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BRIEF REPORT

Seronegative Mediastinal Coccidioidomycosis as a Novel Presentation of CTPS1 Combined Immunodeficiency

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Inborn errors of immunity may present with susceptibility to coccidioidomycosis. This is especially so in disorders impairing the interferon-γ and interleukin 12 signaling axis. We describe the first case of cytidine nucleotide triphosphate synthetase 1 (CTPS1) deficiency, a combined immunodeficiency impairing lymphocyte proliferation, presenting with coccidioidomycosis.

Keywords. coccidioidomycosis; CTPS1 deficiency; combined immunodeficiency; fever of unknown origin.

Defects in the interferon gamma (IFN-γ) and interleukin 12 (IL-12) signaling axis have been classically associated with increased susceptibility to disseminated coccidioidomycosis [1]. The United States' prevalence of coccidioidomycosis is expected to increase owing to global warming [2]. Thus, further inborn errors of immunity (IEIs) may present with susceptibility to coccidioidomycosis. Our case expands the spectrum of known IEIs with susceptibility to coccidioidomycosis to include cytidine nucleotide triphosphate synthetase 1 (CTPS1) deficiency, a rare autosomal recessive primary immunodeficiency disorder that causes an impaired T- and B-cell proliferation in response to antigen receptor–mediated activation [3]. The disorder is characterized by early-onset, severe, recurrent viral infections, particularly to Epstein-Barr virus (EBV) and varicella zoster virus, as well as recurrent sinopulmonary infections from encapsulated bacteria. Patients have a high risk of childhood mortality due to EBV-driven lymphoproliferation [3].

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CASE REPORT

A 5-year-old boy with a history of moderate atopic dermatitis, recurrent herpes simplex virus (HSV) stomatitis, severe cutaneous molluscum, chronic loose stools, and recurrent sinopulmonary infections was admitted for evaluation of a 1-month history of recurrent fever of unknown origin. His medical history was notable for multiple upper respiratory infections despite adenotonsillectomy, chronic acyclovir suppression for recurrent HSV stomatitis with recent perianal HSV infection, hospitalizations for pneumonia requiring intubation, and preseptal cellulitis. He was followed by an outside immunologist and prior immune evaluations showed unremarkable serum immunoglobulins, vaccine antibody responses, and lymphocyte subsets.

His initial laboratory tests were significant for anemia; however, serum electrolytes and liver enzymes were unremarkable (Table 1). Serum immunoglobulin G (IgG), immunoglobulin A, and immunoglobulin M (IgM) all were within the age-adjusted reference range. $CD8^+$ T cells, $CD19^+$ B cells, and natural killer cells were decreased; however, $CD4^+$ T cells were within the reference range (Table 1). He had 3 of 13 vaccine titers ≥1.3 μg/mL post–13-valent pneumococcal conjugate vaccine (PCV13) series, consistent with suboptimal seroconversion. Peripheral monocyte subsets were within the reference range: $CD14^+$, 342 (173–637 cells/μL); $CD123^+$ (plasmacytoid dendritic cells), 12 (4–26 cells/μL); and $CD11c^+$ (myeloid dendritic cells), 60 (14–84 cells/μL). He had low lymphocyte response to phytohemagglutinin, concanavalin A mitogens, and *Candida* and tetanus antigens, but normal response to pokeweed mitogen.

Notably, his coccidioidal serology (enzyme-linked immunoassay) resulted negative for both IgG and IgM, and complement fixation titer was also negative. His EBV polymerase chain reaction in blood was negative.

His initial chest radiograph showed right paratracheal fullness and right upper lobe pneumonia. Computed tomography (CT) of the chest further characterized the right upper lobe lesion as necrotizing (Figure 1*A*). Bulky hilar and mediastinal lymphadenopathy were also noted (Figure 1*B*). Imaging of his sinuses showed the presence of extensive bilateral sinusitis. He subsequently underwent interventional radiology–guided lung biopsy with pathology revealing both acute and chronic inflammation with coccidioidomycosis. Culture grew *Coccidioides immitis* species. He was started on intravenous fluconazole (10 mg/kg/day), as well as cefepime for empiric treatment of possible bacterial superinfection and his sinusitis. Lumbar puncture and bone scan did not show evidence of dissemination to cerebrospinal fluid or bone. Magnetic resonance imaging of the limbs ruled out bony involvement. Targeted immunodeficiency genetic

