CASE REPORT

Disseminated Coccidioidomycosis With Fungemia and Possible *Strongyloides* Co-infection

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ABSTRACT

Introduction: Coccidioidomycosis is most often an asymptomatic or mild self-limited respiratory infection, but in rare cases it can become disseminated and cause severe disease.

Case Presentation: A 29-year-old man who was originally from Thailand and had been living in Arizona for 2 years presented with intermittent fevers, fatigue, and other nonspecific symptoms, including abdominal pain, nonbloody diarrhea, and pruritic rash. Initial laboratory values showed significant peripheral eosinophilia. Extensive evaluation revealed possible *Strongyloides* species infection. Shortly after, *Coccidioidies* species fungemia was found. Fevers and symptoms resolved after adequate treatment.

Discussion: Disseminated coccidioidomycosis with fungemia is very rare in immunocompetent individuals. Co-infection with *Stronglyloides* species is only reported in two other case reports.

Conclusions: We report this case to raise awareness of a rare infection. In adequate epidemiological circumstances, co-infections *Coccidioides* and *Strongyloides* species should be considered in presence of fever and eosinophilia.

INTRODUCTION

Coccidioidomycosis is caused by the dimorphic fungus *Coccidioides immitis (C immitis)* or *Coccidiodes posadasii.* Infection with either species has a similar clinical presentation. *C immitis* is most found in soil in the southwestern United States, parts of Mexico, and South America. Highly endemic areas include southern Arizona and California's southern San Joaquin Valley.[1] Coccidioides grows as a mold with septate hyphae that develop arthroconidia in the soil, which can then become aerosolized and inhaled. Once inhaled, the warm environment of the lungs triggers a morphological change into spherules. The spherules then rupture and release endospores.[2] Sixty percent of coccidiomycosis infections are asymptomatic or present as a mild self-limited respiratory infection, and less than 1% become disseminated.[3] Extrapulmonary coccidioidomycosis most commonly involves the skin, bone, and meninges and less commonly involves the liver, spleen, lymph nodes, kidney, eye, and endocrine glands.[3] Risk factors for disseminated disease include immunocompromised status (HIV infection, steroid use, therapy with immunobiological modulation, malignancy), pregnancy, male sex, and ethnicity (Filipino, Asian, and/or African).[4] *Coccidioides* species fungemia is an even rarer event and almost universally found in immunosuppressed patients.[3,5]

We present a case of coccidiomycosis fungemia in an immunocompetent, Asian male patient with possible *Strongyloides* co-infection. There are only two other case reports identified in the medical literature of *Strongyloides* and coccidioidomycosis coinfection.[6]

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CASE PRESENTATION

The patient is a 29-year-old man from Thailand. He had a 3-week history of intermittent fever, chills, night sweats, increasing fatigue, intermittent nonlocalizing headache, generalized arthralgias, left-sided cramping abdominal pain, and watery nonbloody diarrhea associated with pruritic nodular erythematous

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rash on his arms and legs. He reported having a very similar episode about 5 years before admission when he lived in Thailand; however, it was not treated and the symptoms at that time fully resolved. He did not have any visual symptoms, rhinorrhea, chest pain, dyspnea, cough, hemoptysis, nausea, vomiting, neurologic symptoms, dysuria, urgency, or frequency.

His past medical history included untreated hypertension with no pertinent prior surgical history. He was not taking any medications and did not report any allergies. His family history was unremarkable. He was born and raised in Thailand, but he immigrated to the United States 2 years prior and had been living in Arizona. In the few weeks before admission, he moved to Omaha, Nebraska. He reported social alcohol use and occasionally smoked marijuana. He denied tobacco use, illicit drug use, or any recent sexual activity. He had tattoos done professionally in Thailand. He was not employed. Bacille Calmette-Guerin vaccination status was unknown.

