Hyper IgE Syndrome Related Disease Treated with Dupilumab: A Case Report

Andrew Kao[1], Hany Deirawan[1], Pavadee Poowuttikul[2], and Steven Daveluy[1]

[1]Wayne State University School of Medicine
[2]Central Michigan University College of Medicine

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Abstract

We describe a case of a 2-month-old female displaying clinical phenotype of HIES related disease with severe eczematous dermatitis recalcitrant to corticosteroids. Genetic panel showed a variant of unknown significance in key immune regulator of PGM3. Patient achieved nearly complete response from off-label use of dupilumab.

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Authors: Andrew S. Kao[1], Hany Deirawan[2], Pavadee Poowuttikul[3], Steven Daveluy[2]

Affiliations:

[1]Wayne State University School of Medicine

[2]Wayne State University School of Medicine, Department of Dermatology

[3]Central Michigan University, Department of Pediatrics, Division of Allergy, Immunology, and Rheumatology

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Andrew S. Kao: Writing and revision of manuscript.

Hany Deirawan: Followed up with patient's disease progression and directed manuscript drafting.

Pavadee Poowuttikul: Supervised genetic workup and overall manuscript development.

Steven Daveluy: Supervised dermatology clinical management and overall manuscript drafting.

Introduction

Hyper IgE syndrome (HIES), a primary immunodeficiency disorder with autosomal dominant or recessive inherence patterns characterized by significantly elevated IgE, severe eczema, sinopulmonary infections, and musculoskeletal deformities.[1] Multiple variants are identified to contribute to HIES-like disorders: *PGM3, TYK2, DOCK8, STAT3, IL6, IL6ST, IL6R, ZNF341, TGFBR1, TGFBR2, SPINK5, CARD11* .[2-8] Among the variants, phosphoglucomutase 3 (*PGM3*) gene encodes a glycosylation enzyme in N-glucans biosynthesis that catalyzes the conversion of N-acetylglucosamine-6 to N-acetylglucosamine-1, a step in the production of precursor proteins of both the innate and adaptive immune system. One clinical phenotype of*PGM3* -HIES related diseases resulting in neutropenia, lymphopenia, and progressive bone marrow failure lead to a clinical presentation resembling that of severe combined immunodeficiency (SCID).[9-10] Early neurologic consequences include developmental delay, intellectual disability, ataxia, dysarthria, sensorineural hearing loss, myoclonus and seizures.[11]Eczematous involvement primarily of face and scalp are common during first several weeks of life, and mildly elevated IgE level ($<$ 2000 IU/mL) is typical under 2 years of age in HIES related disorders.[2,12] Here we describe a case of a 2-month-old female displaying clinical phenotype of HIES related disease with severe eczematous dermatitis recalcitrant to corticosteroids and achieved nearly complete response from off-label use of dupilumab.

Case History/Examination

A 2-month-old female developed three episodes of severe eczematous dermatitis with impetiginization, herpetic infection, and Staphylococcal osteomyelitis requiring multiple hospitalizations over a six-month period. Newborn screening for severe combined immunodeficiency was negative, no history of abnormal bleeding, chronic diarrhea, failure to thrive, and no known family history of atopy or immunodeficiency syndromes. Significant cutaneous erythema and dry excoriation were seen on the forehead, hairline, cheeks (Figure 1), chest, abdomen, bilateral forearms, and ankles. No honey-crusting or vesicular lesions were noted. Neurology and other exams did not reveal significant findings. She had achieved all development milestones on time.

Differential Diagnosis, investigations, and treatment

Differential diagnosis included hyper-IgE syndrome, common variable immunodeficiency, hyper IgM syndrome, and other primary immunodeficiency diseases. Workup demonstrated hypereosinophilia of 3.9 K/mm^3 (0-0.6 K/mm^3) and elevated IgE 1521 IU/mL (3-423 IU/mL) with normal levels of IgG, A, and M. Her antibody responses to pneumococcal, diphtheria and tetanus antigens were adequate. Lymphocyte subsets showed slightly low absolute CD3 and CD4 count, with normal absolute B cells and NK cells. Mitogen proliferation assays to Phytohemagglutinin, Concanavalin A, and Pokeweed antigens were normal, suggestive of adequate T-cell function.

A next generation sequencing NGS gene panel for inherited immune dysfunction syndromes showed a variant of unknown significance in key immune regulator of *PGM3* , including a heterozygous missense mutation c.337C>G (p.Pro113Ala) on exon 4. Other genes that can lead to HIES-related diseases were negative: *TYK2, DOCK8, STAT3, IL6, IL6ST, IL6R, ZNF341, TGFBR1, TGFBR2, SPINK5, CARD11* .

