are no conflicts of interest.

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