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Refractory Disseminated Coccidioidomycosis & Mycobacteriosis in Interferon-γ Receptor 1 Deficiency

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Abstract

Severe coccidioidomycosis is rare and specific genetic susceptibility unidentified. We report a patient with disseminated recalcitrant coccidioidomycosis with autosomal dominant interferon (IFN)-γ receptor 1 deficiency due to a heterozygous *IFNGR1* 818del4 mutation. Therefore, the IL-12/IFN-γ axis appears to be critical for control of coccidioidomycosis.

Coccidioidomycosis is caused by the thermally dimorphic molds, *Coccidioides immitis* or *Coccidioides posadasii*, endemic to regions of the United States, Mexico, and South America. Infection occurs after inhalation of an arthroconidial spore; within the lung, the fungus grows as spherules. Successful containment of *Coccidioides* spp. is histologically represented by necrotizing granulomata [1,2]. Most cases are either subclinical or manifest with self-limited respiratory disease; <1% of all infections lead to extrathoracic dissemination [3]. There are increased rates of extrathoracic disease in certain ethnic groups. However, only select HLA allele polymorphisms and blood group antigen B have been associated with severe disease [1].

Monogenic susceptibilities to *M. tuberculosis* complex and nontuberculous mycobacteria (NTM), result from defects in the IL-12/-23/interferon (IFN)-γ axis [4–6]. Mutations in the autosomal genes encoding IL-12 p40 subunit (shared with IL-23), IL-12 receptor β1 subunit (IL12Rβ1), tyrosine kinase 2 (Tyk2), IFN-γ receptor ligand binding chain (IFN-γR1), IFN-γ receptor accessory chain (IFN-γR2), signal transduction and activator of transcription 1 (STAT1), as well as the X-linked nuclear factor κ B (NFκB) essential modulator (NEMO), predispose to severe mycobacterial disease and infections with other select bacteria (e.g. *Salmonella* spp.) and viruses. Mutations affecting IFN-γR1 and IL-12Rβ1 have been linked to severe histoplasmosis [7] and paracoccidiomycosis [8], respectively. We report a patient who had wide-spread coccidioidomycosis and disseminated *M. kansasii* with a mutation in *IFNGR1*.

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Case

An 11-month old Caucasian boy native of Texas was admitted with a 1-month history of progressive wheezing, cough and fever with right upper and middle lobe infiltrates with pleural effusion and leukocytosis. Occlusion of the right mainstem bronchus was due to noncaseating granulomatous lesions. Bronchial washings had rare acid fast bacilli (AFB) but no fungi. The tuberculin purified protein derivative (PPD) skin test was 7–8 mm (intermediate reaction); skin tests for aspergillosis, coccidioidomycosis, and histoplasmosis were negative. He was presumptively diagnosed with tuberculosis and received isoniazid, rifampin, and pyrazinamide. Two months later, he had worsening stridor and dyspnea. Review of culture results showed that an organism identified as "*M. chelonei*" had grown from multiple respiratory specimens. His regimen was modified and he slowly improved over the ensuing 9 months.

At age 11 while living in Phoenix, Arizona, he was admitted with fever, cough, anorexia, weight loss, erythema nodosum and a right lower lobe mass with mediastinal and hilar lymphadenopathy compromising the main stem bronchi and right pulmonary artery. PPD was negative but anti-coccidioidal complement-fixing serum antibodies were detected at 1:1024. Fluconazole 200 mg daily caused minimal improvement. One month later, the right hilar mass increased with right middle lobe collapse. He was again PPD positive but sputa were negative for AFB. Mediastinoscopy with lymph node biopsy showed granulomatous inflammation with numerous coccidioidal spherules without AFB. Fluconazole was continued. Bone scan uptake at T12, L4, and areas of the right costovertebral junction at T4 and T10 was presumed to be coccidioidal osteomyelitis. Amphotericin B was given for 6 months with some clinical improvement, followed by fluconazole. Despite antifungal therapy, the skeletal lesions progressed. Coccidioidal antibody titers never fell below 1:16. Fluconazole was changed to itraconazole, which temporarily appeared to stabilize his condition. At age 18, sacral lesions and pre-sacral lymphadenopathy prompted amphotericin B followed by voriconazole. When this was not tolerated, he was maintained on itraconazole.

