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CASE REPORT

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Hyper IgE syndrome-related disease treated with dupilumab: A case report

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Abstract

Phosphoglucomutase 3 (PGM3) catalyzes the glycosylation of immune system precursor proteins. Its impairment leads to severe infections and other developmental, musculoskeletal, and nervous system defects. We present a case of a 2-month-old female patient with recurrent infections and diffuse eczematous dermatitis recalcitrant to corticosteroids. A next-generation sequencing NGS gene panel for inherited immune dysfunction syndromes revealed multiple variants of unknown significance in key immune regulators, specifically heterozygous mutation c.337C⟩G (p.Pro113Ala) on exon 4 of PGM3 as a novel variant in the PGM3 associated diseases. Off-label use of dupilumab resulted in rapid improvement.

KEYWORDS

dupilumab, HIES-related disease, pediatric dermatology

1 | INTRODUCTION

Hyper IgE syndrome (HIES) is a primary immunodeficiency disorder with autosomal dominant or recessive Inheritance 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 the 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.

2 | CASE PRESENTATION AND INVESTIGATION

A 2-month-old female developed three episodes of severe eczematous dermatitis with impetiginization, herpetic infection, and staphylococcal osteomyelitis requiring

multiple hospitalizations over a 6-month period. Newborn screening for SCID was negative; there was 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 examinations did not reveal significant findings. She had achieved all development milestones on time.

Differential diagnosis included HIES, 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.

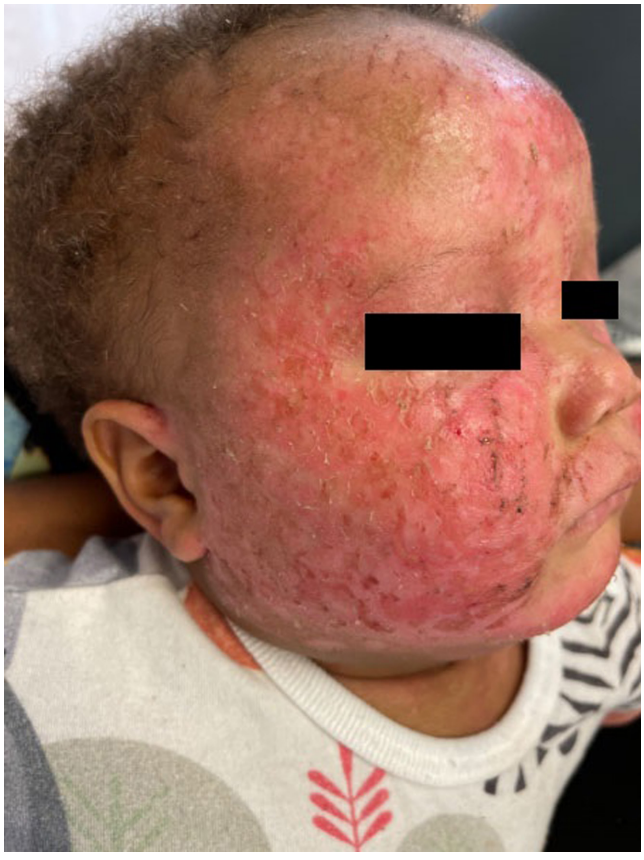

FIGURE 1 Initial presentation: diffuse erythematous scaly patches with excoriations and hemorrhagic crusting.

A next generation sequencing 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 and multiple blinking spells concerned of seizures at 10 months. Between the ages of 1 and 2, she had two bacterial pneumonias, one requiring 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. Four months from the first hospitalization, betamethasone 0.05% ointment and 1 mg/kg of prednisolone daily were initiated, which only resulted partial response. At the end of the 6-month period, dupilumab was initiated with a loading dose of 120 mg (12 mg/kg) and a maintenance dose of 60 mg (6 mg/kg) every 4 weeks.

Over 1 month, her skin rash and pruritus significantly improved (Figure 2) without adverse effects with dupilumab use, permitting a tapered discontinuation of prednisone. The patient's eczema is adequately managed with dupilumab maintenance dose and continual application of emollients, and topical hydrocortisone 2.5% on the face, triamcinolone 0.1% on the torso as needed. Regarding the seizures, long-term electroencephalogram and further neurological workup of the patient's blinking spells did not reveal seizures or significant findings. Six months since initiation of dupilumab, the patient had an incidence of pneumonia that resolved with oral suspension of

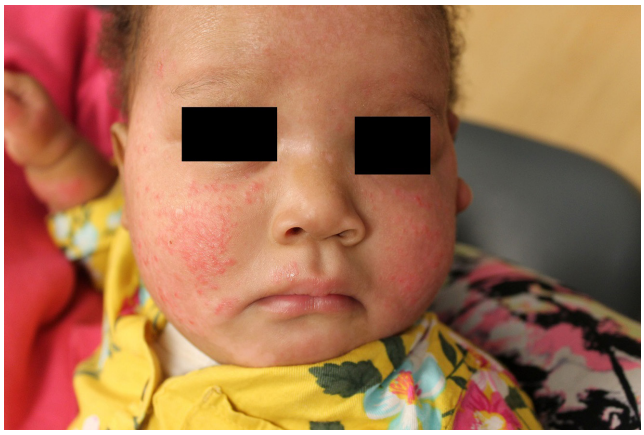

FIGURE 2 One month after initiation of dupilumab: improvement in facial involvement with only macular erythema and fine scaling.

7 mL of amoxicillin 200 mg/5 mL every 8 h. Otherwise no other serious events were reported.

3 | DISCUSSION

Multiple observations have shown that monoallelic mutations of the *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 the *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 the RNA splicing site, is 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, and 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 immunoglobulin 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 transplantation is another therapeutic option for AD-HIES, but case reports have shown failure to resolve immunologic impairment in disease with elevated IgE levels.[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 be successful in the treatment of 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, is the most common adverse event.[20] There were also cases of 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.

4 | CONCLUSION

Clinical manifestation of severe eczema, recurrent sinopulmonary infections, and initial immunologic workup revealing HIES-like disorders should prompt further investigation of possible contributory genes. This case highlights the potential involvement of variant of unknown significance in the *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.

AUTHOR CONTRIBUTIONS

Andrew S. Kao: Writing – original draft; writing – review and editing. **Hany Deirawan:** Conceptualization; investigation; supervision; writing – review and editing. **Pavadee Poowuttikul:** Conceptualization; investigation; supervision; writing – review and editing. **Steven Daveluy:** Conceptualization; investigation; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest. No other disclosures are reported.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

CONSENT

Written informed consent was obtained from the patient's guardian to publish this case and images.

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