Table 1. Pertinent Laboratory Values on Admission

Laboratory Test	Result	Reference Range
WBC count	4.3 K/mL	5.5–15.5 K/mL
Hemoglobin	8.5 g/dL	11.5–13.5 g/dL
Platelets	340 K/μL	140–450 K/μL
C-reactive protein	4.7 mg/dL	<0.9 mg/dL
IgG	627 mg/dL	386–1470 mg/dL
IgA	87 mg/dL	29–256 mg/dL
IgM	36 mg/dL	37–224 mg/dL
$CD4^+$ T cells	984 cells/μL	700–2200 cells/μL
$CD8^+$ T cells	345 cells/μL	490–1300 cells/μL
$CD19^+$ B cells	124 cells/μL	390–1400 cells/μL
$CD16^+CD56^+$ NK cells	39 cells/μL	130–720 cells/μL

Abbreviations: IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; NK, natural killer; WBC, white blood cell.

testing identified a pathogenic homozygous splice acceptor variant in *CTPS1*, c.1692-1G > C, confirming CTPS1 deficiency. The patient's mother subsequently underwent genetic testing and was found to be a heterozygous carrier for the *CTPS1* variant. His father was not available for testing. To their knowledge, there is no consanguinity between the patient's parents.

After 11 days' hospitalization, he was discharged on oral fluconazole (10 mg/kg/day) and started on valacyclovir for HSV prophylaxis. Intravenous immunoglobulin (IVIG) 0.5 g/kg every 4 weeks was initiated, and repeat trough IgG was 1014 mg/dL. His frequency of upper respiratory tract infections has decreased since starting IVIG. Repeat CT imaging of his chest 5 months postdischarge revealed improving mediastinal and hilar lymphadenopathy, as well as decrease in size of his right upper lobe lung mass. He is currently undergoing evaluation for allogeneic hematopoietic bone marrow transplantation.

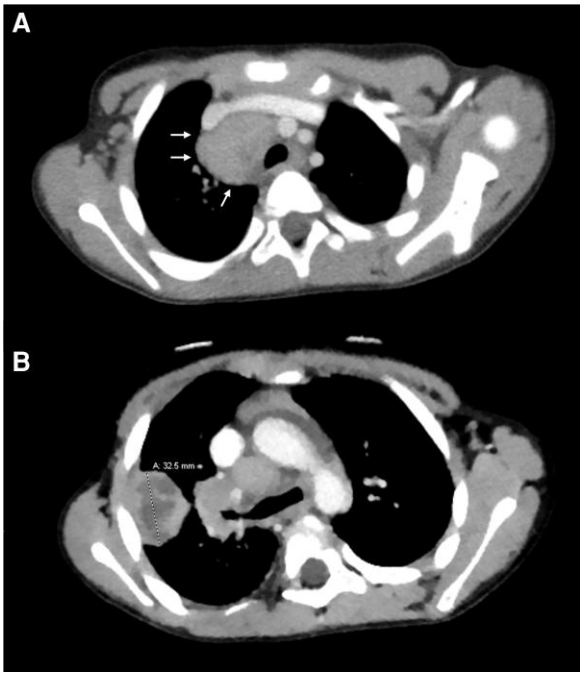

Figure 1. Cross-sectional computed tomographic imaging of the chest with arrows indicating the presence of a right paratracheal lung mass (*A*) and hilar adenopathy with a large necrotic right pulmonary mass measuring 32.55 mm in diameter (*B*).

DISCUSSION

Coccidioidomycosis is caused by the pathogenic dimorphic fungi *Coccidioides immitis* and *Coccidioides posadasii* [1, 2, 4]. These fungi are endemic in the soil in the southwestern United States and can also be found in Central America and South America. Coccidioidomycosis occurs after inhalation of airborne fungal spores and typically causes a mild respiratory illness in most affected patients that is self-limited, though it may lead to disseminated disease [2]. Diagnosis of coccidioidomycosis can be made via immunological assays, direct microscopy on histopathology, or tissue culture. Most commonly, serological testing with either immunodiffusion or complement fixation assay is taken into consideration with the clinical history to make a diagnosis. However, serological tests rely on the patient having a functioning immune response. Our patient had decreasing titers to the PCV13 vaccine, suggestive of waning T- and B-cell functional response to protein antigens. Thus, confirmatory testing via culture and antigen testing should be pursued, particularly since the complement fixation assay carries a high false-negative test rate in immunocompromised patients [5].