At age 21, biopsy of a tender erythematous nodule over the right iliac crest was not diagnostic. Numerous new bony lesions were seen in the lumbar vertebrae, sacrum, sacro-iliac joints, and iliac wings. At surgical debridement with implantation of amphotericin B-impregnated beads, microbiological cultures for bacteria and fungi were negative. He was switched to posaconazole.

For worsening pain in his back, hips, and shoulders MRI demonstrated worsening vertebral and paravertebral lesions and irregularly enhancing fluid collections in the posterior shoulder soft tissues. More bony lesions led to multiple surgical debridements with placement of amphotericin B-impregnated beads over the next 10 months. Liposomal amphotericin B was given without benefit. During this period, no fungal organisms were identified from specimens and his coccidioidal serology ranged from 1:2 to 1:4.

At age 22, progressive destruction of his cervical spine caused instability and a retropharyngeal abscess. Cervical debridement and drainage of the abscess showed no AFB but yielded several colonies of *Mycobacterium kansasii*.

Because of disseminated NTM and coccidioidomycosis, an immune defect was sought. $CD3^+$ T cells and subsets, $CD20^+$ B cells, and $CD16^+$ natural killer cells were normal. HIV testing was repeatedly negative. Neutrophil oxidative burst was normal. HLA was A* 24, 32 and DRB1* 01, 04. He was blood type A. Exceptionally bright staining of peripheral blood monocytes for IFN-γR1 indicated its overaccumulation on the cell surface, consistent with the autosomal dominant form of IFN-γR1 deficiency. He had blunted production of TNF-α in

response to IFN-γ stimulation in vitro. Sequencing of *IFNGR1* proved heterozygosity for the hotspot 818del4 mutation.

Therapy directed at *M. kansasii* was initiated with azithromycin, levofloxacin, and ethambutol. Fluconazole was continued for the coccidioidomycosis. Adjunctive subcutaneous IFN-γ (50 $\mu g/m^2$) was given 3 times weekly. Four months after beginning this regimen, the patient continues to demonstrate remarkable clinical improvement.

Discussion

Exposure to *Coccidioides* spp. is common within geographically restricted encatchments, typically resulting in a localized granulomatous infection. Disseminated disease occurs in <1% of those infected [3]. These severe cases may provide insight into human immunity to this fungus. This is the first report of a Mendelian trait causally related to disseminated coccidioidomycosis.

Study of immunity to coccidioidomycosis has primarily focused on T lymphocytes [2]. Murine studies show the importance of T cells [9,10]. Classical human risk factors for disseminated disease include advanced HIV, chemotherapy for hematological malignancy, and immunosuppression for solid organ transplant [3], also supporting the central role of T cells. However, symptomatic coccidioidomycosis in association with TNF-αantagonists also implicates macrophages and granulomata in the containment of latent infection [11]. In these iatrogenic situations, however, concomitant broad-spectrum immunosuppression precludes definitive assignment of which immune component is essential. This case demonstrates the essential role of IFN-γ signaling in resistance to coccidioidomycosis and the macrophage is likely the key effector.

This is the first report of a primary immunodeficiency associated with disseminated coccidiodomycosis. Severe coccidioidomycosis has not been reported in genetic immunodeficiencies affecting T lymphocytes (e.g. severe combined immunodeficiencies, SCID), nor in patients with idiopathic CD4+ T-lymphocytopenia. These observations suggest that the IL-12/IFN-γ axis, rather than the T cell *per se*, determines susceptibility to *Coccidioides* spp. Although histologic and microbiological evidence of infection was obtained only from mediastinal lymph nodes, the patient's extensive vertebral and pelvic osteomyelitis was controlled by antifungal drugs for ~10 years, during which time his coccidioidal antibody titers decreased from 1:1024 to 1:2. His subsequent deterioration appears to be related to the emergence of the *M. kansasii* infection diagnosed at age 22.

