

Clinical Communications

Treatment of severe atopic dermatitis and eosinophilic esophagitis with dupilumab in a 14-year-old boy with autosomal dominant hyper-IgE syndrome

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Clinical Implications

- Autosomal dominant hyper-IgE syndrome is associated with recurrent infections, severe atopic dermatitis, and may be associated with eosinophilic esophagitis. Use of dupilumab may improve atopic dermatitis and eosinophilic esophagitis in this patient population.

Autosomal dominant hyper-IgE syndrome (AD-HIES), also known as Job syndrome and Buckley syndrome, is characterized by elevated IgE levels, eosinophilia, recurrent cutaneous and internal organ abscesses, pneumonia leading to pneumatoceles, mucocutaneous candidiasis, characteristic facies, delayed shedding of primary teeth, bone fractures due to minor trauma, joint hypermobility, and scoliosis.¹ In addition, allergic disorders such as atopic dermatitis (AD), food allergy, and eosinophilic esophagitis (EoE)² may be associated with AD-HIES. AD-HIES is caused by a heterozygous mutation of signal transducer and activator of transcription 3 (*STAT3*) that results in dominant negative loss of function (LOF) of *STAT3*.^{3,4} Here we report a 14-year-old boy with AD-HIES with severe AD and EoE treated with dupilumab.

The patient is a 14-year-old boy with AD-HIES due to heterozygous *STAT3* LOF mutation (c. 1294 G>A; p. Val432Met performed by Steve Holland, National Institutes of Health, courtesy of Akaluck Thatayatikom). The genetic defect was inherited from his father. Consistent with AD-HIES, he suffered from recurrent cutaneous abscesses requiring incision and drainage and retropharyngeal abscess, pneumonia, esophageal candidiasis, onychomycosis of fingernails, and fungal skin infections treated with fluconazole. Immunologic evaluation demonstrated elevated serum IgE (8587 IU/mL), eosinophilia (800 eosinophils/mm³), decreased CD4+TH17+ cells (0.07%, normal 0.31%-1.18%), and decreased protective *Streptococcus pneumoniae* antibody titers 22/23 serotypes, 4% (normal ≥70%). Medical management was sulfamethoxazole/trimethoprim 400/80 mg daily and oral nystatin. The patient had limited infections on prophylactic antimicrobials and thus did not require immunoglobulin replacement.

He had severe AD involving arms, legs, trunk, and face treated with Vaseline daily, bleach baths, and pimecrolimus 1%, mometasone 0.1%, and mupirocin 0.2%, as needed for acute flares, which only partially controlled his eczema. He had frequent flares every 2 to 3 days, scoring atopic dermatitis index 60. In addition, he had EoE that was symptomatic with dysphagia and abdominal pain treated with swallowed budesonide 2 mg daily and omeprazole 20 mg daily. Specific IgE to egg (36.60 kU/L) and milk

(8.31 kU/L) were elevated, but the patient did not avoid any foods. Endoscopy revealed elevated eosinophilic infiltrate of the distal esophagus consisting of 135 eosinophils/high power field (hpf), while prescribed omeprazole but with reportedly poor adherence. The patient did not report any lower gastrointestinal (GI) tract symptoms and has not had endoscopy of the lower GI tract.

Because his eczema was not optimally controlled, dupilumab was initiated with a loading dose of 600 mg followed by 300 mg every 2 weeks. The dosage was weight-based for this pediatric patient, given weight >60 kg. Two months after starting dupilumab, his AD was dramatically improved and with nearly complete resolution, and he no longer required topical mometasone for exacerbations (Figure 1). His scoring atopic dermatitis index improved to 10. In addition, symptoms of EoE resolved with no dysphagia nor abdominal pain. Repeat endoscopy 6 weeks after starting dupilumab and distal esophageal biopsy revealed only 6 eosinophils/hpf (Figure 2). He was on swallowed budesonide and omeprazole in addition to dupilumab. The patient remains on dupilumab, which is to be continued moving forward.

Dupilumab is a humanized monoclonal antibody that binds to the alpha chain subunit of the interleukin-4 receptor (IL-4R) and interleukin-13 receptor (IL-13R), blocking signaling of IL-4 and IL-13 stimulation, which leads to inhibition of Th2-type allergic responses.⁵ Dupilumab has proved effective and safe in treating adolescents and adults with moderate-to-severe AD in clinical trials.⁵ This case adds to the growing literature that TH2-mediated IL-4 and/or IL-13 signaling plays a role in AD in HIES and other primary immune deficiencies.

