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Hemoptysis in a Patient with Elevated Immunoglobulin E

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Abstract

Recurrent pneumonia with cavitation leading to pneumatoceles, secondary fungal infections, and hemoptysis are major causes of mortality and morbidity in patients with hyper-IgE syndrome. Prevention and aggressive treatment of pneumonia in these patients are essential to prevent further lung damage, but treatment may be delayed because the classic signs/symptoms of infection such as fever, chills, or rigors may be lacking. Early imaging to identify infection is essential for diagnosis and treatment. The mainstay of therapy is continuous, full-dose daily trimethoprim-sulfamethoxazole and commonly fungal coverage. Because hyper-IgE syndrome is a progressive disease, patients' condition may worsen despite compliance with prophylactic therapy.

Keywords

Aspergilloma; Immunodeficiency; Eczema; hyper-IgE syndrome; STAT3

CHIEF COMPLAINT

The patient is a Peruvian 22-year-old engineering student who was referred to Mount Sinai for evaluation of an episode of recurrent pneumonia, accompanied by a high serum IgE level. He had a history of eczema, 2 skin abscesses, and a right upper lobectomy for recurrent pneumonia at age 3 years. He developed stage II non-Hodgkin lymphoma at age 8 years, for which he received chemotherapy and has remained in remission since then. He also had a history of a wrist fracture following a minor trauma and a cholecystectomy for acute cholecystitis. On physical examination he had diffuse, hypopigmented skin lesions secondary to chronic eczema. His examination was also notable for a wide nasal bridge, surgical scars from a previous lobectomy and cholecystectomy, and onychomycosis of a right finger nail. He had 1 retained primary tooth because other retained primary teeth had been surgically removed. The patient healed normally after his cholecystectomy and

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multiple dental surgeries. Shortly after his first clinic visit, and after a long airline flight, he was admitted to the hospital for hemoptysis. At that time, a chest computed tomography revealed a nonocclusive pulmonary embolism of the right lung. The patient's recent long-haul flight and the presence of concomitant lung inflammation were both contributing factors for the development of a pulmonary embolism. He was started on heparin, but his hemoptysis worsened. The heparin was discontinued, and an inferior vena cava filter was placed. The chest computed tomography showed substantial bilateral bronchiectasis, and also a 4.8-cm apical bilobed lesion, with adjacent patchy consolidation consistent with a mycetoma in this region (Figure 1, A and B). An aspergilloma was suspected, and bronchoscopy was performed. Although no organism was identified, he was started on voriconazole and discharged from the hospital.

However, 2 months later, while on both trimethoprim-sulfamethoxazole and voriconazole, the patient was readmitted for hemoptysis. The recurrence of the hemoptysis despite 2 months of appropriate therapy was suggestive of an invasive aspergillosis. A pulmonary embolism was not identified; a chest computed tomography continued to show the mycetoma (Figure 1, C). The serum test for (1–3)- β -d-glucan (Fungitell, ViraCor-IBT Laboratories, Lee's Summit, MO) was positive (65; normal range [NR], <60), but galactomannan antigen was negative. Given the proximity of the lesion to the lower lobe bronchus, bronchiectasis, and scarring of the right middle lobe, thoracic surgery recommended a right pneumonectomy. However, because his left lung already had cystic changes and his lung disease was progressive, we were quite concerned about future respiratory failure. Therefore, selective bronchial artery embolization was performed to control bleeding. The patient was initially stable and discharged home; however, he was readmitted for submassive hemoptysis 1 week later. Despite 3 attempts by interventional radiology to selectively embolize his right bronchial artery, the hemoptysis was not controlled, and the patient underwent a right pneumonectomy. His lung culture was positive for *Aspergillus fumigatus* and methicillin-resistant *Staphylococcus aureus*.

