# Letter to the Editor

## Endemic mycoses in patients with *STAT3*-mutated hyper-IgE (Job) syndrome

*To the Editor:*

*STAT3*-mutated hyper-IgE (Job) syndrome (*STAT3* HIES) is characterized by highly elevated serum IgE level, recurrent episodes of pneumonia, eczema, skin abscesses, mucocutaneous candidiasis, and dental, vascular, and skeletal abnormalities.[1] STAT3 also promotes CD4 $T_H17$ differentiation and expression of the associated cytokines IL17 and IL22.[2] $T_H17$ cells are believed to enhance mucosal immunity through antimicrobial peptides, impairment of which may explain the typical epithelial infections in patients with *STAT3* HIES.

*Cryptococcus*, *Histoplasma*, and *Coccidioides* are endemic fungi that may cause disseminated infection involving the brain or the gastrointestinal (GI) tract in patients with *STAT3* HIES, a pattern distinct from other primary immunodeficiences.[3-5] We report 5 cases and review the literature on endemic fungal infections complicating HIES (see Table E1 in this article's Online Repository at www.jacionline.org). The patients described in these clinical cases were enrolled in protocols approved by the institutional review board of the National Institute of Allergy and Infectious Diseases at the National Institutes of Health. The patients and/or their families provided written informed consent.

Histoplasmosis (H) 1: STAT3 HIES was diagnosed at age 7 years in a boy with recurrent otosinopulmonary infections, skin abscesses, radial and skull fractures, eczema, and oral aphthous ulcers.

At age 10 years, he had fever, abdominal pain, and hives. Computed tomography showed bilateral lung infiltrates (Fig 1, *A* and *B*) and hepatosplenomegaly. Histoplasma was diagnosed by urine and blood antigen; Gomori-methenamine silver staining showed small yeasts in bronchial lavage. Secondary hemophagocytic lymphohistiocytosis was apparent with fever and 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; reference, 206-369 K/uL). He received liposomal amphotericin B with defervescence in 3 days. C-reactive protein, hepatic, and hematologic values normalized in 7 days. Infiltrates resolved by 3 months. Liposomal amphotericin B was replaced with itraconazole at 3.5 weeks because of 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 years in a girl with *Staphylococcus aureus* skin infections, sinusitis, asthma, minimal trauma fractures, and retained primary teeth.

At age 13 years, she presented with abdominal pain, weight loss, severe iron deficiency 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) and 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 1, *C* and *D*). Urine histoplasma antigen level was elevated at 14.42 ng/mL. Liposomal amphotericin B was replaced with itraconazole after 1 week because of nephrotoxicity. She improved rapidly, and her urine histoplasma antigen level decreased after 2 months; 3 years later, she remains well and continues on itraconazole.

Case H3: STAT3 HIES was diagnosed at age 38 years in a woman with recurrent otitis in childhood, retained primary teeth, scoliosis, cavitary lung lesions, and chronic pulmonary infections.

At age 21 years, she had months of fever, night sweats, and dysphonia. Ear, nose, and throat physicians diagnosed laryngeal histoplasmosis (limited records available on means of diagnosis), and she was 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 years in a boy with eczema, skin abscesses, and an affected father. At age 18 years, computed tomography of the chest showed a lung lesion and sputum culture grew *Cryptococcus gattii*. He was not adherent to voriconazole therapy. Five months later, *C gattii* meningitis was suspected because of headache, neck stiffness, and vomiting and confirmed by cerebrospinal fluid (CSF) antigen and culture. Liposomal amphotericin B and flucytosine led to rapid improvement. Amphotericin was replaced with voriconazole after 1 week because of nephrotoxicity. Headache and vomiting returned, and he resumed liposomal amphotericin with aggressive hydration. Headache cleared rapidly, but he had papilledema with high intracranial pressure (peak opening pressure, 45 mm Hg) without other neurologic findings. He received liposomal amphotericin for 7 weeks, followed by fluconazole. Serum creatinine level fell below 1 mg/dL over 4 months on stopping liposomal amphotericin. The opening pressure remained elevated for about 2 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 years in a girl from the Midwest with recurrent pneumonia, thrush, eczema herpeticum, oral aphthous ulcers, retained primary teeth, and minimal trauma fractures.