To date, known primary immunodeficiencies in which patients have an increased risk of developing coccidioidomycosis are mostly due to loss of function mutations in the IL-12/IFN-γ pathway, which results in compromised macrophage–lymphocyte communication [6]. Patients with NF-κB signaling defects, interleukin 17 signaling defects, GATA2 deficiency, STAT3 loss of function, and STAT1 gain of function mutations have also been shown to be affected. In 2017, Odio et al reported on 8 patients with proven primary immunodeficiency and disseminated coccidioidomycosis. Six patients had defects in IL-12/IFN-γ signaling and 2 had STAT3 loss of function [2]. Hung et al described all known-to-date genetic defects that predispose to disseminated coccidioidomycosis and emphasized that diminished innate recognition and signaling are central factors in the development of disseminated coccidioidomycosis [6]. Our patient is the first reported with a lack of proliferative response after T-cell activation due to CTPS1 deficiency. Since our patient also had a history of moderate eczema with molluscum, we attempted to obtain dupilumab, an anti–interleukin 4Ra monoclonal antibody to suppress Th2 inflammation. Eosinophilia and high immunoglobulin E levels are associated with a worse prognosis in coccidioidomycosis [7]. Dupilumab, in concert with IFN-γ, has been used to treat disseminated coccidiomycosis in a pediatric patient by decreasing Th2 responses

[8]. We were constrained by lack of insurance approval for both dupilumab and IFN-γ.

CTPS1 is involved in de novo synthesis of the CTP nucleotide from uridine triphosphate and glutamine, which is a required precursor for DNA synthesis. It is strongly upregulated in T cells after T-cell receptor activation, and necessary to elicit a normal proliferative response. Thus, deficient T cells have drastically impaired proliferative responses after antigen stimulation and compromised T-cell expansion, resulting in a poor immune response to viral and bacterial infections. Martin et al first reported on 8 patients from 5 different families with *CTPS1* mutations in 2014, 4 presenting with a severe mononucleosis, 3 with lymphoproliferative disease, and 1 patient with chronic EBV viremia [9]. All patients had a history of severe herpesvirus in childhood as well as encapsulated bacterial infections. Since then, only a small number of additional patients with CTPS1 deficiency have been identified and described in the literature. Every patient has the identical homozygous c.1692-1G > C mutation [10]. Early diagnosis prior to positive EBV status may improve patient morbidity, as patients have improved outcomes following hematopoietic stem cell transplantation [3].

Our case highlights the importance of establishing a diagnosis of coccidioidomycosis despite negative serology and expands the spectrum of IEI with susceptibilities to *Coccidioides* infection. This case highlights that defects in lymphocyte proliferation such as CTPS1 deficiency may present with apparently normal immunoglobulins despite likely poor antibody affinity. Furthermore, paratracheal extension of the coccidioidomycosis mass could harbor significant risk for upper airway obstruction, as the mass could expand following initiation of conditioning chemotherapy prior to allogeneic transplantation for CTPS1 deficiency. Early-onset and/or extrapulmonary coccidioidomycosis in the pediatric patient should warrant consideration for an immunodeficiency evaluation.

Notes

Patient consent. Consent from the patient's guardian was obtained prior to publication. The case report was deemed as exempt by the local Phoenix Children's Hospital institutional review board.

Potential conflicts of interest. The authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Bays DJ, Thompson GR III. Coccidioidomycosis. Infect Dis Clin North Am **2021**; 35:453–69.
2. Odio CD, Marciano BE, Galgiani JN, Holland SM. Risk factors for disseminated coccidioidomycosis, United States. Emerg Infect Dis **2017**; 23:308–11.
3. Nademi Z, Wynn RF, Slatter M, et al. Hematopoietic stem cell transplantation for cytidine triphosphate synthase 1 (CTPS1) deficiency. Bone Marrow Transplant **2019**; 54:130–3.
4. Cavazos SP, De la Cruz RAC, Bejarano JIC, Aparicio DNV, de Los Santos AHM, del Carmen Zárate Hernandez M. Disseminated coccidioidomycosis as the first presentation of a C-terminal NFKB2 pathogenic variant: a case report and review of the literature. Pediatr Infect Dis J **2022**; 41:140–4.
5. Navalkar KA, Johnston SA, Woodbury N, et al. Application of immunosignatures for diagnosis of Valley fever. Clin Vaccine Immunol **2014**; 21:1169–77.
6. Hung CY, Hsu AP, Holland SM, Fierer J. A review of innate and adaptive immunity to coccidioidomycosis. Med Mycol **2019**; 57(Suppl 1):S85–92.
7. Cox RA, Baker BS, Stevens DA. Specificity of immunoglobulin E in coccidioidomycosis and correlation with disease involvement. Infect Immun **1982**; 37: 609–16.
8. Tsai M, Thauland TJ, Huang AY, et al. Disseminated coccidioidomycosis treated with interferon-gamma and dupilumab. N Engl J Med **2020**; 382:2337–43.
9. Martin E, Palmic N, Sanquer S, et al. CTP synthase 1 deficiency in humans reveals its central role in lymphocyte proliferation. Nature **2014**; 510:288–92.
10. Martin E, Minet N, Boschat AC, et al. Impaired lymphocyte function and differentiation in CTPS1-deficient patients result from a hypomorphic homozygous mutation. JCI Insight **2020**; 5:e133880.