The spectrum of fungal infections in IL-12/IFN-γ defects is distinct from that of chronic granulomatous disease (CGD), an inherited defect in the phagocyte NADPH oxidase. In CGD, patients develop infections with hyaline septated molds, primarily *Aspergillus* spp., certain yeasts (e.g. *Candida* spp., *Trichosporon* sp.) and dematiaceous molds. The one reported case of coccidioidomycosis in CGD resolved without antifungal treatment [12]. In sharp contrast, fungal infections associated with defects in the IL-12/IFN-γ pathway include thermally-dimorphic endemic mycoses and *Cryptococcus* sp., fungi which are not known to be pathogens in CGD. Zerbe and Holland [7] reported a child with disseminated *Histoplasma capsulatum* who developed disseminated MAC with the same autosomal dominant *IFNGR1* 818del4 mutation as in this case. de Moraes-Vasconcelos et al. [8] described a patient with BCG adenitis in infancy, a 7-year bout with disseminated *Salmonella enterica* serotype Typhimurium, followed by widespread disease with *Paracoccidioides brasiliensis* who had recessive complete IL-12Rβ1 deficiency. Rezai et al. [13] described a child with chronic systemic illness, disseminated *Cryptococcus neoformans*, and an unspecified IL-12R deficiency. The contrast

between the fungal infections in IL-12/IFN-γ defects and CGD illustrate that distinct pathways mediate defenses against distinct fungi.

Filipinos and African Americans are at 10–175 times higher risk for disseminated disease than their Caucasian counterparts, independent of exogenous risk factors or exposure [1]. However, only certain HLA alleles (e.g. DRB1*1301) and blood type B have been associated with disseminated disease, molecular phenotypes that may simply be surrogate markers for the at-risk ethnic populations. Mutation in *IFNGR1* in this case helps to focus on specific pathways for investigation in these at-risk populations. Although primary immunodeficiencies in the IL-12/IFN-γ axis have primarily manifested with NTM infections, polymorphisms affecting the same pathways are associated with susceptibility to *M. tuberculosis* in certain populations [14,15]. Additionally, patients have been identified with disseminated NTM disease in association with autoantibodies to IFN-γ [16–20], mostly in women of East Asian descent. It will be interesting to determine whether a similar phenomenon contributes to susceptibility to disseminated coccidioidomycosis in those of Filipino descent.

The 818del4 mutation results in partial *IFNGR1* deficiency, leading to over-accumulation of mutant IFN-γR1 on the cell surface, impairing the function of the wild-type receptor. Pharmacologic doses of IFN-γ can overcome this partial defect. Adjunctive IFN-γ has previously been used with success in the treatment of refractory disseminated coccidioidomycosis [21]. Whether susceptibility in these at-risk groups represents a complex trait resulting from anomalies in the IL-12/IFN-γ axis remains to be determined.

The identification of a primary immunodeficiency permissive for disseminated coccidioidomycosis expands our understanding of immunity to *Coccidioides* spp.

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References

1. Ampel NM. The Complex Immunology of Human Coccidioidomycosis. Ann N Y Acad Sci 2007;1111:245–258. [PubMed: 17363432]
2. Shubitz LF, Dial SM, Perrill R, Casement R, Galgiani JN. Vaccine-Induced Cellular Immune Responses Differ from Innate Responses in Susceptible and Resistant Strains of Mice Infected with Coccidioides posadasii. Infect Immun 2008;76:5553–5564. [PubMed: 18852250]
3. Laniado-Laborin R. Expanding Understanding of Epidemiology of Coccidioidomycosis in the Western Hemisphere. Ann N Y Acad Sci 2007;1111:19–34. [PubMed: 17395731]
4. Bustamante J, Zhang S-Y, von Bernuth H, Abel L, Casanova J-L. From Infectious Diseases to Primary Immunodeficiencies. Immunol Allergy Clin North Am 2008;28:235–258. [PubMed: 18424331]
5. Rosenzweig SD, Holland SM. Defects in the interferon-{gamma} and interleukin-12 pathways. Immunol Rev 2005;203:38–47. [PubMed: 15661020]
6. Minegishi Y, Saito M, Morio T, et al. Human Tyrosine Kinase 2 Deficiency Reveals Its Requisite Roles in Multiple Cytokine Signals Involved in Innate and Acquired Immunity. Immunity 2006;25:745–755. [PubMed: 17088085]
7. Zerbe CS, Holland SM. Disseminated Histoplasmosis in Persons with Interferon-{gamma} Receptor 1 Deficiency. Clin Infect Dis 2005;41:e38–e41. [PubMed: 16028145]
8. de Moraes-Vasconcelos D, Grumach AS, Yamaguti A, et al. Paracoccidioides brasiliensis Disseminated Disease in a Patient with Inherited Deficiency in the Î^{2}1 Subunit of the Interleukin (IL) â€“12/IL-23 Receptor. Clin Infect Dis 2005;41:e31–e37. [PubMed: 16028144]
9. Beaman L, Pappagianis D, Benjamini E. Significance of T cells in resistance to experimental murine coccidioidomycosis. Infect Immun 1977;17:580–585. [PubMed: 332628]