At age 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 level 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

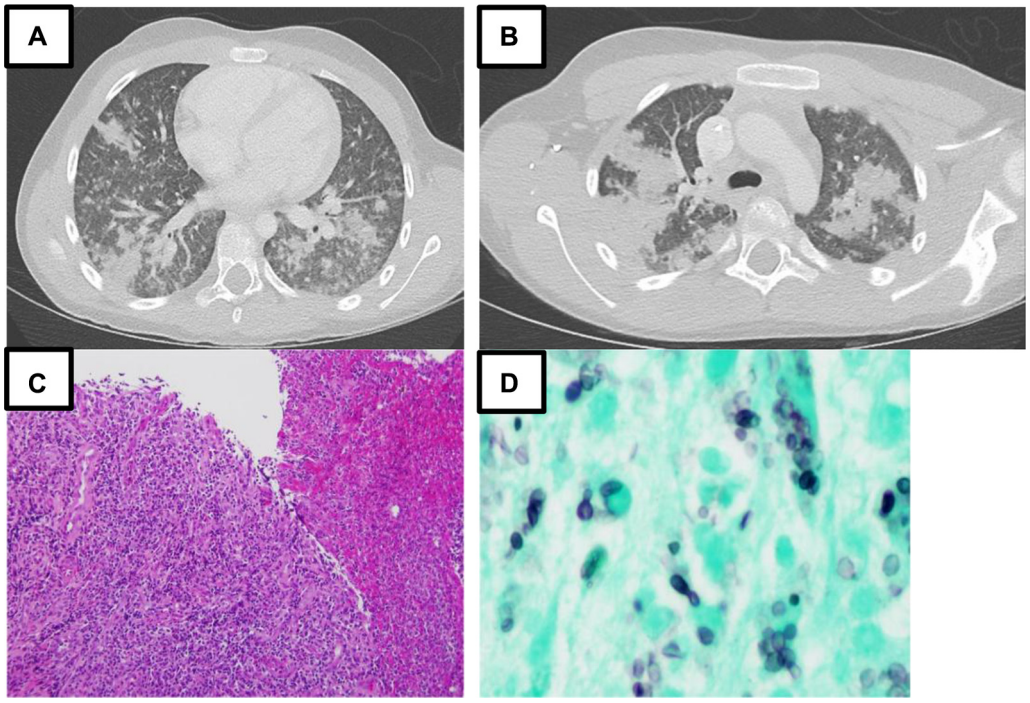



**FIG 1.** Case H1. Chest CT with nodular infiltrates; bronchoscopy positive for *Histoplasma* (**A** and **B**). Case H2. Ulcerated duodenal mucosa with fibrinopurulent exudate **(C)** and budding *Histoplasma* yeast forms **(D)**. *CT,* Computed tomography.

fluconazole with low serum and urine *Coccidioides* antigen levels of 0.27 and 0.21 ng/mL, respectively (normal level, 0 ng/mL).

We reviewed PubMed, Web of Science, and Scopus using the search terms Job's syndrome, hyperimmunoglobulin E syndrome, and *STAT3* HIES combined with the terms fungi, mycosis, coccidioidomycosis, cryptococcus, histoplasmosis, and blastomycosis. We identified 11 cases of endemic fungal infection in clinically diagnosed Job syndrome (testing not performed for STAT3, or other causes of HIES phenotype such as PGM3 or DOCK8): 5 with histoplasmosis,[E1-E5] 1 with histoplasmosis followed by cryptococcal meningitis,[E6] 3 with cryptococcosis alone,[E7-E9] and 2 with coccidioidomycosis.[E10,E11] Histoplasmosis generally presented with abdominal symptoms, often without pulmonary disease; 1 case was mistaken for Crohn disease.[E4] *Cryptococcus* infection localized to the GI tract and meninges, and our patients closely mimicked 2 reported cases.[E7,E8] Specifically, patient Cr2 had *Cryptococcus neoformans*, causing a Crohn disease-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 2 reported cases,[E10,E11] and two-thirds of the patients had concomitant lung infection and/or coccidioidomycosis-related stroke.

