

Letter to the Editor

Persistent nodal histoplasmosis in nuclear factor kappa B essential modulator deficiency: Report of a case and review of infection in primary immunodeficiencies

To the Editor:

Histoplasma capsulatum var. *capsulatum* is an endemic dimorphic intracellular fungus that typically causes asymptomatic and self-limited infections in immunocompetent individuals.¹ Inversely, immunocompromised patients, particularly patients with the acquired immunodeficiency syndrome and other cell-mediated immune defects, are at increased risk for disseminated histoplasmosis.¹

Here, we report the first case of persistent nodal histoplasmosis in a patient deficient in nuclear factor kappa B (NF- κ B) essential modulator (NEMO). NEMO is required for activation of NF- κ B, a key transcription factor for both innate and adaptive immunity. Multiple cell surface receptors converge on the induction of NF- κ B activation, including CD40, the Toll-like receptors, TNF- α receptor, IL-1 receptor, and the receptor for ectoderm formation, ectodysplasin.²

Amorphic mutations in the X-linked gene for NEMO (*IKBKG*) are lethal prenatally in males, but cause *incontinentia pigmenti* in females.³ Lyonization allows cells with normal NEMO expression to survive; however, those cells with completely absent expression die with inflammatory consequences.³ Hypomorphic NEMO mutations resulting in reduced activation of NF- κ B permit male survival and cause a spectrum of conditions, including ectodermal dysplasia, invasive pneumococcal diseases, and mycobacterial disease.^{3,4}

Reduced natural killer cell function, variable hypogammaglobulinemia, and impaired function of the receptors of innate immunity predispose to viral, pyogenic bacterial, and mycobacterial infections.⁵ NEMO mutations can also impair CD40 signaling in monocytes, leading to diminished IL-12 secretion and therefore impaired IFN- γ production and increased susceptibility to mycobacterial infections, suggesting

that activation of NF- κ B by NEMO is essential for the destruction of intracellular pathogens.⁴

A 52-year-old man with NEMO deficiency presented to our institution with 1 year of mildly worsening dyspnea and intermittent night sweats. A mutation had been identified previously in exon 1b of *IKBKG* (c.1-16C>G), resulting in abnormally spliced transcripts.⁶ He had a history of *Haemophilus influenzae* pericarditis in childhood and disseminated *Mycobacterium avium* predominantly involving the thigh and perineum in his 30s, which was treated successfully with antimycobacterials and IFN- γ . His nontuberculous mycobacterial infection had been well controlled for over 10 years on ethambutol, azithromycin, and moxifloxacin, but IFN- γ had been stopped.

Computed tomography (CT) of the chest showed a new right superior perihilar mass (2.2 cm $\times$ 1.6 cm) with necrosis and areas of peribronchial thickening (Fig 1, A). Repeat chest CT 3 months later showed interval increase (2.5 cm $\times$ 1.8 cm) of the perihilar mass with development of tree-in-bud opacities and larger mediastinal lymph nodes.

Histopathology of a paratracheal lymph node biopsy showed chronic inflammatory changes with granulomatous inflammation and rare small yeast forms (Fig 1, B). Fungal culture from the lymph node biopsy grew *H capsulatum*. Urine was also positive for *Histoplasma* antigen. Bronchoalveolar lavage, blood, and urine fungal cultures were all negative. Posaconazole 300 mg daily was initiated. At 3 months, he was clinically improved and CT showed improvement in lung opacities and right hilar lymphadenopathy.

A search of the National Institutes of Health patient databases for unpublished cases of histoplasmosis in patients with known primary immunodeficiencies (PIDs) was conducted. All patients had provided informed consent on approved protocols of the National Institute of Allergy and Infectious Diseases at the National Institutes of Health. We identified 4 unpublished cases of histoplasmosis: disseminated histoplasmosis in GATA2 deficiency (patient 1), CD40L deficiency (patient 2), and idiopathic CD4 lymphocytopenia (ICL; patient 4) and