10. Beaman LV, Pappagianis D, Benjamini E. Mechanisms of resistance to infection with Coccidioides immitis in mice. Infect Immun 1979;23:681–685. [PubMed: 313369]
11. Bergstrom L, Yocum DE, Ampel NM, et al. Increased risk of coccidioidomycosis in patients treated with tumor necrosis factor alpha antagonists. Arthritis Rheum 2004;50:1959–66. [PubMed: 15188373]
12. Galgiani JN, Payne CM, Jones JF. Human polymorphonuclear-leukocyte inhibition of incorporation of chitin precursors into mycelia of Coccidioides immitis. J Infect Dis 1984;149:404–12. [PubMed: 6715897]
13. Rezai MS, Khotael G, Kheirkhah M, Hedayat T, Geramishoar M, Mahjoub F. Cryptococcosis and deficiency of interleukin12r. Pediatr Infect Dis J 2008;27:673. [PubMed: 18520441]
14. Pacheco A, Cardoso C, Moraes M. IFNG +874T/A, IL10 -1082G/A and TNF -308G/A polymorphisms in association with tuberculosis susceptibility: a meta-analysis study. Hum Genet 2008;123:477–484. [PubMed: 18414898]
15. Sahiratmadja E, Baak-Pablo R, de Visser AW, et al. Association of polymorphisms in IL-12/IFN-gamma pathway genes with susceptibility to pulmonary tuberculosis in Indonesia. Tuberculosis (Edinb) 2007;87:303–11. [PubMed: 17392024]
16. Madariaga L, Amurrio C, Mart G, et al. Detection of anti-interferon-gamma autoantibodies in subjects infected by Mycobacterium tuberculosis. Int J Tuberc Lung Dis 1998;2:62–68. [PubMed: 9562113]
17. Hoflich C, Sabat R, Rosseau S, et al. Naturally occurring anti-IFN-{gamma} autoantibody and severe infections with Mycobacterium cheloneae and Burkholderia cocovenenans. Blood 2004;103:673–675. [PubMed: 12947000]
18. Doffinger R, Helbert MR, Barcenas-Morales G, et al. Autoantibodies to Interferon-{gamma} in a Patient with Selective Susceptibility to Mycobacterial Infection and Organ-Specific Autoimmunity. Clin Infect Dis 2004;38:e10–e14. [PubMed: 14679469]
19. Kampmann B, Hemingway C, Stephens A, et al. Acquired predisposition to mycobacterial disease due to autoantibodies to IFN-gamma. J Clin Invest 2005;115:2480–8. [PubMed: 16127458]
20. Patel SY, Ding L, Brown MR, et al. Anti-IFN-{gamma} Autoantibodies in Disseminated Nontuberculous Mycobacterial Infections. J Immunol 2005;175:4769–4776. [PubMed: 16177125]
21. Kuberski TT, Servi RJ, Rubin PJ. Successful Treatment of a Critically Ill Patient with Disseminated Coccidioidomycosis, Using Adjunctive Interferon-{gamma}. Clin Infect Dis 2004;38:910–912. [PubMed: 14999639]
22. Wieden MA, Galgiani JN, Pappagianis D. Comparison of immunodiffusion techniques with standard complement fixation assay for quantitation of coccidioidal antibodies. J Clin Microbiol 1983;18:529–534. [PubMed: 6415091]

