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Endemic Mycoses in Patients with STAT3 Mutated Hyperimmunoglobulin E (Job's) Syndrome

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To the Editor:

STAT3 mutated hyper-IgE (Job's) syndrome (*STAT3* HIES) is characterized by highly elevated serum IgE, recurrent pneumonias, eczema, skin abscesses, mucocutaneous candidiasis, and dental, vascular and skeletal abnormalities[1]. STAT3 also promotes CD4 Th17 differentiation and expression of the associated cytokines IL17 and IL22[2]. Th17 cells are believed to enhance mucosal immunity through antimicrobial peptides, impairment of which may explain the typical epithelial infections in *STAT3* HIES.

Cryptococcus, Histoplasma, and Coccidioides are endemic fungi that may cause disseminated infection involving the brain or gastrointestinal tract in patients with *STAT3* HIES, a pattern distinct from other primary immunodeficiences[3–5]. We report five cases and

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review the literature on endemic fungal infections complicating HIES (Online Repository Table 1).

Case Reports

Histoplasmosis (H) 1

STAT3 HIES was diagnosed at age 7 in a boy with recurrent oto-sinopulmonary infections, skin abscesses, radial and skull fractures, eczema and oral aphthous ulcers.

At 10 years, he had fever, abdominal pain and hives. Computerized tomography (CT) showed bilateral lung infiltrates (Fig. 1A,B) and hepatosplenomegaly. Histoplasma was diagnosed by urine and blood antigen; Gomori-methenamine silver (GMS) staining showed small yeasts in bronchial lavage. Secondary hemophagocytic lymphohistiocytosis was apparent with fever, elevated liver enzymes (5–10 times the upper limit of normal), ferritin (16.5 times the upper limit of normal) and thrombocytopenia to 63 K/uL (ref 206–369 K/uL). He received liposomal amphotericin B with defervescence in 3 days. CRP, hepatic and hematologic values normalized in 7 days. Infiltrates resolved by 3 months. Liposomal amphotericin B was replaced with itraconazole at 3.5 weeks due to nephrotoxicity. Itraconazole was poorly tolerated and was changed to posaconazole. He remains well on posaconazole 12 months later.

Case H2

STAT3 HIES was diagnosed at age 5 in a girl with *Staphylococcus aureus* skin infections, sinusitis, asthma, minimal trauma fractures, and retained primary teeth.

At 13 years, she presented with abdominal pain, weight loss, severe iron deficient anemia, and elevated inflammatory markers. Endoscopy showed plaques in the distal two-thirds of her esophagus with diffuse exudative ulceration in her descending duodenum, terminal ileum, and transverse colon. Biopsies showed hyphae but were not cultured. Presumed candidiasis was treated with fluconazole. Despite initial improvement, abdominal pain recurred. Repeated endoscopy showed persistent ulceration (duodenum, transverse colon), patchy mucosal eosinophilia with granulomatous infiltrates (gastric antrum, duodenum, ascending, transverse, and descending colon); fungal elements were noted (esophagus, duodenum, terminal ileum, transverse colon, left colon). *Histoplasma capsulatum* grew on culture from the terminal ileum and colon (Fig. 1C,D). Urine histoplasma antigen was elevated at 14.42 ng/ml. Liposomal amphotericin B was replaced with itraconazole after one week due to nephrotoxicity. She improved rapidly and urine histoplasma antigen decreased after 2 months; 3 years later, she remains well and continues on itraconazole.

Case H3

STAT3 HIES was diagnosed at age 38 in a woman with recurrent otitis in childhood, retained primary teeth, scoliosis, cavitary lung lesions, and chronic pulmonary infections.

At age 21, she had months of fever, night sweats and dysphonia. ENT diagnosed laryngeal histoplasmosis (limited records available on means of diagnosis) and treated with

amphotericin B followed by ketoconazole. She required reconstructive laryngoplasty. Thirty years later she has no recurrence of histoplasmosis.

