Severe Ophthalmic Involvement in Hyperimmunoglobulin E Syndrome; a Potentially Blinding Disease

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Abstract

Objective: To describe clinical and flow cytometry findings of an unusual case of hyper immunoglobulin E syndrome with severe ophthalmic involvements.

Method: A Case report.

Report: A 13-year-old boy was reported with infectious dermatitis, dental sinus with positive *Actinomyces israelii* culture, severe blepharitis, follicular conjunctivitis, and dysmorphic, vascularized cornea with no light perception visual acuity in both eyes. In immunophenotyping with the flow cytometry, a decrease in T-cell markers (CD2, CD3, CD4, CD5, CD7) was prominent. CD34 and CD117, hematopoietic stem cell, and circulating progenitor cell markers were negative.

Conclusion: This is the first known reported case of flow cytometry findings, especially the lack of $CD34^{+}$ and $CD114^{+}$ cells in hyper immunoglobulin E patient with severe anterior and posterior segment involvement. Proper antimicrobial interventions are important in infectious flare-ups.

Introduction

Hyperimmunoglobulin E syndrome (HIES) is infrequent primary immunodeficiency [1]. Different mutations in genes have been described as the cause of HIES. STAT3, DOCK8, PGM3, ERBIN, IL6ST, and CARD11 are some of them that are translated to clinical phenotypes. STAT3 defects are the most well-known mutations causing autosomal-dominant HIES. It affects fewer than 1 per million people [2]. An Autosomal recessive HIES has also has been described that was associated with mutations in *TYK2* [3]. The main clinical manifestations of HIES are atopic eczema, staphylococcal dermatitis, cellulitis and folliculitis, recurrent pneumonia, pulmonary abscesses, osteopenia, and recurrent bone fracture [4]. *Staphylococcus aureus*, *Streptococcus pneumonia*, *Haemophilus influenza*, and *Candida albicans* are the most frequent pathogens which cause infection in HIES patients [5]. The most consistent laboratory finding is an increase in the serum IgE level of more than 2000 U/mL [6]. Ophthalmic manifestations in HIES are rare. There are reports of keratoconus [7], severe blepharitis [8], conjuctivitis [9], and endophthalmitis [10], marginal corneal ulcer [11], and retinal detachment [12] in HIES patients.

Case Report

A 13-year-old boy was referred to our clinic to evaluate his ophthalmic symptoms. He received all of his programmed vaccinations on time. He did not have parental consanguinity, and his two siblings were healthy. His symptoms started with postulated ulcers 8 years ago. He mentioned several recurrences of these lesions that caused hospitalization. He also had 4 episodes of feverless pneumonia leads to intravenous antibiotic therapy, which was the last six months ago. He had a history of three lower limb fractures. He pointed out that his vision began to decrease from one year ago. On physical examination, his vital signs were stable. His weight was 30 kg and height 131 cm, which were both under the fifth percentile. Diffuse eczematous exfoliative rashes and discharging ulcerative lesions stood on the face, neck, chest,

limbs, and oral and nasal mucosa (Fig. 1). A prominent discharging orifice was observed on his left submental area. Visual acuity was no light perception (NLP) bilaterally. The skin of eyelids was eczematous with telangiectatic vessels and dysmorphic lashes. Severe ulcerative blepharitis and palpebral follicular conjunctivitis were seen in both eyes. Diffuse vertical and horizontal symblepharons were formed in the lower and upper conjunctival fornix of both eyes, and ocular movements were limited. Vigorous corneal conjunctivalization due to spontaneous corneal perforation was observed on the exam. Cornea seemed to be dysmorphic with haziness and deep vascularisation (Fig. 2, A, and B). B-scan showed a phthisic pattern of the posterior segments.