To our knowledge, this is the third case report of treating AD and the first treating EoE in a patient with HIES. Lévy et al⁶ reported the successful treatment with dupilumab in a 48-year-old woman with autosomal-recessive HIES caused by *ZNF341* mutation with severe AD. The response to dupilumab was rapid and dramatic with improvement after 3 injections. Serum IgE levels also decreased with treatment. Subsequently, Sogkas et al⁷ reported successful treatment of severe AD in a 33-year-old woman with AD-HIES due to heterozygous *STAT3* mutation. Her eczema also significantly improved after the second week of treatment. Likewise, her IgE levels decreased with treatment. These observations of rapid improvement of AD in 2 patients with HIES are like the observation in our patient who had improvement within 2 months of treatment. It is important to note that dupilumab, as a monoclonal antibody, is an expensive treatment option. Cyclosporin has been reported⁸ as one possible therapeutic option, which would be more affordable than dupilumab. In this situation, dupilumab was preferred over cyclosporin and other immunosuppressants given the already elevated increased risk for infections in AD-HIES.

Although not classically associated with AD-HIES, a recent review of 70 patients with AD-HIES showed that 60% of patients complained of 1 or more GI symptoms (gastroesophageal reflux disease in 40%, dysphagia in 31%, abdominal pain in 24%, and vomiting in 21%), and this incidence was found to increase with age. Of 17 patients who had an indication for esophagogastroduodenoscopy and had esophageal biopsies



FIGURE 1. (A) Severe widespread atopic dermatitis before dupilumab treatment and (B) marked improvement after dupilumab treatment.

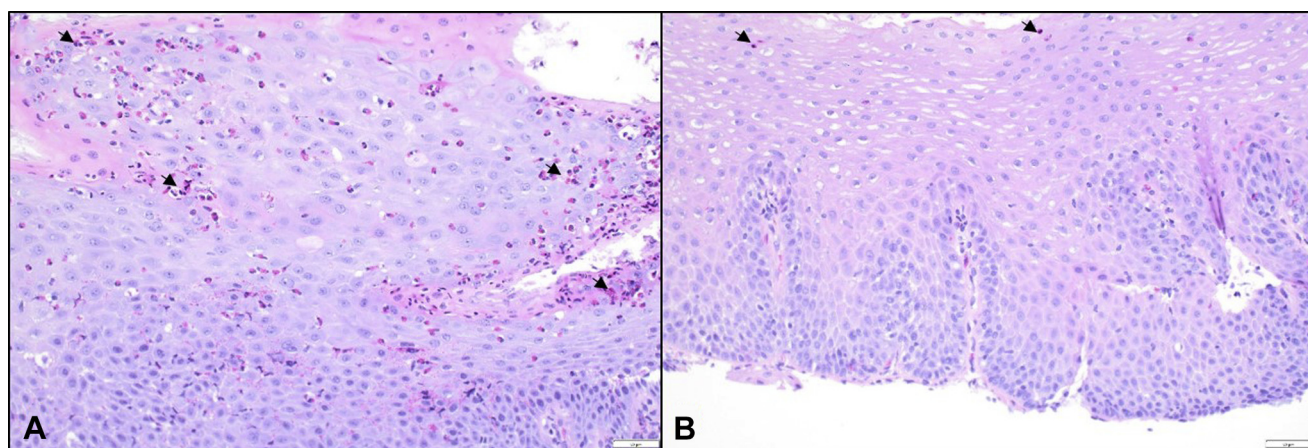


FIGURE 2. Histopathological findings of esophageal biopsies. (A) Initial esophageal biopsy showed numerous intraepithelial eosinophils (arrows). (B) Follow-up biopsy after dupilumab treatment showed marked improvement with only rare intraepithelial eosinophils present (arrows). Hematoxylin and eosin: original magnification $\times 20$. Courtesy of Dr. Miguel A. Guzman, Department of Pathology.

performed, 11 (65%) had greater than 15 eosinophils/hpf, consistent with EoE. Thus, comorbid EoE may not be uncommon in AD-HIES.²

Dupilumab is currently being evaluated in the treatment of EoE. Hirano et al⁹ recently reported a phase 2 randomized trial of adults (aged 18–65 years) with active EoE. Twenty-three patients were randomized to receive dupilumab and 24 received placebo. Dupilumab treatment significantly reduced symptoms of dysphagia by 10 weeks of treatment. A phase 3 trial evaluating dupilumab for EoE in both adults and adolescents is underway ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study?term=NCT03633617) Identifier: NCT03633617). In our patient, symptoms of dysphagia and abdominal and mid-esophageal eosinophil infiltrates on biopsy resolved within 2 months. In summary, we report a 14-year-old boy with AD-HIES whose severe AD and EoE improved markedly with dupilumab.

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