These 16 cases, 7 with confirmed STAT3 mutations, highlight the susceptibility of patients with HIES to endemic fungi. Impaired $T_H17$ 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 tract predominant dissemination, frequently without pulmonary disease, in *STAT3* HIES suggests that $T_H17$ cells may be important in the upregulation of GI tract's epithelial antimicrobial peptides for host control of *Histoplasma* and *Cryptococcus*.

The 3 patients with *STAT3* HIES and *Coccidioides* presented with meningeal disease, whereas 5 documented patients with coccidioidomycosis and IL-12/IFN-γ/STAT1 defects experienced lung, bone (4 of 5), and lymph node disease (3 of 5).[E12-E14] Thus, the specific immune pathway affected may determine the site of fungal dissemination.

These findings underscore the importance of considering endemic fungal infections in patients with *STAT3* HIES with gastrointestinal complaints, especially because Crohn disease is not common in these patients[8] and delay in antifungal therapy prolongs the course of disease. Although disseminated endemic fungal infection remains uncommon in patients with *STAT3* HIES, recognition of this susceptibility is important for those living in or traveling to endemic regions. Because of the severity of some of the infections, such as the risk of meningitis with *Coccidioides* exposure, strong consideration should be given to 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 the patients with STAT3-HIES 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.

*Camila D. Odio, BA*[a]
*Ki Lee Milligan, MD*[a]
*Katherine McGowan, BS*[a]
*Amanda K. Rudman Spergel, MD*[a]
*Rachel Bishop, MD, MPH*[b]
*Lisa Boris, CRNP*[c]
*Amanda Urban, CRNP*[c]
*Pamela Welch, RN*[c]
*Theo Heller, MD*[d]
*David Kleiner, MD*[e]
*Mary Anne Jackson, MD*[f]
*Steven M. Holland, MD*[a]
*Alexandra F. Freeman, MD*[a]

From [a]the National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH), [b]the National Eye Institute, NIH, [c]Clinical Research Directorate/Clinical Monitoring Research Program, Leidos Biomedical Research, Inc, [d]the National Institute of Diabetes and Digestive and Kidney Diseases, NIH, [e]the National Cancer Institute, NIH; and [f]Children's Mercy Hospital, Bethesda, Md. E-mail: freemaal@mail.nih.gov.

This study was funded in part by the Division of Intramural Research, National Institute of Allergy and Infectious Diseases and the National Cancer Institute, National Institutes of Health (NIH), Bethesda, Maryland. This project has been funded in part with federal funds from the National Cancer Institute, NIH (contract no. HHSN261200800001E). C.D.O. was funded through the NIH Medical Research Scholars Program, a public-private partnership supported jointly by the NIH and by generous contributions to the Foundation for the NIH from Pfizer, Inc, The Doris Duke Charitable Foundation, The Alexandria Real Estate Equities, Inc, Mr and Mrs Joel S. Marcus, and the Howard Hughes Medical Institute, as well as other private donors. For a complete list, please visit the foundation's Web site at: http://fnih.org/work/education-training-0/medical-research-scholars-program. The views expressed in this article are those of the authors and do not reflect the official policy of the US government. This research was supported in part by the Division of Intramural Research, National Institute of Allergy and Infectious Diseases, NIH.

Disclosure of potential conflicts of interest: The authors declare that they have no relevant conflicts of interest.