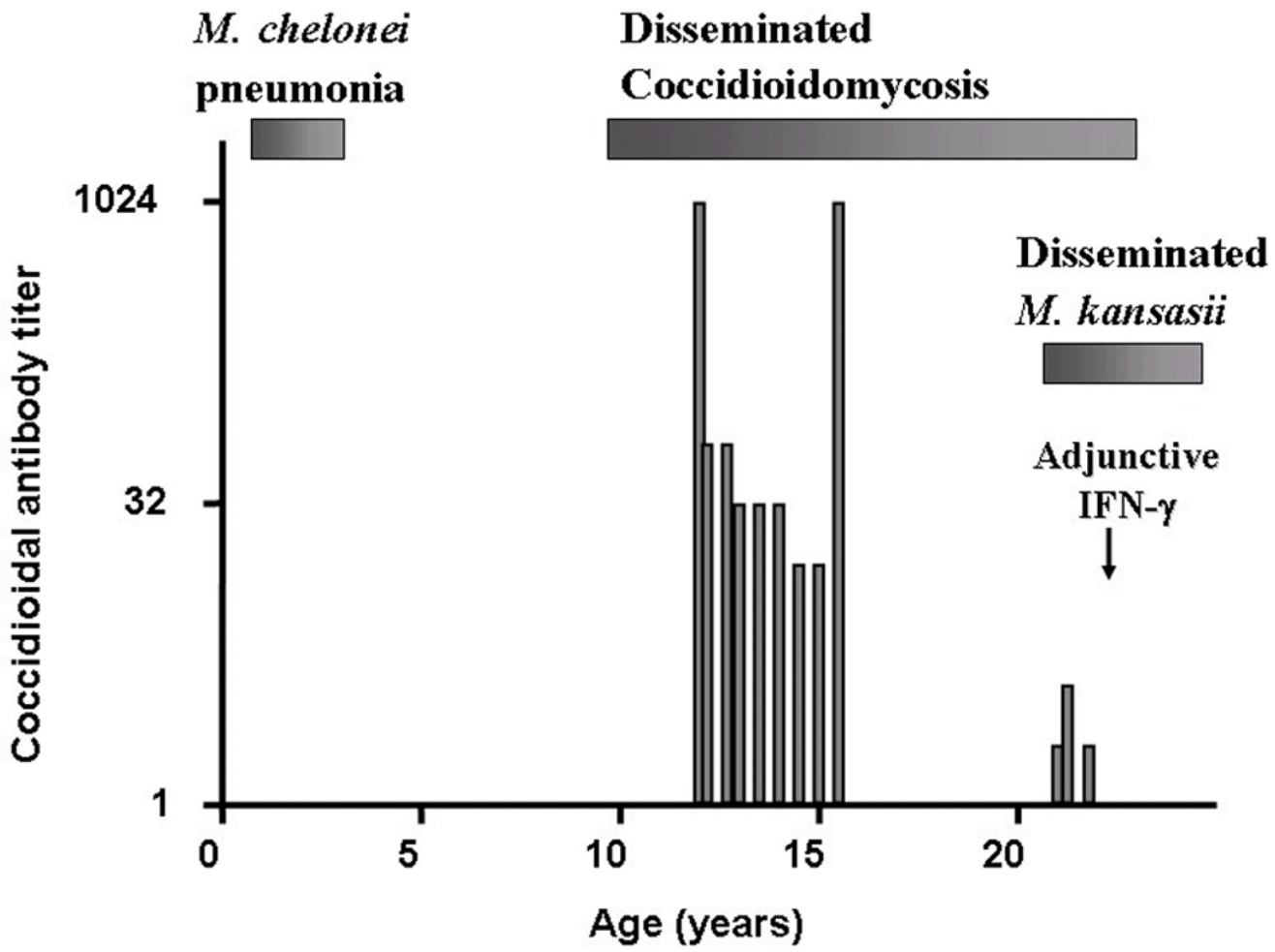

Figure 1.
Timeline graphic illustrating the course of infections and correlation with coccidioidal antibody titers. Coccidioidal serology was performed at University of California, Davis, California by complement fixation (from age 12 to 15) and at the Southern Arizona Veterans Affairs Health Care System, Tucson, Arizona by quantitative immunodiffusion (from age 21 to present) as previously described [22].