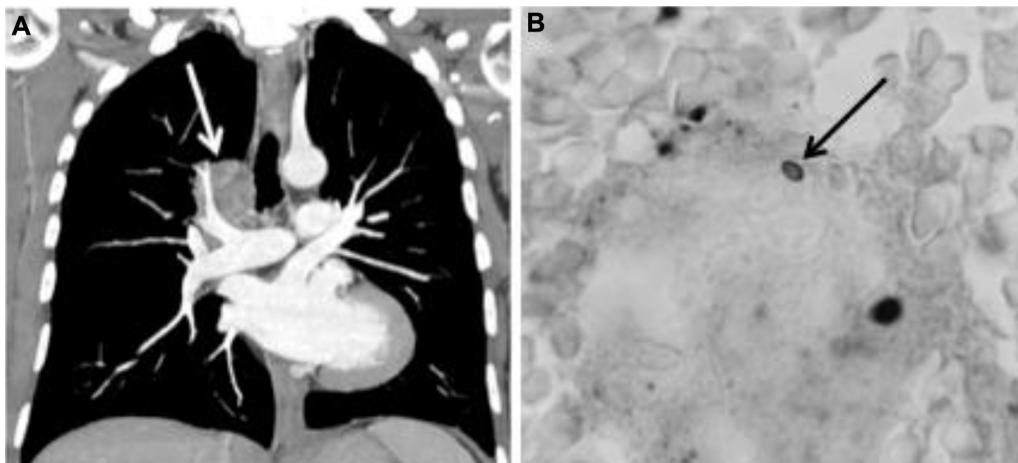


FIG 1. A, Coronal CT with contrast showing superior perihilar mass. B, Grocott's methenamine silver stain of right paratracheal lymph node showing a small yeast form.

lymphadenitis in CD40L deficiency (patient 3). Patients' clinical descriptions are provided in this article's Online Repository at www.jacionline.org and are summarized in Tables E1 and E3 in this article's Online Repository at www.jacionline.org.

A systematic search of all published cases of histoplasmosis in patients with PID was conducted through August 2015. In PubMed, PubMed Central, Scopus, Embase, and Web of Science, search terms were histoplasma, histoplasmosis, disseminated, and immunodeficiency. All publications involving secondary or acquired immune deficiencies were excluded. For specific PIDs that can be defined clinically or molecularly, the following descriptive terms were used: X-linked hyper-IgM = CD40L deficiency; hyper-IgM syndrome = clinical phenotype; STAT3 deficiency = autosomal-dominant hyper-IgE; hyper-IgE syndrome = clinical phenotype.

We identified 47 patients with histoplasmosis and a PID defined molecularly or clinically. All references are summarized in Tables E1 and E3. We classified infections as disseminated on the basis of original classification in the publication, the presence of *H capsulatum* in 2 or more tissues, or the suspected involvement of multiple tissues and a positive urine or serum *Histoplasma* antigen (see Table E1).

Disseminated histoplasmosis was classified in 32 of 47 patients (68%) with PID identified in our review. Two deaths occurred because of progression of disseminated histoplasmosis. All 8 documented recurrences of histoplasmosis occurred in the context of disseminated infection. Disseminated histoplasmosis had variable clinical manifestations, most commonly with systemic symptoms (82%), pulmonary symptoms (74%), splenomegaly (56%), and lymphadenopathy (56%) (see Table E2 in this article's Online Repository at www.jacionline.org). Notably, out of 10 cases of histoplasmosis in molecularly or clinically diagnosed autosomal-dominant hyper-IgE syndrome (STAT3 deficiency), 8 patients presented with gastrointestinal complaints, including 3 cases each of small and large intestinal ulcers and 1 case of terminal ileal perforation.

The PIDs of 22 of 47 patients (47%) were diagnosed molecularly. Most ($n = 18$ [82%]) of these patients presented with disseminated histoplasmosis. Nine of these 18 patients (50%) had mutations in the IL-12/IFN- γ /STAT1 pathway: IL-12R β 1 deficiency (4 patients),^{E1-E3} STAT1 gain-of-function mutations (3 patients),^{E4} IFN- γ receptor deficiency (1 patient)^{E5}; 1 patient had anti-IFN- γ autoantibodies.^{E6} The other 9 cases (50%) of disseminated disease presented in patients without mutations in this pathway: STAT3 deficiency (5 patients),^{E7-E11} CD40L deficiency (1 patient),^{E12} and GATA2 deficiency (3 patients), a disorder characterized by impaired phagocytic activity.^{E13,E14}

Additional cases of disseminated histoplasmosis were reported in patients with PIDs diagnosed on the basis of clinical history and/or immunoglobulin levels: ICL (4 patients),^{E15-E18} common variable immunodeficiency (CVID) (3 patients),^{E19-E21} chronic mucocutaneous candidiasis (CMC) (3 patients),^{E22-E24} hyper-IgM syndrome (2 patients),^{E25,E26} hyper-IgE syndrome (1 patient),^{E27} and a clinically suspected case of Warts, Hypogammaglobulinemia, Infections, Myelokathexis syndrome (1 patient).^{E28}

Reports of localized histoplasmosis included laryngeal histoplasmosis in STAT3 deficiency (1 patient)^{E11,E29}; gastrointestinal histoplasmosis in hyper-IgE syndrome (3 patients)^{E30-E32} and CD40L deficiency (1 patient)^{E33}; cutaneous infections in

hyper-IgM (1 patient)^{E34} and ICL (1 patient)^{E35}; adenitis in CD40L deficiency (1 patient)^{E33} and ICL (1 patient)^{E36}; meningitis in CVID (1 patient)^{E37}; and adrenal gland histoplasmosis in ICL (1 patient).^{E38} Localized pulmonary infections presented in dedicator of cytokinesis 8 deficiency (1 patient),^{E39} CVID (1 patient),^{E40} ICL (1 patient),^{E41} and CMC (1 patient).^{E42} The immunologic profiles of patients with clinically defined immunodeficiencies are compiled in Table E4 in this article's Online Repository at www.jacionline.org.