Laboratory

On the first admission, the patient had eosinophilia (11.4%; absolute, 600 μ L³). Liver functions were mildly abnormal: alkaline phosphatase, 226 U/L (NR, 30–110 U/L); aspartate aminotransferase (AST), 75 U/L (NR, 1–50 U/L); and alanine aminotransferase (ALT), 78 U/L (NR, 1–53 U/L). His serum IgE level was 32,090 units/mL (0–100 units/mL) and the IgG level was elevated (1713 mg/dL; NR, 700–1600 mg/dL). He had no protective titers to diphtheria or tetanus. He had protective antibodies to only 1 of 14 pneumococcal serotypes. Unfortunately, the patient refused any vaccinations. With the emerging clinical course and suspicion of hyper-IgE syndrome (HIES), testing for signal transducer and activator of transcription signal 3 (STAT3) gene mutation was done, and he was found to have a heterozygous mutation in the DNA-binding domain: 1144C>T, p.Arg382Trp (R382W).

DIFFERENTIAL DIAGNOSIS

The patient was originally referred to a local allergy practice because he had a high serum IgE level in the setting of pneumonia of unclear nature. Although he had evidence of severe atopic dermatitis, he did not have asthma or other atopic conditions. Although atopic dermatitis may lead to very high serum IgE levels,¹ most patients do not have deep skin abscesses. Recurrent pneumonia or lobectomy, onychomycosis, retained primary teeth, and wide nasal bridge would also suggest a different diagnosis. Hagl et al² have recently proposed a diagnosis workflow to distinguish patients with severe atopic dermatitis from patients with HIES (eczema, recurrent infection, and elevated serum IgE level). Bronchiectasis, a pathologic response to repeated pyogenic infections and/or airway inflammation, could result from cystic fibrosis, ciliary dysfunction, recurrent aspiration, or alpha-1 antitrypsin deficiency, but with the patient's skin, lung infections, fungal lesions, and history of dental abnormalities, we suspected an underlying primary immune defect.

Primary immunodeficiencies associated with increased serum IgE levels and significant infections include defects of DOCK 8, phosphoglucomutase 3, Tyk2, IPEX, Omenn syndrome, Wiskott-Aldrich syndrome, and Buckley-Job syndrome (see Table I). DOCK8 deficiency was considered unlikely here because our patient did not have any history of viral infections.³ In the absence of systemic defects of glycosylation or with developmental delay and/or neurological symptoms, human phosphoglucomutase 3 was unlikely.⁴ With these pulmonary findings and in the absence of endocrinopathies (diabetes type I) and/or severe chronic enteropathy (diarrhea), IPEX was ruled out. Omenn syndrome was not considered here because of the patient's older age as Omenn syndrome is usually diagnosed during infancy (due to its severity). The diagnosis of Wiskott-Aldrich syndrome was not considered because of the lung findings and lack of thrombocytopenia. Tyk2 was ruled out because the patient did not have any mycobacterial disease or herpes infections.⁵ Our patient also did not have any significant infection from the vaccination with Bacillus Calmette Guérin; this would suggest that Tyk2 deficiency would be unlikely. In view of recurrent pneumonias leading to cavitation and presence of characteristic facies (large nasal bridge) and skin (skin abscesses, onychomycosis), dental (retained primary teeth), and skeletal abnormalities (wrist fracture following a minimal trauma), HIES was considered the most likely diagnosis. Using the National Institutes of Health scoring system for HIES, we found that he had a score of 50, which is highly suggestive of this diagnosis (score, >40).⁶

Clinical signs associated with HIES

HIES was first described and named Job syndrome in 1966. The syndrome was characterized by the triad of pulmonary infections, eczematoid dermatitis, and recurrent skin infections.⁷ In 1972, Buckley et al⁸ recognized that elevated IgE level was part of the spectrum. A rash in the newborn period is usually the first manifestation of HIES.⁹ The rash is typically pustular and eczematoid and first appears on the face and scalp.¹⁰ Bacterial cultures are likely to show *Staphylococcus aureus*. Boils, deep skin abscesses, also begin early in life and are nearly universal, unless antistaphylococcal therapies are used.