Cryptococcus* (Cr) 1—STAT3* HIES was diagnosed at age 3 in a boy with eczema, skin abscesses, and an affected father. At age 18, chest CT showed a lung lesion, and sputum culture grew *Cryptococcus gattii*. He was not adherent to voriconazole therapy. Five months later, *Cryptococcus gattii* meningitis was suspected because of headache, neck stiffness and vomiting and confirmed by CSF antigen and culture. Liposomal amphotericin B and flucytosine led to rapid improvement. Amphotericin was replaced with voriconazole after one week due to nephrotoxicity. Headache and vomiting returned, and he resumed liposomal amphotericin with aggressive hydration. Headache cleared rapidly but he had papilledema with high intracranial pressure (ICP) (peak opening pressure 45 mm Hg) without other neurologic findings. He received liposomal amphotericin for 7 weeks, followed by fluconazole. Serum creatinine fell below 1mg/dL over 4 months upon stopping liposomal amphotericin. Opening pressure remained elevated for about two years but without symptoms or vision loss. Three years later, he remains on fluconazole with negative CSF cryptococcal antigen, but positive serum cryptococcal antigen. He has a normal opening pressure and no other neurologic issues.

Coccidioides* (Co) 1—STAT3* HIES was diagnosed at age 9 in a girl from the Midwest with recurrent pneumonia, thrush, eczema herpeticum, oral aphthous ulcers, retained primary teeth, and minimal trauma fractures.

At 4.5 years, following a visit to Arizona, she had fever, headache, vomiting and a seizure accompanied by eosinophilia (counts 690 – 1012 K/uL) and IgE levels of 5642 mg/dL. Pulmonary and meningeal *Coccidioides immitis* infection was diagnosed by cultures of bronchoscopic lavage and CSF. She received amphotericin B lipid complex for 6 days but developed renal insufficiency with peak creatinine of 1.0 mg/dL; fluconazole was continued with good response. Her course was complicated by an internal capsule cerebral vascular accident and hydrocephalus requiring ventriculoperitoneal shunt.

Seven years later, she has residual left hemiparesis, but no other coccidioidomycosis complications. She remains on fluconazole with low serum and urine *Coccidioides* antigen levels of 0.27 and 0.21 ng/mL, respectively (normal level 0 ng/mL).

Literature Review

We reviewed Pubmed, Web of Science, and Scopus using the search terms Job's syndrome, hyperimmunoglobulin E syndrome, *STAT3* HIES, combined with the terms fungi, mycosis, coccidioidomycosis, cryptococcus, histoplasmosis, and blastomycosis. We identified eleven cases of endemic fungal infection in clinically diagnosed Job's syndrome (testing not performed for STAT3, or other causes of HIES phenotype such as PGM3 or DOCK8): five with histoplasmosis[E1–5], one with histoplasmosis followed by cryptococcal meningitis[E6], three with cryptococcosis alone[E7–9], and two with coccidioidomycosis[E10–11]. Histoplasmosis generally presented with abdominal symptoms, often without pulmonary disease; one case was mistaken for Crohn's disease[E4]. *Cryptococcus* infection localized to the GI tract and meninges, and our patients closely mimicked two reported cases[E7–8].

Specifically, Patient Cr2 had *C. neoformans* causing a Crohn's-like picture with a chronic perirectal abscess and a constricting lesion of the colon. Patient Cr3 had hematemesis from an esophageal ulcer, which grew *C. neoformans*. Meningeal *Coccidioides* occurred in our patient (Co1) and in two reported cases[E10–11], and 2/3 of the patients had concomitant lung infection and/or coccidioidomycosis related stroke.

Discussion

These sixteen cases, seven with confirmed STAT3 mutations, highlight the susceptibility of HIES patients to endemic fungi. Impaired Th17 cell differentiation is a consistent immune defect in *STAT3* HIES, which may mediate protection against *Cryptococcus* and the other endemic mycoses[6,7]. The GI predominant dissemination, frequently without pulmonary disease, in *STAT3* HIES suggests that Th17 cells may be important in upregulation of GI epithelial antimicrobial peptides for host control of *Histoplasma* and *Cryptococcus*.

