

Severe Necrotic Reaction to 23-Valent Polysaccharide Pneumococcal Vaccine in a Patient with STAT3 Deficiency



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Autosomal-dominant hyper-IgE syndrome (AD-HIES) is a primary immunodeficiency caused by loss-of-function mutations in signal transducer and activator of transcription 3 (STAT3) leading to defective T_H17 immunity and abnormal B-cell function. Although immunoglobulin levels are generally normal in AD-HIES, patients are variably affected by specific antibody deficiency. Thus, boosting their antipneumococcal immunity is important to prevent respiratory infections.

We report a 6-year-old girl who developed an extensive inflammatory skin reaction at the vaccination site following a single dose of the 23-valent pneumococcal polysaccharide vaccine (PPSV23). The vaccine was prescribed because of a history of recurrent respiratory tract infections with no previous pneumococcal vaccines. The reaction began 2 hours after immunization, with local erythema and edema, expanding in 48 hours to a bullous lesion with ill-defined borders. Within 3 weeks, it progressively evolved to a deep necrotic lesion that required surgical debridement. The subsequent skin defect required surgical repair with a split-thickness skin graft. The complete wound healing process took about 5 months, leaving a large scar. [Figure 1](#) shows the photographic progression of the vaccination site.

The patient had a history of severe recurrent infections including severe neonatal pneumonia that required ventilation support, a colonic perforation with secondary peritonitis and septic shock that required hemicolectomy during infancy, recurrent oral candidiasis, recurrent multifocal pneumonias and acute otitis media, recurrent dental abscesses, a cervical phlegmon, and multiple kidney abscesses. Immunologic workup showed eosinophilia (850 cells/mm³), elevated IgE (1850 mg/dL), and normal IgG, IgA, IgM, and lymphocyte subsets (CD3, CD4, CD8, CD16,

CD56). Peripheral T_H17 cells were markedly decreased (0.6% vs 3.7% of normal control). Specific pneumococcal antibodies evaluated 1 month after PPSV23 revealed 50% in protective titers (>1.3 ng/mL). Thorax computed tomography showed bilateral multilobar bronchiectasis. STAT3-HIES was suspected, with an AD-HIES National Institutes of Health score of 40. A novel heterozygous missense variant in STAT3 affecting the SH2 domain (p.Lys591Glu) was found by next-generation sequencing. A variant in the same position (p.Lys591Met) has been previously reported in AD-HIES (ClinVar).

Serious adverse reactions to PPSV23 were reported by Sowerwine et al¹ in 9 of 12 (75%) patients with AD-HIES after immunization.¹ Seven had a large local cellulitis-like reaction, 5 were hospitalized for intravenous antibiotics, and 2 were hospitalized for pneumonia within 24 hours. In this series, 6 of 9 developed the reaction after the first PPSV23 dose, like in our patient. In addition, no patients had adverse reactions to the protein-conjugate pneumococcal vaccine, suggesting that reactions are specific to PPSV23.

Excessive TLR-2 and TLR-4 activation by PPSV23 components with subsequent inflammasome activation via IL-1 β in a predisposed host could explain the rapid onset of adverse reactions, as has been hypothesized in patients with Behçet disease in whom severe PPSV23 reactions have also been reported. Patients with AD-HIES also have increased proinflammatory cytokine production following TLR stimulation, providing biological plausibility to this hypothesis in patients with AD-HIES as well.²

The case presented raises awareness on the risk of severe reactions to PPSV23 in patients with STAT3 deficiency. The benefits and risks of immunizing patients with AD-HIES with PPSV23 should be weighed carefully by medical providers.

Acknowledgments

Genetic sequencing was kindly provided by Drs Raif Geha and Janet Chou at the Division of Immunology, Allergy, Rheumatology and Dermatology, Boston Children's Hospital, Harvard Medical School.

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This study was supported by Fondo Nacional de Desarrollo Científico y Tecnológico (grant no. 1160858).

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication January 9, 2019; revised January 11, 2019; accepted for publication January 14, 2019.

Available online February 15, 2019.

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J Allergy Clin Immunol Pract 2019;7:1631. 2213-2198

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<https://doi.org/10.1016/j.jaip.2019.01.033>

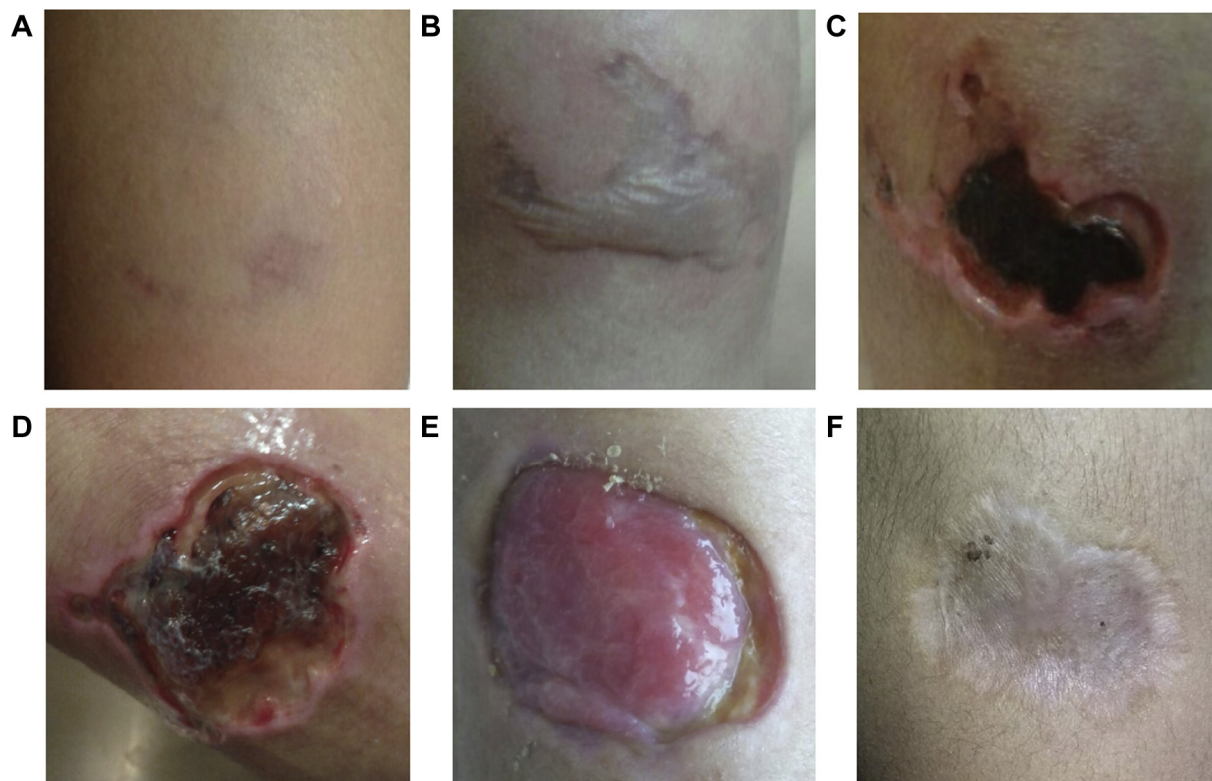


FIGURE 1. Progression of local adverse reaction to the PPSV23 at injection site. **A**, Erythema at day 1. **B**, Blisters confluent to become a large bulla. **C**, Necrotic ulcer. **D**, Ulcer after surgical debridement. **E**, Lesion after skin graft. **F**, Scar after 6-month follow-up.

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