White blood cell count was 9200×10^9 /L with 40.4% neutrophils, 24.7% lymphocytes, 28.7% eosinophils, hemoglobin 10.7 g/dL, and platelet count was 424×10^9/L. Erythrocyte sedimentation rate increased to 24 mm/h and C-reactive protein reached to102 mg/L. Blood biochemistry values were normal. An enzyme-linked immunosorbent assay (ELISA) was performed to quantify immunoglobulins count. Serum IgG, IgA, and IgM levels were in normal ranges, but IgE level significantly increased to 2250 IU (normal range < 250 IU). Nitroblue tetrazolium test, a neutrophil function index, was normal. In immunophenotyping with the flow cytometry, a decrease in T-cell markers (CD2, CD3, CD4, CD5, CD7) was prominent. CD19, CD20, and CD22 were in the normal range, and CD11b, CD13, CD15, CD43 had elevated percentages. CD56, an NK cell marker, had low level than the normal range. CD34 and CD117 were negative. Real-time PCR analysis for STAT3 mutations did not show any mutation in the coding and intronic regions.

Eye discharge culture and blood culture were negative. Skin lesions biopsy showed acanthosis, basketweave appearance, and cell nuclei enlargement that concluded as wart-like plaque lesion; its smear and culture also were positive for *Staphylococcus aureus*. The culture of dental sinus showed *Actinomyces israelii* and HSV-1 and HSV-2 were detected in PCR study for oral lesions.

Penicillin G 12 MU/day/IV, amikacin 20 mg/kg/day/IV and acyclovir 10 mg/kg/day/IV were started. Topical erythromycin ointment twice daily, ciprofloxacin ophthalmic droplet every four hours and frequent artificial tear for both eyes and mupirocin ointment for skin lesions were used. After ten days, skin lesions and dental sinus began to get well, and their discharges disappeared. Conjunctivitis and eye discharge also improved. After two months, the skin lesions and the conjunctivitis were resolved (Fig. 2, C, and D), but the visual acuity was yet NLP.

Discussion

HIES is a primary immunodeficiency. Mutations in *STAT3* result in failure of Th17 differentiation, leads to susceptibility to fungi and extracellular bacteria [14], but the common mechanisms between HIES and responsible genes remain undefined at present [15]. HIES immunologic characteristics include eczema (100%), serum IgE > 2000 IU/ml (97%) and eosinophilia (93%) and its non-immunologic characteristics include characteristic face (83%), retained primary teeth (72%) and minimal trauma fractures (71%) [5]. Ophthalmic complications are not common in HIES, but in this case, severe ophthalmic involvement was seen. Table 1 summarized the ophthalmic findings in the reported cases of HIES. Most of the ophthalmic involvement was infectious with different bacteria and fungi, but non-infectious findings have also been

reported. No light perception visual acuity due to corneal blindness, like what was in our patient, had not described previously in HIES. The more damaging nature of the infection in these patients could be effective in this profound vision loss.

Table 1
Differences and similarities across reported cases

Case reports	Age, gender	Laterality	Chief compliant	Main ophthalmic problem	Isolated microorganism	Final best-corrected visual acuity
Kim et al [5]	28, Male	bilateral	Severe eye itching.	Keratoconus	N/A	20/25 right eye 20/30 left eye
Haslett et al [6]	24, Female	Unilateral	Decreased vision	Endophthalmitis	*Candida albicans*	Hand movement
Frohn et al [7]	8, Female	Bilateral	Photophobia	Marginal keratitis	*Staphylococcus aureus* Chlamydia	-
Arora et al [3]	15, Male	unilateral	Decreased vision	Retinal detachment	N/A	Light perception
Destafeno et al [4]	16, Female	unilateral	Eyelid mass	Chalazia	*Staphylococcus aureus*	20/20
Orhan et al [8]	8, Female	unilateral	Conjunctival injection	Spontaneous corneal perforation	*Negative culture*	-

Paranasal sinusitis and upper respiratory tract infections are reported frequently in the HIES, and *Staphylococcus aureus*, *Haemophilus influenza*e are the common causes [16], but the dental sinus with a positive culture of *Actinomyces israelii* is novel finding in a HIES patient. Actinomycosis is a rare non-acute infection caused by the gram-positive filamentous non-acid fast anaerobic microorganism. Dental caries and chronic pulmonary disease are some of its risk factors [17] that existed in our patient.

