ABSTRACT

Hyper-IgE syndrome (HIES), or Jobs disease, is a rare immunologic disorder characterized by the triad of staphylococcal abscesses, pneumonia with pneumatocele formation, and elevated IgE. It has been shown to have multiple modes of inheritance, autosomal dominant being more common than autosomal recessive, with sporadic cases as well. A mutation in signal transducer and activator of transcription 3 (STAT3) gene has been linked to the development of the sporadic and dominant forms of HIES. Peripheral eosinophilia, typically greater than two standard deviations from the normal population, is often seen in association with HIES. Despite these elevated levels of blood eosinophils, there have been no reported cases of invasive eosinophilic disease, such as eosinophilic esophagitis. Here we report the first description, to our knowledge, of a patient with HIES with a STAT3 mutation involving exon 12, Thr389Ile, and invasive eosinophilic disease of the esophagus. STAT3 modulates the expression of several genes that control central cell processes such as growth and death in response to external soluble stimuli. A mutation in the STAT3 molecule may affect the eosinophil’s response to IL-5 and thus reduce the chemotactic ability of those cells to migrate into tissues. This may then explain the paucity of eosinophilic infiltrative disease in patients with STAT3 mutations. The level of eosinophilic involvement may be related to the site or type of mutation within the STAT3 molecule. As more data are collected, we may be able to assess whether certain mutations dictate different clinical outcomes, which could prove helpful in directing therapy.

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The authors have no conflicts of interest to declare pertaining to this article

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Published online December 13, 2012
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### Table 1  Scoring system with clinical and laboratory tests for individuals in kindreds with HIES

| Clinical Findings                                      | Points* |
|--------------------------------------------------------|---------|
| Highest serum–IgE level (IU/mL)#                       | 0 1 2 3 4 5 6 7 8 9 10 |
| <200                                                   | 200–500 | 501–1000 | 1001–2000 | >2000 |
| Skin abscesses                                         | None    | 1–2      | 3–4       | >4    |
| Pneumonia (episodes over lifetime)                     | None    | 1        | 2         | >3    |
| Parenchymal lung anomalies                              | Absent  | 1        | 2         | 3     |
| Retained primary teeth                                 | None    | 1–2      | 3         | >3    |
| Scoliosis, maximum curvature                           | <10°    | 10–14°   | 15°–20°   | >20°  |
| Fractures with minor trauma                            | None    | 1–2      | >2        |
| Highest eosinophil count (cells/μL)§                   | <700    | 700–800  | >800      |
| Characteristic face                                    | Absent  | Mild     | Present   |
| Midline anomaly¶                                       | Absent  |          | Present   |
| Newborn rash                                           | Absent  |          | Present   |
| Eczema (worst stage)                                   | Absent  | Mild     | Moderate  | Severe |
| Upper respiratory infections per year                  | 1–2     | 3        | 4–6       | >6    |
| Candidiasis                                            | None    | Oral     | Fingernails | Systemic |
| Other serious infections                                | None    |          | Severe    |
| Fatal infection                                         | Absent  |          | Present   |
| Hyperextensibility                                     | Absent  |          | Present   |
| Increased nasal width||                                | <1 SD   | 1–2 SD   | >2 SD    |
| High palate                                            | Absent  |          | Present   |
| Young-age correction                                   | >5 yr   | 2–5 yr   | 1–2 yr    | ≤1 yr  |

*The entry in the farthest right column is assigned the maximum points allowed for each finding.

#Normal, <130 IU/mL.

§700/μL = 1 SD, 800/μL = 2 SD above the mean value for normal individuals.

¶For example, cleft palate, cleft tongue, hemivertebrae, other vertebral anomaly, etc. (see Ref. 1).

||Compared with age- and sex-matched controls (see Ref. 3).
esophagus, and fixed rings. Microscopic examination of the biopsy specimens requires at least 15 eosinophils per high-powered field (HPF). Treatments consist of dietary approaches that are focused on eliminating exposure to food allergens, topical corticosteroids, and esophageal dilation. The following is the first description of a patient with HIES and invasive eosinophilic disease of the esophagus.

A 35-year-old African American male presented with complaints of dysphagia for several weeks, resistant to a trial with proton pump inhibitors. Patient also complained of constipation with soy and hives when he ate fish. The patient had an extensive medical history that consisted of many recurrent infections including staphylococcal pneumonia, skin abscesses, and esophageal candidiasis. He had undergone a left lung pneumonectomy secondary to a pneumatocele formation after severe pneumonia several years ago. On physical exam the patient was noted to have coarse facies, a widened nasal bridge, moderate eczema, and hyperextensibility. A complete blood cell count with differential was within normal limits and revealed 12% eosinophils and 1% basophils, with an absolute eosinophil count of 432/μL. His total IgE was 2728 kU/L. The patient’s HIES National Institutes of Health score was 53. He received points for his IgE level, skin abscesses, pneumonia, pneumatocele, fractures, characteristic face, eczema, upper respiratory infections, candidiasis, hyperextensibility, and increased nasal width. Genotyping showed an STAT3 mutation involving exon 12, Thr389Ile, which is consistent with the diagnosis of HIES.

