An unanticipated case of disseminated coccidioidomycosis

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Introduction: Coccidioidomycosis is commonly associated with mild symptoms, and disseminated disease is rare in healthy individuals.

Case Presentation: A 2-month-old male presented for further management of Stenotrophomonas maltophilia pneumonia. Respiratory and blood cultures showed a yeast-like growth that was later identified and confirmed as Coccidioides species.

Conclusion: We present a fatal case of disseminated coccidioidomycosis in a 2-month-old infant with unclear exposure and mode of transmission. The diagnosis of coccidioidomycosis may have been complicated by the premature diagnosis of Stenotrophomonas maltophilia, highlighting the importance of further investigation into co-infection or alternative pathogens when patients do not respond to initial therapy.

Keywords: amphotericin B; coccidioidomycosis; disseminated infection.

Introduction
Coccidioides is a dimorphic fungus that is endemic in northern Mexico, South America, and areas of the USA (San Joaquin Valley of California and Arizona) (Centers for Diseases Control and Prevention, http://www.cdc.gov/fungal/diseases/coccidioidomycosis/causes.html). Both species of Coccidioides, Coccidioides immitis and Coccidioides posadasii, are causative agents of coccidioidomycosis and are morphologically indistinguishable, although C. immitis is endemic mainly in California (Fisher et al., 2002). Exposure to the fungus is extremely common in individuals from these areas, but infections may occur due to recent or remote visits to an endemic area or by exposure to fomites from an area of endemic disease (Pappagianis, 1988). In Coccidioides infections, 60 % of individuals are asymptomatic or present with self-limited pulmonary disease resembling a respiratory tract infection. Extrapulmonary disseminated disease develops in about 1 in 200 people and is associated with high morbidity and mortality (Connelly & Zerella, 2000). Individuals who are at increased risk for disseminated disease include the immunocompromised, pregnant women, African–Americans, Hispanics, native Americans and Filipinos, although the mechanism relating to increased risk for dissemination in these groups is not defined (Pappagianis, 1988). The risk of disseminated disease appears to be elevated in the elderly and in paediatric populations. A study among the American Indian population found that children under the age of 5 years and adults older than 50 years were significantly more susceptible to disseminated coccidioidomycosis (Sievers, 1974). Paediatric cases of disseminated coccidioidomycosis involving the brain, spine, gallbladder and soft tissue have been reported (Nolt & Geertsma, 2007; Sydorak et al., 2001; Wrobel et al., 2001). Here, we present a fatal case of disseminated coccidioidomycosis in a 2-month-old infant with unclear route of infection.

Case report
A 2-month old male presented to the Children’s Hospital Los Angeles (CHLA) Emergency Department for further management of Stenotrophomonas maltophilia pneumonia resulting in hypotension and respiratory failure. His past medical history included premature birth at 25 weeks of gestation, requiring initial ventilation. The patient was born in a hospital located in a Coccidioides-endemic area and remained in the hospital prior to transfer to CHLA (Fig. 1). At day 42 of life, the patient developed aponea/bradycardia and was re-intubated at the outside facility. An endotracheal aspirate was sent for culture and grew Klebsiella oxytoca, Staphylococcus aureus and rare Stenotrophomonas maltophilia. All other laboratory findings,
including blood cultures and a respiratory viral panel, were insignificant and, to the best of our knowledge, fungal cultures were not performed at this time. A chest X-ray revealed coarse infiltrates with cystic air spaces and dense opacities throughout both lungs and was indicative of pneumonia. The patient was placed on broad-spectrum antimicrobial therapy, comprising vancomycin, cefepime, piperacillin/tazobactam, meropenem and trimethoprim/sulfamethoxazole, to treat the pneumonia. A 7-day course of azithromycin and a 10-day course of micafungin was also initiated on day 47 of life. During this time, the patient experienced two coding events and was transferred to CHLA on day 57.