HIES increases the susceptibility to the infection with a virus or family of viruses. There are some reports of HSV-1 infection in HIES patients, but HSV-2 infection is uncommon [1]. T-cells and NK cells are a critical part of the immune system in preventing HSV-2 infection [18], and a decreased proportion of these cells in our patient can play a role in the incidence of HSV-2 infection.

Symblepharon and severe corneal conjunctivalization represent chronic and severe inflammation in the ocular surface due to long-term infective conjunctivitis; despite our evaluation, the conjunctival swab was negative. Flow cytometry of peripheral blood sample showed a decrease in T-cell ratio. Mineghishi et al. suggested impaired Th17 cell development and impaired induced regulatory T-cell generation may account for the immunological abnormalities of the HIES [19]. A significant finding was the lack of $CD34^{+}$ and

$CD117^+$ cells. These are hematopoietic stem cell and circulating progenitor cell markers. Keratocytes are the satellite cells of the corneal stroma. Inactivated keratocytes express CD34 in vivo [20]. It works as an adhesion molecule promoting the holding of keratocytes in the corneal stroma. There are reports of the disappearance of $CD34^+$ keratocytes in the traumatic cornea [21]. Also, $CD117^+$ corneal stroma-derived mesenchymal stem-like cells can heal wounds and have an immunomodulatory and regenerative role in the corneal tissue [22]. The lack of $CD34^+$ and $CD117^+$ cells may play a role in severe corneal damage in our patient. Therefore this relationship can be evaluated in the subsequent studies. In our patient, different B-cell subtypes were in the normal range. However there are reports of memory B-cell reduction in HIES [23]. We showed elevated levels of CD markers that were associated with granulocytes, monocytes, neutrophils, and eosinophils which were consistent with other hematologic findings of patient.

In conclusion, in this study, a HIES patient with unique findings like corneal blindness, dental sinus with positive *Actinomyces israelii* culture, and novel flow cytometry findings was reported. Despite favorable antimicrobial agents' response in HIES, multidisciplinary care may require long-term management.

Abbreviations

IgE: Immunoglobulin E

HIES: Hyperimmunoglobulin E syndrome

STAT3: Signal transducer and activator of transcription 3

DOCK3: Dedicator of cytokinesis 8

PGM3: Phosphoglucomutase 3

ERBIN: Erythroblastic oncogene B interacting protein

IL6ST: Interleukin 6 signal transducer

CARD11: Caspase recruitment domain-containing protein 11

TYK2: Tyrosine kinase 2

NLP: no light perception

ELISA: enzyme-linked immunosorbent assay

CD: cluster of differentiation

NK: Natural killer

PCR: Polymerase chain reaction

HSV: Herpes simplex virus

Th17: T-helper cell 17

Declarations

Acknowledgments:

none.

Consent for publication:

This study followed the tenets of the Declaration of Helsinki, and informed consent was obtained from the patient and his parent.

Competing interests:

All authors declare that they have no financial disclosure and competing interests.

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Availability of data and materials:

Our data are available in medical records of Farabi Eye Hospital.

Authors’contributions:

MM visited the patient at first presentation, performed treatment and collatedthe patient data and also revised the manuscript. HG wrote the manuscript.HH and AA revised the manuscript. All authors read and approved the finalmanuscript.

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Figures

Figure 1

Eczematic lesions on the face (A), crusted lesions with purulent discharge exist on the conjunctiva (B), and oral mucosa (C). Active ulcerative skin lesions and old scars with hypopigmentation are visible on the limbs (D).