An endoscopy with biopsy specimens was performed. The patient was noted to have a ringed esophagus (Fig. 1), and microscopic examination of biopsy specimens revealed an average number of 20 eosinophils/HPF and focally up to 60 eosinophils/HPF (Fig. 2), consistent with a diagnosis of EoE. The patient was evaluated for food hypersensitivity via scratch testing and specific IgE testing, which revealed multiple food sensitizations (Tables 2–4). The patient has clinically responded to elimination of foods documented in Tables 2–3 and treatment with

Table 2  Percutaneous food panel

| Food Panel | Reaction |
|------------|----------|
| Shrimp     | 2        |
| Trout      | 2        |
| Barley     | 2        |
| Rye        | 2        |
| Turkey     | 2        |
| Mushroom   | 2        |
| Onion      | 2        |
| Spinach    | 2        |
| String bean| 2        |
| Pear       | 3        |
| Almond     | 3        |
| Walnut     | 3        |
| Wheat      | 3        |
| Flounder   | 3        |
| Cashew     | 4        |

Scratch test results were graded from 0 (saline) to 4 (histamine). Only results that were a≥2 included.
oral topical steroids. The patient was initially started on Pulmicort 0.5% (AstraZeneca Pharmaceuticals LP, Wilmington, DE) twice per day but because of reported intolerance he was switched to and tolerating Flovent at 110/9262 g, 2 puffs twice per day.

STAT3 modulates the expression of several genes that control central cell processes such as growth and death in response to external soluble stimuli.7 This modulation is central for blood eosinophils especially in response to stimulation by IL-5, an eosinophilic chemoattractant.8 A mutation in the STAT3 molecule may affect the eosinophil’s response to IL-5 and thus reduce the chemotactic ability of those cells to migrate into tissues. This may then explain the paucity of eosinophilic infiltrative disease in patients with STAT3 mutations. The level of eosinophilic involvement may be related to the site or type of mutation within the STAT3 molecule.

Because of the novelty of this particular STAT3 mutation in individuals diagnosed with HIES, we are currently unsure whether we will continue to find a clinical and histopathological correlations between EoE and HIES. However, we do know that the clinical spectrum of STAT3 mutations appears to be expanding. As more patients are being identified via genetic studies, the scope of eosinophilic involvement will continue to be elucidated. As more data are collected we may be able to assess whether certain mutations dictate different clinical outcomes, which could prove helpful in directing therapy.

REFERENCES

1. Grimbacher B, Holland SM, Gallin JI, et al. Hyper-IgE syndrome with recurrent infections—An autosomal dominant multisystem disorder. N Engl J Med 340:692–702, 1999. (PubMed PMID: 10053178.)
2. National Institutes of Health. Table 1. Scoring system with clinical and laboratory tests for individuals in kindreds with HIES. Available online at www.niaid.nih.gov/LabsAndResources/labs/aboutlabs/kidc/stat3base/Documents/scoringsystem.pdf; accessed August 6, 2012.
3. Farkas L. Anthropometry of the head and face. 2nd ed. New York, NY: Raven Press; 286–301, 1994.
4. Zhang Q, Davis JC, Lamborn IT, et al. Combined immunodeficiency associated with DOCK8 mutations. N Engl J Med 361:2046–2055, 2009. (PubMed PMID: 19776401.)
5. Grimbacher B, Holland SM, and Puck JM. Hyper-IgE syndromes. Immunol Rev 203:244–250, 2005. (PubMed PMID: 15661034.)
6. Liacouras CA, Furta GT, and Hirano I. Eosinophilic esophagitis: Updated consensus recommendations for children and adults. J Allergy Clin Immunol 128:3–20, 2011. (PubMed PMID: 21477849.)
7. Levy D, and Loomis C. STAT3 signaling and the hyper-IgE syndrome. N Engl J Med 357:1655–1658, 2007. (PubMed PMID: 17881746.)
8. Stout BA, Bates ME, Liu LY, et al. IL-5 and granulocyte-macrophage colony-stimulating factor activate STAT3 and STAT5 and promote Pim-1 and cyclin D3 protein expression in human eosinophils. J Immunol 173:6409–6417, 2004. (PubMed PMID: 15528381.)