On admission at CHLA, the patient had a temperature of 37.3 °C, heart rate of 178 beats min⁻¹, respiratory rate of 31 breaths min⁻¹ and blood pressure of 67/29 mmHg. A complete blood count at the time of admission included a white blood cell count of 3.9 × 10⁹ cells l⁻¹ accompanied by a left shift with 67 % neutrophils (34 % of bands), 14 % lymphocytes and 16 % eosinophils, haemoglobin of 11.8 g dl⁻¹ and a platelet count of 54 × 10⁹ cells l⁻¹. Other notable laboratory studies included C-reactive protein of 15.8 mg dl⁻¹, alanine aminotransferase of 103 U l⁻¹ and aspartate aminotransferase of 103 U l⁻¹.

Investigation for other infectious aetiologies was initiated, as the severity of the patient’s clinical presentation did not corroborate with typical *Stenotrophomonas maltophilia* pneumonia. In addition to trimethoprim/sulfamethoxazole [7.5 mg, intravenous (IV), every 8 h, 7.5 ml h⁻¹], vancomycin (27 mg, IV, every 8 h, 5.4 ml h⁻¹) and meropenem (36 mg, IV, every 8 h, 3.6 ml h⁻¹) therapy, Infectious Diseases team recommended initiation of ciprofloxacin (18 mg, IV, every 12 h, 9 ml h⁻¹) for potential resistant Gram-negative bacteria coverage, and liposomal amphotericin B (5.4 mg, IV, once a day, 2.7 ml h⁻¹) for fungal coverage.

On day 1 of admission, an endotracheal tube specimen and blood were obtained for bacterial and fungal cultures. The endotracheal tube sample was plated onto blood agar, chocolate agar, MacConkey agar and colistin–naldixic acid (CNA) agar for bacterial culture. After 24 h of incubation, a few bacterial colonies were observed from the respiratory bacterial culture and identified as *Stenotrophomonas maltophilia* by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. After 48 h of incubation, yeast-like growth was observed on the CNA plate, and was subcultured onto potato dextrose agar. After 48 h of incubation, a white cottony colony was observed. A tease preparation revealed barrel-shaped alternating arthroconidia separated by empty disjunctor cells, as shown in Fig. 1.

**Fig. 1.** Timeline of patient’s clinical progression and laboratory work-up. Description of the patient’s hospital course from the onset of symptoms on day 42 of life to death on day 60, including antimicrobial therapy and laboratory work-up and the final diagnosis of coccidioidomycosis. ETT, endotracheal tube; PDA, potato dextrose agar; OSH, outside hospital.
which, in combination with the colony morphology, were indicative of \textit{Coccidioides} species. A result of \textit{C. immitis} was detected based on an AccuProbe \textit{C. immitis} culture identification test (Hologic), although this test does not differentiate between \textit{C. immitis} and \textit{C. posadasii} (McGinnis et al., 2006); thus, \textit{Coccidioides} species was reported. \textit{Coccidioides} species was also recovered from a fungal work-up of the blood specimen on day 5 of incubation. Bacterial blood culture was reported as having no growth after 5 days of incubation.

On day 3 of admission (day 60 of life), the patient experienced respiratory failure and died prior to laboratory diagnosis of disseminated coccidioidomycosis. An autopsy was declined by the family.

\section*{Discussion}

Primary coccidioidomycosis is typically acquired via inhalation of \textit{Coccidioides} spores into the lungs. Isolation of \textit{Coccidioides} from the patient’s respiratory specimen suggested that inhalation may have been the route of infection – an unexpected finding as, to the best of our knowledge, the patient remained in hospital from birth.

Pregnancy is one of the risk factors for development of severe and disseminated coccidioidomycosis. There have been reported cases of pregnancy complicated by coccidioidomycosis, but there are limited data on the risk of acquiring \textit{Coccidioides} during pregnancy. A large survey of pregnant women at three healthcare facilities over a 5-year period in Tucson, AZ, USA, an endemic area for \textit{Coccidioides}, revealed 10 cases among 47 120 deliveries, four of which were only presumptive for coccidioidomycosis, and no fatalities associated with coccidioidomycosis during pregnancy (Wack et al., 1988). This suggests that, although pregnant women are at higher risk of disseminated coccidioidomycosis, coccidioidal infection during pregnancy is uncommon (Wack et al., 1988). Some argue that the prevalence may be higher because of misdiagnosis or underdiagnosis, especially in areas where coccidioidomycosis is not endemic. Even so, this is most likely to be due to mild symptoms or low clinical suspicion in these cases (Arnold et al., 2008).