Lung manifestations

Recurrent pyogenic pneumonias often start in early childhood. The most common infecting organisms are *Staphylococcus aureus* and *Haemophilus influenzae*. The extent of the pneumonia may be out of proportion to the systemic signs of illness (absence of fever or systemic clinical signs), and the patients may feel healthy even with a significant pneumonia. The relative lack of symptoms in the face of infections that delays treatment with antibiotics and abnormal healing in HIES put patients at a higher risk of development of pneumatoceles and bronchiectasis.¹¹ These abnormalities are usually irreversible. When present, the spectrum of pulmonary pathogens may change¹² and tend to be similar to the infections seen in patients with cystic fibrosis. These infections include gram-negative bacteria (typically *Pseudomonas aeruginosa*, nontuberculous mycobacteria, or filamentous molds such as *Aspergillus fumigatus* or *Scedosporium*). These secondary infections are difficult to eradicate and are responsible for both mortality and morbidity in HIES.¹³ Mycetoma/aspergilloma created by *Aspergillus fumigatus* can cause hemoptysis, which can lead to massive pulmonary hemorrhage with risk of hemodynamic instability and death.¹³ Surgical resection of these cavities remains controversial because patients have significant difficulty with healing. A previous study has shown that the risk of bronchopleural fistulae was as high as 47% compared with 4.7% in the general population.¹⁴ Multiple lung resections also increase the risk of respiratory failure because the lung disease in HIES is progressive. Other infections can include mucocutaneous candidiasis, including onychomycosis, vaginal infections, or oral thrush.¹⁵

Other manifestations of Job syndrome

Specific facial features include a wide nasal bridge, high palate, and/or wide or deep-set eyes with a prominent forehead. These features may not be easily appreciated until later in childhood. Bony abnormalities such as craniosynostosis,¹⁶ Chiari type I malformation, scoliosis, osteoporosis, and fractures with minimal trauma are common.¹⁷ Many patients with HIES do not shed primary teeth easily, requiring surgical extraction and/or procedures that encourage secondary teeth to emerge. An increased risk of vascular abnormalities such as berry aneurysms or coronary aneurysms leading to myocardial infarctions has been reported.^{17–19} An increased risk of non-Hodgkin lymphoma has also been suggested.²⁰ However, earlier reports did not distinguish subjects with mutations in DOCK 8. Further studies have shown that patients with HIES do not seem to be at increased risk of other cancers.^{21,22}

Signal transducer and activator of transcription 3

The underlying genetic mutation responsible for this multisystem disease was found to be mutations in signal transducer and activator of transcription 3 (STAT3), which was discovered in 2007.^{23–25} STAT3 is a transcription factor that transmits signals to the nucleus after activation by a number of cytokines and growth factors, including IL-2, IL-6, IL-12, IL-15, IL-21, IL-23, and IL-27.^{26,27} After cytokine stimulation, Janus kinase 1 and 3 (JAK 1 and 3) phosphorylate the cytokine receptore-associated kinases STAT3. Then, 2 STAT molecules homodimerize or heterodimerize via their Src homology domain and translocate to the nucleus to bind to specific DNA to regulate gene expression. STAT3 promotes and

regulates the transcription of target genes involved in the cell cycle (eg, MYC), apoptosis (eg, Caspase 4), and signaling (eg, JAK2). Total absence of STAT3 is embryonically lethal.²⁸

Mutations in STAT3 in HIES are generally inherited in an autosomal-dominant pattern as they inhibit the activity of the wild-type allele^{23–25}; however, sporadic cases have been reported.^{23,24} Disease-causing mutations are often missense or in-frame deletions located primarily in the DNA-binding, SH2, and transactivation domains. Several mutational hotspots within the DNA-binding domain and the SH2 domain are the most common mutations in HIES, including R382W/Q (50% of the cases), R382W (as in our patient), and V637M/L. Unfortunately, there is no correlation between the genotype and phenotype in patients with STAT3 mutations.