Host defense against *H capsulatum* relies on both innate and adaptive immunity. *H capsulatum* is initially phagocytosed by macrophages, resulting in the production and release of IL-12, which binds to IL-12R on T_H1 and natural killer cells, stimulating the release of TNF- α and IFN- γ .⁷ IFN- γ binding to its receptor on macrophages induces STAT1 phosphorylation, dimerization, and nuclear translocation to activate IFN-induced genes necessary for intracellular killing. TNF- α binding to its macrophage receptor results in the activation of NF- κ B.

The presentation of disseminated histoplasmosis in patients with mutations or lesions at different points in the IL-12/IFN- γ /STAT-1 pathway indicates that the host's ability to produce and respond to IFN- γ is essential to controlling infection. Although our patient represents the only case yet identified of histoplasmosis in NEMO deficiency, susceptibility to disseminated histoplasmosis in CD40L deficiency also confirms the importance of intact activation of NF- κ B. These observations suggest that the administration of IFN- γ might be therapeutic, as reported in a patient with autosomal-dominant IFN- γ receptor 1 deficiency and recurrent *Histoplasma* osteomyelitis who progressively cleared all bone lesions only after the addition of IFN- γ to his antifungal regimen.^{E5}

A damaged IL-12/IFN- γ /STAT-1 pathway, however, does not explain the presentation of disseminated disease in patients without lesions in this pathway, particularly STAT3 deficiency. A complementary pathway of macrophage defense against *H capsulatum* occurs via the GM-CSF, resulting in the heterodimerization of STAT3 and STAT5.⁸ Disseminated histoplasmosis in STAT3 deficiency may indicate the necessity of intact GM-CSF signaling for the control of *Histoplasma*. However, there have been no reports of histoplasmosis in patients with GM-CSF autoantibodies, a relatively common condition predisposing to pulmonary alveolar proteinosis.

Multiple PIDs, including STAT3 deficiency, are characterized by poor T_H17 differentiation, suggesting a possible function of T_H17 cells in the defense against *H capsulatum*.^{E11} Furthermore, the common presentations of gastrointestinal and oral histoplasmosis in STAT3-deficient patients suggests the potential roles of STAT3 and T_H17 cells in the epithelial cell defense against *H capsulatum*.^{E11}

For other PIDs without molecular diagnoses (eg, syndromically determined Warts, Hypogammaglobulinemia, Infections, Myelokathexis syndrome, CMC, hyper-IgM syndrome, and CVID), elucidating the defective pathways resulting in susceptibility to histoplasmosis is difficult. There are no reports of histoplasmosis in X-linked agammaglobulinemia, suggesting that antibodies may not be an important part of the protective host response against *Histoplasma*. The recent identification of a variety of combined immune defects in patients previously diagnosed as suffering from CVID leaves open the possibility that those patients diagnosed with CVID, in fact, had more complex underlying immune defects, including such entities as

STAT1 gain of function or GATA2 deficiency. Similarly, CMC has been linked to a heterogeneous group of immunologic disorders that also predispose to histoplasmosis, including dominant negative STAT3 mutations, gain-of-function STAT1 mutations, and IL-12R β 1 deficiency,^{E1} indicating that patients with known CMC and histoplasmosis likely have a primary immune defect.

Cases of ICL were included in this review because disseminated histoplasmosis itself can cause CD4 lymphocytopenia due to bone marrow infiltration, and successful treatment of histoplasmosis can restore CD4 T-cell counts.⁹ In many cases, sequential measurements of cell counts before and after infections support the diagnoses of ICL; however, CD4 lymphocytopenia subsequent to uncontrolled histoplasmosis may be misinterpreted as the predisposing condition to disseminated histoplasmosis, and another immune defect may be overlooked.

Our review of severe histoplasmosis suggests that in the absence of a known acquired or secondary immune deficiency, patients with disseminated histoplasmosis should be investigated for selected PIDs. Most immune defects identified molecularly in patients with disseminated histoplasmosis converge on the pathways involving IL-12/IFN- γ , NF- κ B, and STAT3.

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