She later developed recurrent wheezing responsive to asthma treatment at 4 months old and multiple blinking spells concerned of seizures at 10 months old. Between ages of 1-2, she had two bacterial pneumonia, one required hospitalization. The recurrent eczema flares were unresponsive to initial treatment of topical 0.1% triamcinolone and 2.5% hydrocortisone, antihistamine, emollient, bleach baths, and wet wraps. She also received topical mupirocin for impetiginization. At the fourth months mark since first hospitalization, betamethasone 0.05% ointment and 1mg/kg of prednisolone daily were initiated, which only resulted partial response. At the end of six-month period, dupilumab was initiated with a loading dose of 120mg (12mg/kg) and maintenance dose of 60mg (6mg/kg) every four weeks.

Outcome and Follow-up

Over one month, her skin rash and pruritus significantly improved (Figure 2) without adverse effects with dupilumab use, permitting a tapered discontinuation of prednisone. Patient's eczema is adequately managed

with dupilumab maintenance dose and continual application of emollients, and topical hydrocortisone 2.5% on face, triamcinolone 0.1% on torso as needed. In concern of seizure, long-term electroencephalogram (EEG) and further neurological workup of the patient's blinking spells did not reveal seizures or significant findings. Six months since initiation of dupilumab, patient had an incidence of pneumonia that resolved with antibiotics but otherwise no other serious events.

Discussion

Multiple observations have shown that monoallelic mutations of*PGM3* gene can lead to idiopathic focal epilepsy, whereas biallelic mutations are associated with glycosylation impairment and severe immunodeficiency.[13-14] In our case, we speculated that the variant of uncertain significance in *PGM3*gene may explain the moderate severity of the clinical phenotype over a spectrum of HIES-related disease. The heterozygous mutation c.337C>G (p.Pro113Ala) in exon 4, leading to alteration of RNA splicing site, has yet to be reported in population databases of*PGM3* -related conditions.[1,13-14] Available evidence is insufficient to determine the pathogenicity of this variant. However, atopy, recurrent infections, seizure episodes are features of HIES-like disorder, along with the immunologic profile of increased IgE, low T-cell counts and hypereosinophilia.

Management of *PGM3* deficiency is challenging, with a lack of evidence to guide decisions. Prognosis is poor in cases of elevated IgE, as recurrent pulmonary infections create pneumatoceles for colonization of bacteria and fungi, leading to pulmonary hemorrhage and systemic infections.[15] Our patient's disease remained uncontrolled with oral corticosteroids. In addition to antibiotic prophylaxis, high dose intravenous immunoglobulins (IVIG) has been shown to be effective in patients with autosomal dominant HIES. However, its use is limited to those with poor vaccine response and low serum immunoglobulins, which were not observed in our patient. Hematopoietic stem cell transplant is another therapeutic option for AD-HIES, but case reports have shown failure to resolve immunologic impairment in disease with elevated IgE level.[16]

Hallmarks of severe TH2 immune dysregulation with exuberant eczematous and allergic phenotype were evident in this case. Dupilumab is a humanized IgG4 monoclonal antibody that blocks the IL-4R alpha subunit of receptor complex, thereby inhibiting the IL-4 and IL-13 signaling pathways that promote the release of pro-inflammatory cytokines and immunoglobulin E. It is indicated for the treatment of atopic diseases including moderate-to-severe atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyps, and eosinophilic esophagitis.[17] Dupilumab has been reported to successfully treat atopic dermatitis in patients with autosomal dominant*STAT3* mutation HIES, not *PGM3* -HIES specifically.[2,18-19] A recent meta-analysis showed that ocular involvement, particularly conjunctivitis followed by blepharitis, are the most common adverse events.[20]There were also cases facial erythema, alopecia, and arthralgia.[20] However, these are yet to be seen as the patient's clinical course continued to improve significantly with dupilumab therapy. Further studies are still warranted to assess the long-term adverse events.

Conclusion

Clinical manifestation of severe eczema, recurrent sinopulmonary infections, and initial immunologic workup revealing of HIES-like disorders should prompt further investigation of possible contributory genes. This case highlights the potential involvement of variant of unknown significant in *PGM3* gene. To treat the persistent eczema refractory to topical and systemic corticosteroids, we urge clinicians to recognize dupilumab as an efficacious alternative with high safety profile.

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Figure Legends:

Figure 1. Initial Presentation: diffuse erythematous scaly patches with excoriations and hemorrhagic crusting.

Figure 2. One month after initiation of dupilumab: improvement of facial involvement with only macular erythema and fine scaling.