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http://dx.doi.org/10.1016/j.jaci.2015.07.003

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**TABLE E1.** Cases and literature review of patients with HIES with endemic fungal infections

| Case (reference) | Age (y)/ sex/race | STAT3 mutation (domain) | Endemic mycosis | Pulmonary disease | Extrapulmonary disease | Therapy* | Complications |
|---|---|---|---|---|---|---|---|
| H1 | 10/M/W | V432M (DNA binding) | *Histoplasma* | Y | Assumed dissemination to liver and spleen | Liposomal amphotericin, itraconazole, posaconazole | Renal insufficiency from amphotericin |
| H2 | 15/F/W | F621V (SH2) | *Histoplasma* | N | GI | Liposomal amphotericin, itraconazole | Duodenal stricture, renal insufficiency from amphotericin |
| H3 | 22/F/W | W479C (DNA binding) | *Histoplasma* | N | Laryngeal | Ketoconazole | Reconstructive laryngoplasty |
| H4[E1] | 4/F/ND | ND | *Histoplasma* | N | Rectal | Unknown | ND |
| H5[E2] | 14/F/ND | ND | *Histoplasma* | N | Ileocecal | Itraconazole (12 mo) | ND |
| H6[E3] | 27/F/B | ND | *Histoplasma* | N | Cecum, colon, bone marrow | Amphotericin B (ND), ketoconazole (2 mo) | ND |
| H7[E4] | 16/M/ND | ND | *Histoplasma* | N | Ileum, cecum, regional lymph nodes | Ketoconazole (6 mo) | Misdiagnosis as Crohn disease |
| H8[E5] | 2/M/ND | K591M (SH2) | *Histoplasma* | Y | Disseminated | ND | Respiratory distress; hypoxia |
| H9[E6] | 33 and 37/M/W | ND | *Histoplasma and Cryptococcus* | Age 33 y: *Histoplasma* | Age 33 y: Tongue (*Histoplasma*) Age 37 y: Meningitis (*Cryptococcus*) | Ketoconazole (ND; *Histoplasma*); amphotericin B (ND), fluconazole (ND; *Cryptococcus*) | Lobectomy for *Histoplasma*-related bronchiectasis |
| Cr1 | 18/M/A | R423Q (DNA binding) | *Cryptococcus gattii* | *C gattii* | *C gattii* meningitis | Liposomal amphotericin B, flucytosine, voriconazole | Papilledema and increased opening pressures without vision changes |
| Cr2[E7] | 29/F/B | ND | *Cryptococcus neoformans* | N | Colon, perirectal abscess | Amphotericin B (10 wk) and 5-flucytosine (ND) | ND |
| Cr3[E8] | 31/M/W | ND | *C neoformans* | N | Esophageal | Amphotericin B (6 wk) and 5-flucytosine (6 wk) | ND |
| Cr4[E9] | 13/M/ND | ND | *C neoformans* | N | Meningitis | Amphotericin B (10 wk), 5-flucytosine (6 wk), dexamethasone (12 wk), fluconazole (6 mo) | Myeloperitoneal shunt |
| Co1 | 4/F/W | V713M (transactivation) | *Coccidioides immitis* | Y | Meningitis | Liposomal amphotericin, fluconazole | Stroke, hydrocephalus, bilateral VP shunt, hypercalcemia |
| Co2[E10] | 17/F/ND | T412S (DNA binding) | *C immitis* | Y | Meningitis, cerebral abscess | Amphotericin B (3 wk), fluconazole (lifelong) | Altered mental status requiring temporary intubation |
| Co3[E11] | 4/F/ND | ND | *Cimmitis* | N | Meningitis | Amphotericin B (ND), fluconazole (ND) | Strokes |

*A*, Asian; *B*, black; *N*, no; *ND*, not documented; *W*, white; *Y*, yes.
*Remains on secondary prophylaxis, unless stated otherwise.