



Letter

Hyper-immunoglobulin E-like syndrome in a patient with multiple genetic mutations

A 44-year-old African-American woman with hidradenitis suppurativa, scoliosis, and idiopathic avascular necrosis of the hips presented to the emergency department with transient monocular visual loss, purulent discharge at the site of a gold-plate implant in the left upper eyelid for lagophthalmos secondary to Bell palsy, and a right thigh abscess. Since her diagnosis of hidradenitis suppurativa at 16 years old, she developed multiple abscesses in the axilla, groin, thighs, and nape of the neck requiring incision and drainages, skin grafting, and antibiotics. As a child, she did not have recurrent infections, delayed shedding of her primary teeth, or a history of eczema. Her family history was noteworthy for recurrent abscesses in her mother with diabetes, 2 daughters in their 30s, and a teenage son.

Physical examination was notable for left facial droop and a gold plate protruding from the left eyelid associated with crusting. Multiple comedones with folliculitis were noted on her face and chest. A 3- to 4-cm abscess was present on the lateral aspect of her right thigh in addition to multiple tender and nontender subcutaneous nodules in her axillae, groin, and nape of the neck. Healing lesions in the intergluteal fold with some granulation tissue were present.

Complete blood cell count showed microcytic anemia with a normal white blood cell count and differentials, including eosinophils. Erythrocyte sedimentation rate and C-reactive protein were increased at 106 mm/h (normal 0–20 mm/h) and 6.7 mg/L (0–5.0 mg/L), respectively. Culture of pus from the right thigh abscess grew *Staphylococcus lugdunensis*. Culture of the eyelid discharge grew *Corynebacterium amycolatum* and *Staphylococcus epidermidis*. The allergy and immunology service was consulted to evaluate for a potential underlying immunodeficiency. Laboratory analysis was notable for an increased serum immunoglobulin (Ig) E level of 3,185 IU/mL (normal ≤ 180 IU/mL). IgM was normal with increased IgG (2,196 IU/mL, normal 700–1,600 IU/mL) and IgA (1,217 IU/mL, normal 70–400 IU/mL) levels. Neutrophil oxidative burst, thyroid function, syphilis, human immunodeficiency virus, and hepatitis serologies and complement levels were unremarkable. Antinuclear antibody was 1:160 and speckled with negative double-stranded DNA and extractable nuclear antigens. Chest x-ray showed dextroscoliosis of the thoracic spine. Bone densitometry showed osteopenia in the hip and lumbar regions.

The patient was treated for 4 weeks with amoxicillin plus clavulanic acid, doxycycline, and topical clindamycin, benzoyl peroxide, and tretinoin cream. Two weeks after discharge, a new abscess appeared at the nape of her neck, for which amoxicillin plus clavulanic acid was continued. She subsequently remained on prophylactic therapy with trimethoprim plus sulfamethoxazole.

Under suspicion of hyper-IgE syndrome (HIES), outpatient genetic assessment was pursued. The signal transducer and activator of transcription 3 (STAT3), dedicator of cytokinesis 8 (DOCK8), and serine protease inhibitor Kazal type 5 (SPINK5) genes were normal as analyzed by reverse transcription–polymerase chain reaction and sequencing. A heterozygous P820H variant in the tyrosine kinase 2 (TYK2) gene was found. Further analyses of this nonconservative amino acid substitution were inconclusive in predicting its effect on protein structure or function. Although the P820H mutation has been classified in the public database of the National Heart, Lung, and Blood Institute's Whole Exome Sequencing (WES) project as “probably damaging” based on its effect on TYK2 structure and function, it has a minor allele frequency reaching 2.5% in Africans and African-Americans.¹ Targeted analysis of immune-related genes using WES identified multiple variants of unknown significance. These included mutations in the toll interleukin-1 receptor-associated protein (TIRAP), which is involved in the toll-like receptor-4 signaling pathway. This pathway plays a central role in the innate and adaptive immune response and regulates the activation of numerous proinflammatory genes. Mutations in this pathway have been shown to increase susceptibility to severe bacterial infections and autoimmunity.² A mutation also was present in the tumor necrosis factor receptor-associated factor 5 (TRAF5), which is involved in host defense through the regulation of interleukin-6 receptor signaling required for T-helper type 17 cell differentiation.³ Other mutations detected in the JAGN1, ITGB2, ATM, TTC7A, IBTK, and FOXO3 were unlikely to be clinically significant. Genetic testing of the patient's family to assess for familial segregation of the genetic mutations identified was pursued, but the family members declined testing.

We present a case of a middle-aged woman with suspected HIES because of a history of recurrent abscesses, bone disorders (avascular necrosis, scoliosis, and osteopenia), and increased IgE. HIES encompasses a spectrum of multisystem disorders characterized by increased serum IgE levels, susceptibility to cutaneous and sinopulmonary infections, eosinophilia, and distinctive connective-tissue disorders.³ The diagnosis of HIES is based on the presence of increased IgE with a history suggestive of impaired immunity and/or typical phenotypic features and the presence of an associated genetic mutation. Before the discovery of specific genetic mutations, clinical diagnosis was based on the National Institutes of Health scoring system that includes 21 clinical and laboratory findings. Patients with a score of at least 15 were classified as “affected” and “likely to carry the HIES genotype.”⁴ Our patient had a score of at least 20.

The genetic mutations typically associated with HIES include the loss-of-function mutation in STAT3, the autosomal-dominant form

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of the disease, and in DOCK8, the autosomal-recessive form of the disease associated with severe atopy, autoimmunity, viral infections, and lymphomas.^{4,5} Mutations in the TYK2 and phosphoglucomutase 3 (PGM3) genes have recently been discovered.^{6,7} The TYK2 mutation is associated with recurrent staphylococcal disease, predisposition to severe fungal and viral infections, and eczema.⁸ In the PGM3-mutated variant, abnormal glycosylation leads to dysregulation of immune receptors, immunoglobulins, cytokines, and complement proteins, which predispose to HIES and autoimmune disorders.⁶

The underlying P820H in this patient's TYK2 gene was initially considered to be related to her disease. However, it is doubtful this variant is causative because it has an allele frequency greater than 1% in African-American populations. Targeted WES identified mutations in 2 genes, TIRAP and TRAF5, which play a role in immunity and might be associated with this patient's susceptibility to infections. However, the significance of these variants is unknown without functional assessment.

Our patient's clinical history and presentation including onset of recurrent hot and cold abscesses as a teenager; bilateral avascular necrosis in the absence of corticosteroid use, trauma, or sickle cell disease; increased IgE; and a similar phenotype in her children increase the likelihood of a genetic immunodeficiency, although targeted WES showed multiple variants of undetermined significance. Although great advancement has been made in the diagnosis of genetic disorders through the use of WES, numerous challenges and limitations to WES persist. There could be many possible mutations leading to a similar phenotype. The publication of variants discovered through targeted WES in association with extreme clinical phenotypes might allow for the identification of variant combinations likely to play a role in the phenotypic expression of the disease, if confirmed in similar cases.

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Ayobami T. Akenroye, MD, MPH*

Melissa Iammatteo, MD†

Gabriele S. de Vos, MD, MSc*,†

*Department of Medicine

Jacobi Medical Center

†Division of Allergy and Immunology

Montefiore Medical Center

Albert Einstein College of Medicine

Bronx, New York

ayobami.akenroye@post.harvard.edu

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