Evaluation at admission revealed a blood pressure of 163/75 mmHg, heart rate of 110 beats per minute, and a temperature of 38.7 °C. Exam showed an alert, cooperative patient with normal white conjunctiva and oral mucosa without lesions. Lungs were clear with good bilateral breath sounds without wheezes, crackles, or rhonchi. Cardiac exam revealed tachycardia without murmur. Abdominal exam showed hepatosplenomegaly with mild diffuse abdominal tenderness. Dermatologic examination was relevant for a patchy erythematous rash on arms, dorsum of hands, and inner upper thighs (Figure 1). Musculoskeletal exam was normal without muscle tenderness, swelling, or arthritis. His neurological exam was unremarkable without nuchal rigidity. No cervical, axillary, or inguinal lymphadenopathy was identified.

Initial laboratory evaluation revealed an elevated white blood cell count (WBC) 20.8 K/μL (range 4-12 K/μL) with eosinophilia at 34% and absolute eosinophil count (AEC) 7.1 K/μL (range 0-0.4 K/μL), hemoglobin (Hg) 11.9 mg/dl (range 13.5 - 17.5), platelets 363 K/μL (range 140-440 K/μL), normal creatinine, aspartate aminotransferase (AST) 21 IU/L (range 10 - 40 IU/L), and alanine aminotransferase (ALT) 53 IU/L (12 - 78 IU/L). Computed tomography (CT) of abdomen and pelvis with contrast showed hepatosplenomegaly. A chest x-ray was normal. He was empirically started on ceftriaxone and doxycycline. Further workup was obtained as detailed later.

Over the initial 4 to 7 days of hospitalization, the patient continued to experience fevers up to 39.6 °C. Leukocytosis remained persistent and peaked at 30.1 k/μL on day 4 with an AEC up to 11.4 k/μL. His liver enzymes, creatinine, hemoglobin, and platelets remained normal. On day 4, a fungal blood culture was obtained, cultured on Sabouraud agar, inhibitory mold agar, and mycosel agar, and incubated at 30 °C ambient air.

With persistent fevers and eosinophilia, fluconazole 400mg/daily was added on day 4. On day 5, ceftriaxone was changed to meropenem and albendazole was added. On day 8, the patient underwent a lumbar puncture with overall unremarkable findings: blood cell count 0 WBC, 0 RBC, glucose 52 mg/dL, protein 38 mg/dL, and opening pressure 9 cm H_20. Further workup showed negative HIV screening, malaria testing, and many other negative/unremarkable results shown in Table 1. He also underwent esophagogastroduodenoscopy that showed duodenum with mild villous blunting with increased lymphoplasmacytic infiltrate within the lamina propria and colonoscopy with no architectural distortion, granulomas, or features of chronicity identified. The lamina propria contained an appropriate amount of eosinophils. Blood flow cytometry showed small, atypical T cell population,

Figure 1. Images of (A) Patient's Right Hand and (B) Left Inner Upper Thigh

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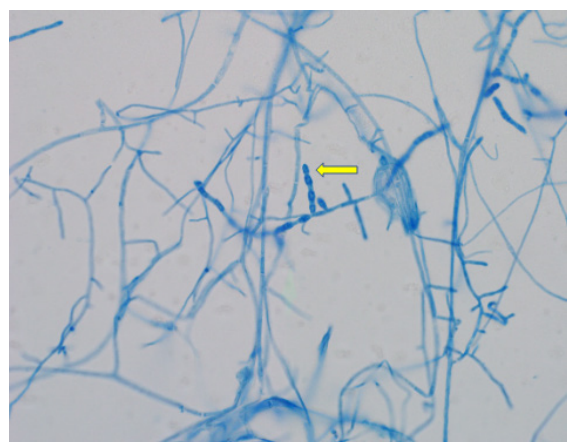
Table 1. Additional Evaluation