Pathogenesis

The increased incidence of fungal infection in patients with HIES appears secondary to the failure of CD4+ T cells with STAT3 mutations, to generate IL-17-secreting (ie, T_H17) cells *in vivo* or *in vitro*, due to insufficient expression of transcriptional regulator, retinoid-related orphan receptor γ .^{15,29,30} Using this fact, a set of diagnostic guidelines for STAT3-deficient HIES has been proposed, which takes into account the number of T_H17 cells, as well as the total IgE levels, cardinal clinical features (recurrent pneumonia, newborn rash, pathologic bone fractures, characteristic facies, and high palate), and family history.³¹ Also, explaining the relative loss of antibody production often observed in HIES and found in our patient,³² IL-21 secretion, important in humoral immunity, is also dependent on STAT3 signaling.³³ Despite the elevated level of IgE, some patients with autosomal-dominant HIES appear to be protected from atopic disease. Boos et al³⁴ did not note an increase in allergen-specific IgE to a large variety of allergens or any increased skin prick test positivity in patients with HIES, compared with nonatopic controls.³⁴ Patients with HIES might have an impairment of mast cells and basophil degranulation in the context of STAT3 mutations.³⁵ Finally, STAT3 signals appear to be critical for certain forms of T-cell CD8+ effectors³⁶ and natural killer cell-mediated cytotoxicity.³⁷ HIES was long considered to be a defect of neutrophil chemotaxis,³⁸ but the role of STAT3 in neutrophil biology has been unclear. However, mice lacking STAT3 have impaired neutrophil mobilization from the bone marrow, impaired CXCR2-dependent chemotactic activity,³⁹ and deregulated actin polymerization responses.⁴⁰

Management of HIES

The first step in the management of HIES is to treat and prevent respiratory infections as well as dental and bony complications. For almost all subjects with HIES, lung infections, pneumonia, cavitary disease, and bronchiectasis are prominent features. The most frequent organisms are *Staphylococcus aureus*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa*. Patients must be on trimethoprim-sulfamethoxazole or an alternative medication, in full doses, throughout their lifetime. For fungal prophylaxis, patients with HIES are generally given itraconazole, voriconazole, or posaconazole. No guidelines exist for the treatment of hemoptysis. Surgery is to be avoided, if possible, because of the significant risk of bronchopleural fistula¹⁴ and respiratory failure. A few case series have reported the efficacy of immunoglobulin replacement therapy in reducing the frequency of

pneumonia.^{41,42} Patients should also be assessed for antibody response to vaccinations. In general, patients with autosomal-dominant HIES have suboptimal vaccine response to conjugate (rather than polysaccharide) vaccine booster. In our case, we did initiate immunoglobulin replacement therapy (400 mg/kg/every 4 weeks) because the patient had a degree of antibody deficiency and is dependent on his remaining left lung. Finally, patients should be immunized with pneumococcal and hemophilus vaccines. Our patient had, before his right pneumonectomy, multiple pneumatoceles. In patients with underlying cystic lung disease or pneumatoceles, life-threatening pneumothorax or fatal systemic air embolization can manifest during air travel.^{43,44} Patients should be informed about this risk.

Skin hydration with daily baths and emollient creams are helpful in controlling dermatitis. Regular bleach baths and topical antistaphylococcus antibiotics may be of use. Antihistamines are usually not helpful in controlling the associated pruritus.

Early attempts of hematopoietic cell transplantation for HIES did not demonstrate long-term benefits.^{45,46} Most recent experiences have been more successful.^{47,48}

After stem cell transplantation, IL-17 was restored, lung function was improved, and the rate of admission for pneumonia was significantly reduced.⁴⁷ The effect of stem cell transplantation on bone marrow density remains unknown at this time.