The three *STAT3* HIES patients with *Coccidioides* presented with meningeal disease, while five documented patients with coccidoidomycosis and IL-12/IFN-γ/STAT1 defects experienced lung, bone, (4/5) and lymph node disease (3/5)[E12–14]. Thus, the specific immune pathway affected may determine the site of fungal dissemination.

These findings underscore the importance of considering endemic fungal infections in *STAT3* HIES patients with gastrointestinal complaints, especially since Crohn's disease is uncommon in these patients[8] and delay of antifungal therapy prolongs disease. Although disseminated endemic fungal infection remains uncommon in *STAT3* HIES, recognition of this susceptibility is important for those living in or traveling to endemic regions. Due to the severity of some of the infections, such as the risk of meningitis with *Coccidioides* exposure, strong consideration should be given for antifungal prophylaxis for those at heightened risk. Itraconazole (5 mg/kg per day; maximum 200 mg daily) can be given to patients residing in areas of increased *Histoplasma* risk, and fluconazole (3–6 mg/kg per day for a maximum of 200 mg daily) can be considered for patients traveling to or residing in *Coccidioides* endemic regions.

Nephrotoxicity occurred in 40% of STAT3-HIES patients within a week of starting amphotericin therapy, despite having normal kidney function at initiation. This compares to a nephrotoxicity rate of approximately 14% in the general population[9]. Although there are insufficient data to suggest heightened toxicity, increased vigilance to nephrotoxicity in this population is prudent.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Holland SM, DeLeo FR, Elloumi HZ, Hsu AP, Uzel G, Brodsky N, et al. STAT3 Mutations in the Hyper-IgE Syndrome. N Engl J Med. 2007; 357:1608–1619. [PubMed: 17881745]
2. Milner JD, Brenchley JM, Laurence A, Freeman AF, Hill BJ, Elias KM, et al. Impaired T(H)17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. Nature. 2008; 452:773–776. [PubMed: 18337720]
3. Sowerwine KJ, Holland SM, Freeman AF. Hyper-IgE syndrome update. Ann N Y Acad Sci. 2012; 1250:25–32. [PubMed: 22268731]
4. Antachopoulos C, Walsh TJ, Roilides E. Fungal infections in primary immunodeficiencies. Eur J Pediatr. 2007; 166:1099–1117. [PubMed: 17551753]
5. Galgiani JN, Ampel NM, Blair JE, Catanzaro A, Johnson RH, Stevens DA, et al. Coccidioidomycosis. Clin Infect Dis. 2005; 41:1217–1223. [PubMed: 16206093]
6. Valdez PA, Vithayathil PJ, Janelsins BM, Shaffer AL, Williamson PR, Datta SK. Prostaglandin E2 suppresses antifungal immunity by inhibiting interferon regulatory factor 4 function and interleukin-17 expression in T cells. Immunity. 2012; 36:668–679. [PubMed: 22464170]
7. Wozniak KL, Hardison SE, Kolls JK, Wormley FL Jr. Role of IL-17A on Resolution of Pulmonary C. neoformans Infection. PLoS ONE. 2011; 6:e17204. [PubMed: 21359196]
8. Alberti-Flor JJ, Granda A. Ileocecal histoplasmosis mimicking Crohn's disease in a patient with Job's syndrome. Digestion. 1986; 33:176–180. [PubMed: 3949095]
9. Mistro S, Maciel I de M, de Menezes RG, Maia ZP, Schooley RT, Badaró R. Does lipid emulsion reduce amphotericin B nephrotoxicity? A systematic review and meta-analysis. Clin Infect Dis Off Publ Infect Dis Soc Am. 2012; 54:1774–1777.