Test Name[a]	Hospital Day Resulted
Blood cultures	Day 1 (finalized day 5)
Thyroid stimulating hormone	Day 1
Mononucleosis spot test	Day 1
COVID-19 PCR (nasal swab)	Day 1
Urinalysis (urine)	Day 1
Hepatitis A IgM, Hepatitis C antibody, Hepatitis B core IgM	Day 1
Gastrointestinal pathogen panel by PCR (stool)	Day 2
Legionella pneumophilia serotype 1 antigen (urine)	Day 2
1st malaria thick/thin smear	Day 2
HIV 4th generation screen	Day 2
1st ova and parasite (O&P) (stool)	Day 4
2nd malaria thick/thin smear	Day 4
Toxoplasma IgG/IgM	Day 5
3rd malaria thick/thin smear	Day 5
Repeat blood cultures	Day 5 (finalized Day 10)
Coxiella burnetii IgG	Day 6
Interferon gamma release assay for *Mycobacterium tuberculosis*	Day 6
Echinococcus IgG/IgM	Day 7
Leptospira IgM by dot blot	Day 7
Cryptococcus antigen	Day 7
Bartonella quintana/henselae IgG/IgM	Day 7
Plasmodium species PCR	Day 7
Antinuclear antibodies	Day 7
Brucella IgG/IgM	Day 8
Celiac panel	Day 8
2nd O&P (stool)	Day 8
Meningitis/encephalitis PCR panel[b] (CSF)	Day 8
3rd O&P (stool)	Day 11
Francisella tularensis IgG/IgM	Day 11
Antineutrophil cytoplasmic antibodies	Day 11
Tropheryma whippleii PCR	Day 12
Trichinella IgG	Day 14

Abbreviations: PCR, polymerase chain reaction; Ig, immunoglobulin; CSF, cerebrospinal fluid.
[a]All studies performed on blood/serum unless otherwise indicated
[b]Cerebrospinal fluid culture, fungal culture, and mycobacterial culture all without growth.

Figure 2. Four-Day-Old Fungal Blood Culture of *Coccidioides* species on Sabouraud Dextrose Agar Showing White Cottony Colonies

Figure 3. Lactophenol Cotton Blue Preparation at 400x Magnification Showing Hyphae of *Coccidioides* Species With Arthroconidia (arrow).



left-shifted myeloid maturation pattern and increased eosinophils. IgE was elevated at 9300 IU/ml (range 0-158 IU/ml), normal IgG subclasses, positive cytomegalovirus IgG, serologies consistent with prior Epstein-Barr virus infection. *Coccidioides* IgG was positive at 10.7 (positive >1.4) by enzyme-linked immunosorbent assay (ELISA), IgM was indeterminate at 1 (negative <1; indeterminate 1.0-1.4). With high levels of IgE, positive *Coccidiode*s IgG and *Strongyloides* IgG, albendazole was changed to ivermectin.

By day 9, the patient's fevers decreased, and the leukocytosis and absolute eosinophil counts started to normalize. On day 11, the Sabouraud agar grew white cottony colonies (Figure 2). On the same day, a lactophenol cotton blue wet preparation from these colonies was performed and demonstrated arthroconidia (Figure 3). On day 12, he was initiated on liposomal amphotericin-B 350 mg intravenous every 24 hours. On day 21, identification of *Coccidioides immitis* was confirmed by matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry at a reference lab. Stool ova and parasite exam was negative.

Hence, disseminated *Coccidiodes immitis* infection with fungemia was diagnosed with possible *Strongyloides* species co-infection. The possible *Strongyloides* infection was treated with an 8-day course of ivermectin 200 mcg/kg/day (15,000 mcg/day). After 3 days of amphotericin-B, the patient was discharged home on day 15 on oral fluconazole 800 mg once daily for 3 months. The leu-

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kocytosis improved to 14,000 K/μL, with AEC 3.1 K/μL on the day of discharge. At the end of treatment, his WBC and eosinophil counts normalized.

DISCUSSION

Fungemia is a rare manifestation of disseminated coccidioidomycosis with a very poor prognosis.[5,7] Overall mortality at 30 days is 62% (70/113; mean survival, 11.4 days).[3,4,8]

Between 1998 and 2008, there were only 113 reported cases of fungemia with *Coccidiodes* species. Forty-three patients (38%) were living with HIV, 20 (18%) were on corticosteroids, 11 (10%) were solid organ transplant recipients, and 5 (4%) were pregnant. Sites of extrapulmonary dissemination were reported for 97 patients (86%), with the most common sites being the liver (26/97 [27%]), spleen (21/97 [22%]), and meninges/central nervous system (17/97 [18%]). The 113 cases thoroughly reviewed by Keckich et al[8] included those by Ampel et al[5] and Rempe.[7] Since then, there have been only a handful of other case reports of *Coccidiodies* species fungemia (Table 2).[9-11] Fungemia is rare and even more-so in patients considered immunocompetent.