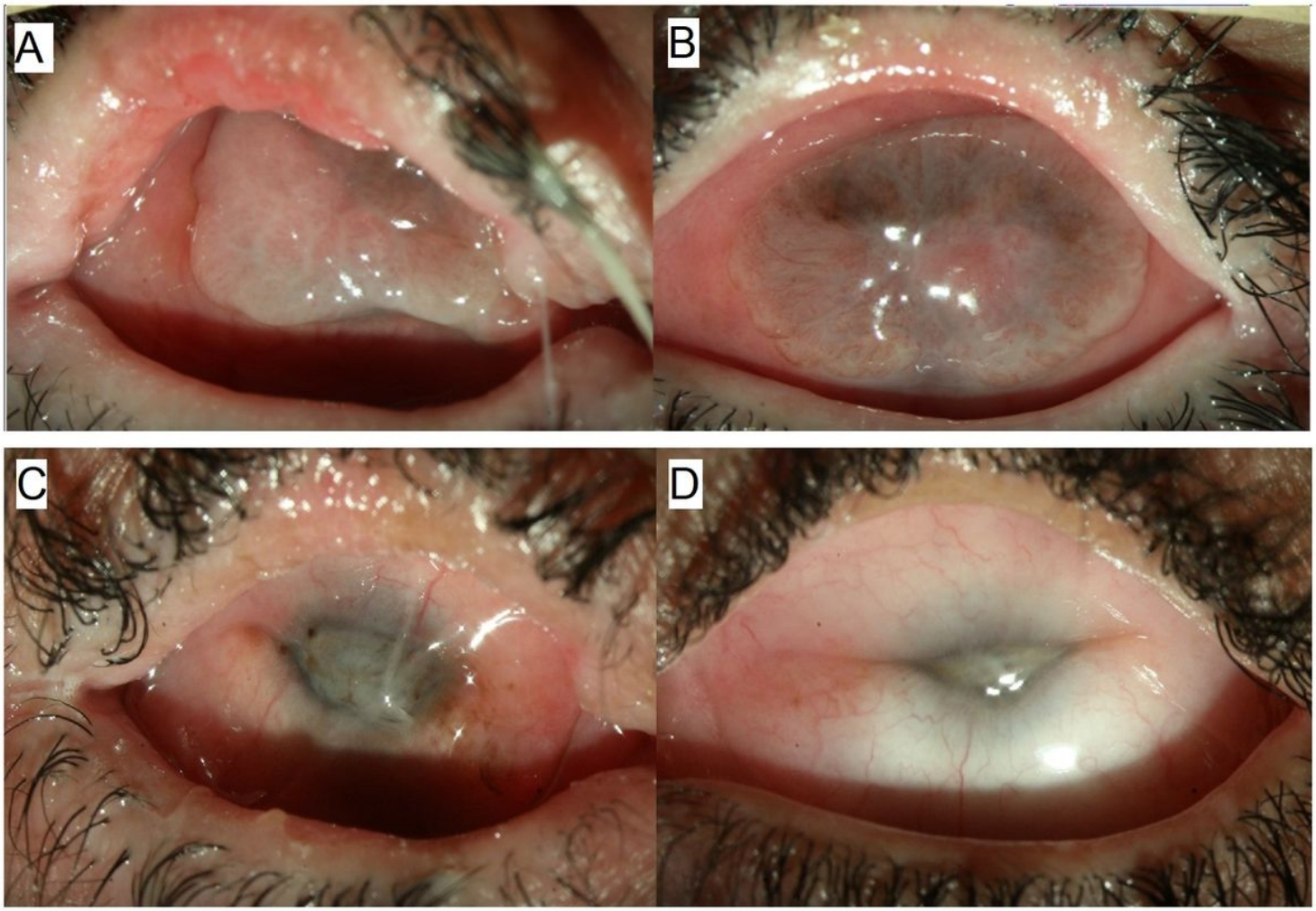

Figure 2

Thick conjuntivalization on the perforated cornea in the right (A) and left (B) eye. After three months, the membranes disappeared, and dysmorphic hazy cornea with the advanced conjunctiva was observed (C and D).