In summary, we present a patient with submassive hemoptysis secondary to an aspergilloma that had developed in a pneumatocele in a patient not previously recognized nor treated for HIES. He had many of the characteristic medical features and physical findings of HIES (see Table II), and presented additional therapeutic challenges due to infections, thrombosis, and uncontrolled hemoptysis.

Acknowledgments

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Abbreviations used

HIES	Hyper-IgE syndrome
NR	Normal range
STAT 3	Signal transducer and activator of transcription signal 3

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FIGURE 1. Chest X-ray, CT chest angiogram, and chest CT

A, Chest X-ray showed 4-cm cavitation likely in the right middle lobe, with an associated 3.7-cm ground glass opacity inferior-medial to the cavitation indicated by the arrow. **B,** Subocclusive right upper lobe segmental pulmonary embolus indicated by the arrow. **C,** A 4.8-cm right apical bilobed mass lesion with internal soft tissue, as indicated by the arrow, consistent with mycetoma. *CT*, Computed tomography.

TABLE I

Different characteristics of diseases with high serum IgE level

Condition	Severe atopic disease	STAT3 AD HIES	DOCK 8	Tyk2	PGM3
Atopy	+++	++	+/+++		+++
Recurrent skin infections	+	++++	+++	++	+++
Skin abscess	-	++++	-	++	-
Pneumonia (X-ray proven)	-	++++	++	-	+
Pneumatoceles/bronchiectasis	-	++++	++	-	++
Other serious infections	-	+++	+++	+++	-
Newborn rash	-	+++	-	-	-
Sinusitis/otitis	-	+++	-	-	++
Candidiasis	-	+++	-	-	-
Hyperextensible	-	+++	-	-	-
Neurologic deficits	-	-	±	-	+++
Cutaneous viral infection	+	+	+++	++	++
Vascular abnormality	-	++	+	-	±
Lymphoma	-	(+)	++	-	++
Scoliosis	+	+++	-	-	++
Retained teeth infection	±	+++	-	-	-
Characteristic face/high palate	-	+++	-	-	-
Renal	-	+	-	-	++
Family history	-	+++	-	++	-
Elevated IgE level	+++	+++	++	±	+++
Immunoglobulins	Normal	Increased/normal	Low (IgM)/normal/high	Normal	High
T lymphopenia	-	±	++	-	++
T _H 17	Normal	Decreased	Normal or increased	?	Normal or increased

AD, Autosomal dominant; PGM3, human phosphoglucomutase 3.

TABLE II

Key points about Job/Buckley syndrome

Elevated serum IgE level, severe eczema in infancy associated with recurrent pneumonia leading to cavitation, presence of dental and skeletal abnormalities, skin abscesses, onychomycosis, and characteristic facies (wide nasal bridge, retained primary teeth, high palate) are characteristic of the HIES diagnosis.

The principal differential diagnosis is atopic dermatitis, which also presents with elevated IgE serum level, eosinophilia, and eczema. However, the absence of all other criteria, as mentioned above, ruled out Job/Buckley syndrome.

The NIH score will help the clinician to discriminate atopic dermatitis from Job/Buckley syndrome.

- Score < 20: patient is unlikely affected by Job/Buckley syndrome.
 - Score > 40: patient is likely affected by Job/Buckley syndrome
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Patients with HIES are lacking the classic signs/symptoms of infection such as fever, chills, or rigors. The physician needs to be very aggressive in his or her search for infection and early imaging is recommended.

Prevention of pneumonia in these patients is essential to prevent further lung damage. Because the principal germs are *Staphylococcus aureus*/*Pseudomonas aeruginosa*, and *Aspergillus fumigatus*, patient should be on lifelong Bactrim and antifungal coverage.

Hemoptysis and severe infections are the major cause of mortality and morbidity in these patients.

NIH, National Institutes of Health.