Table 2. Review of *Coccidiodies* Species Fungemia

Author/Year	No. of Patients	Average Age (Years)	Male Sex (%)	Immunosuppression (% of Total)
Ampel, 1986[5]	15	47	93	Cancer (40%), HIV (20%); CS use (66%)
Rempe, 2007[7]	33	37	94	HIV (87%)
Keckich, 2010[8]	113[a]	42	80	HIV (38%), CS use (18%), SOT (10%)
Blodget, 2011[9]	3	43	100	SOT (100%)
Langilier, 2014[10]	1	54	100	N/A (immunocompetent)
Valdez, 2019[11]	1	33	100	HIV (100%)

Abbreviations CS, corticosteroid; SOT, solid organ transplant; NA, not applicable.
[a]107 by review + 6 from the single center.

Diagnosis of coccidioidomycosis can be done by histology, cultures, urine, and/or cerebrospinal fluid antigen detection, IgM and IgG detection by enzyme-linked immunosorbent assay (ELISA), immunodiffusion, and complement fixation (CF).[3,12,13] The gold standard diagnosis remains growth in culture.[12] For the mold phase, specimens are cultured on Sabouraud dextrose agar or potato dextrose agar and incubated at 25 °C. Incubation at 37 °C can be attempted to recover the yeast phase of most dimorphic organisms. The immunodiffusion and CF tests remain the most reliable methods for the serologic diagnosis of coccidioidomycosis. A less labor-consuming ELISA immune assay was developed as a screening test after which confirmatory test are performed.[3,12,13]

Our patient was diagnosed with *Coccidiodes* infection by recovering the fungus from the blood culture in the setting of a compatible clinical presentation and laboratory findings. He did not have a focus of infection per se. However, we did not think he had developed a focal organ disease, as at the end of the treatment his WBC and AEC were normal. While basic testing for immunodeficiency (HIV, flow cytometry, etc) was completed, extensive testing with functional immune assays was not done given his condition improved significantly once appropriate treatment was started.

Strongyloides species co-infection was suspected based on marked eosinophilia; the presence of a pruritic, erythematous cutaneous eruption consistent with those seen in *Strongyloides* infections; and his epidemiologic association with country of origin where the disease remains prevalent. Lab testing noted positive *Strongyloides* IgG indicating either acute or prior infection. Stool ova and parasite exams were negative. It was not known if he had previously been treated for *Strongyloides* in Thailand. He was not in a refugee camp, and we could not know if he was screened and treated prior to admission to United States. Per the Centers for Disease Control and Prevention, "most refugees receive overseas pre-departure treatment with ivermectin … unless contraindicated [due to] confirmed or suspected concomitant infection with *Loa lo*a … [or] may be presumptively treated on arrival, or screened ("test and treat").[14] As such, the possibility of *Strongyloides* co-infection could not be confirmed or ruled out. Stool nucleic acid amplification test for *Strongyloides* was not performed.

While the patient did have risk factors of being male and of Asian ethnicity and epidemiologic risk factors including living in Arizona and Thailand, our case is a rare presentation of disseminated *Coccidiodes* with fungemia in an otherwise healthy patient without any immunocompromising conditions with possible *Strongyloides* coinfection – the third to be reported.[6]

Treatment of *Coccidiodes* species includes fluconazole, itraconazole, voriconazole, isavuconazole, posaconazole and amphotericin B. Treatment is tailored to the presentation, patient immune status, and extent and/or severity of the disease.[15]

CONCLUSIONS

We report this case to raise awareness of a rare infection. In adequate epidemiological circumstances, co-infections *Coccidioides* and *Strongyloides* species should be considered in presence of fever and very high eosinophil count.

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