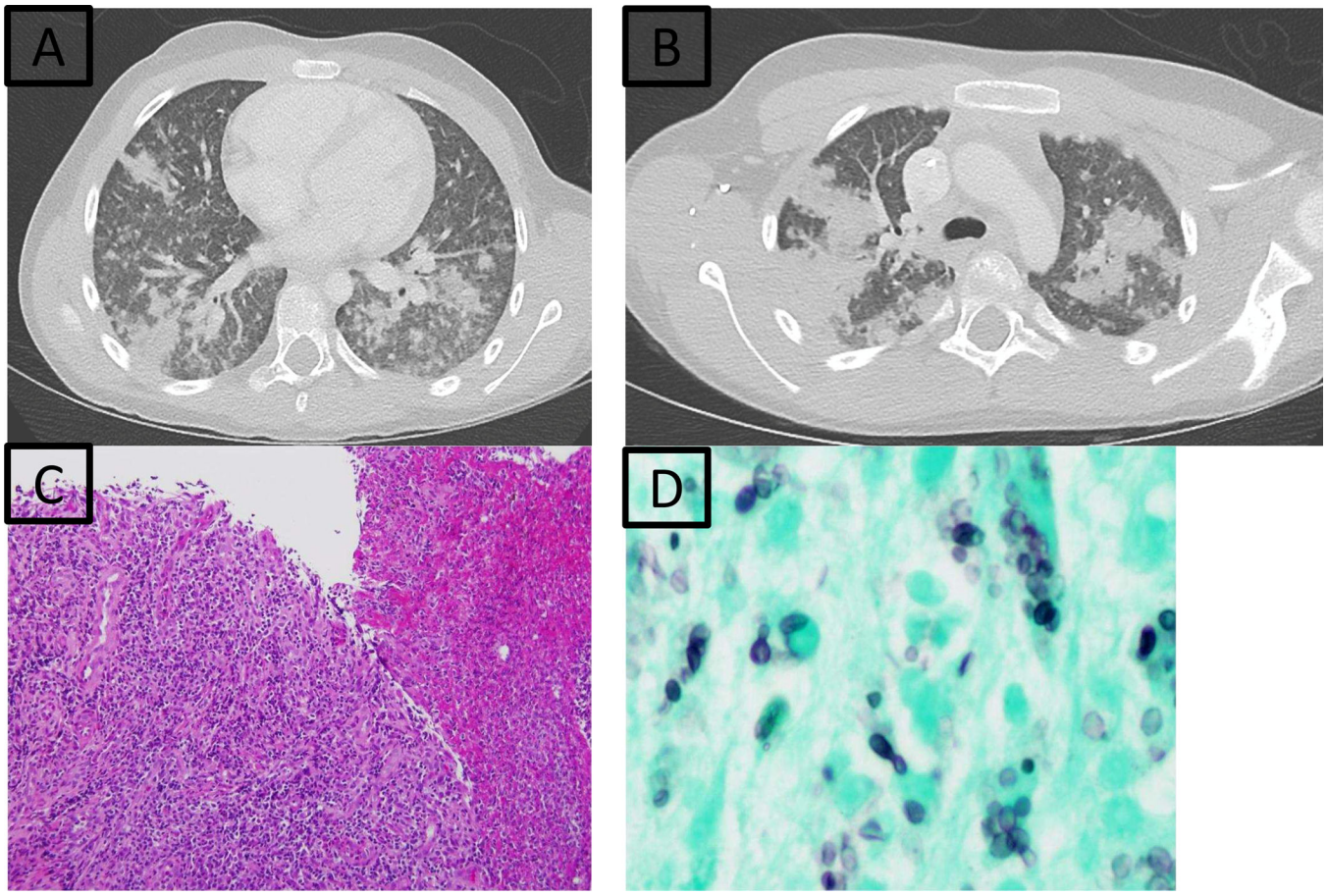

Figure 1.

Case H1: Chest CT with nodular infiltrates; bronchoscopy positive for *Histoplasma* (A and B); Case H2: Ulcerated duodenal mucosa with fibrinopurulent exudate (C) and budding *Histoplasma* yeast forms (D).