Neonatal coccidioidomycosis is also rare, with only a small number of reported cases in the literature (Bernstein et al., 1981; Charlton et al., 1999; Linsangan & Ross, 1999). Transmission of \textit{Coccidioides} from mother to fetus in utero is believed to be unlikely because \textit{Coccidioides} spherules are too large to cross the placenta, a theory that is supported by reported cases of placental coccidioidomycosis without fetal infection (Arnold et al., 2008). Instead, it has been suggested that neonatal cases are acquired through contact with maternal vaginal secretions during birth (Arnold et al., 2008; Bernstein et al., 1981) or ingestion of infected amniotic fluid, as reported in a case of a newborn delivered by Caesarean section (Charlton et al., 1999). Additionally, case reports have shown \textit{Coccidioides} spherules in histological examination of the placenta of infected women (Arnold et al., 2008; Charlton et al., 1999). Our patient was delivered by Caesarean section, ruling out potential vertical transmission. In infants with coccidioidomycosis acquired at birth, signs and symptoms of infections typically appear within the first 30 days of life (Linsangan & Ross, 1999). In one case, the patient was premature, with respiratory distress syndrome at birth and features of trisomy 21 (Linsangan & Ross, 1999). The patient’s condition continued to deteriorate and an endotracheal aspirate specimen demonstrate growth of \textit{Coccidioides} at day 28 of life. Similarly, in a second case of neonatal coccidioidomycosis, the patient was delivered via Caesarean section at 32 weeks of gestation with signs of respiratory distress syndrome that worsened at day 16 of life (Charlton et al., 1999). Our patient developed symptoms indicative of respiratory distress and pneumonia at approximately day 42 of life. Although it cannot be entirely excluded that earlier symptoms were missed, comparison with reported cases of neonatal coccidioidomycosis suggests that if the patient was exposed during gestation or delivery, one would suspect an earlier presentation. It is also unknown whether the patient’s mother was evaluated for coccidioidal infection or exposure during her pregnancy, which could provide insight into the mode of transmission for the patient.

The initial treatment of choice for coccidioidomycosis among higher-risk groups is oral azole antifungal agents, most commonly fluconazole and itraconazole; amphotericin B (non-lipid and lipid formulations) therapy is also appropriate for complicated coccidioidomycosis, particularly in patients presenting with respiratory failure, with rapidly progressing coccidioidal infections or in pregnant women (Galgiati et al., 2005). The patient was given a course of micafungin, an echinocandin antifungal agent, at the outside facility. Echinocandins act by inhibiting synthesis of 1,3-\(\beta\)-D-glucan and could potentially have therapeutic effects against coccidioidomycosis, as the \textit{Coccidioides} cell wall contains 1,3-\(\beta\)-D-glucan and chitin. Caspofungin alone and in combination therapy with amphotericin B or with voriconazole has been shown to be effective in treating coccidioidal infections in murine model and in pediatric refractory coccidioidomycosis, respectively (González et al., 2007; Levy et al., 2013). However, clinical experience remains lacking for echinocandins as treatment for coccidioidal infections. The continued deterioration of our patient suggested that the micafungin had no or little effect in this case. Liposomal amphotericin B was only given 3 days prior to the patient’s death, on admission to our hospital.

The significance of \textit{Stenotrophomonas maltophilia} isolated from the patient’s respiratory specimen remains unclear. \textit{Stenotrophomonas maltophilia} is an environmental Gram-negative bacterium that has emerged as an opportunistic and nosocomial pathogen associated with respiratory infections, particularly in patients with prolonged hospitalization and ventilation (Pathmanathan & Waterer, 2005). Due to its low virulent nature, \textit{Stenotrophomonas maltophilia} is also a common colonizer of the respiratory
tract, and distinction between colonization and infection is challenging (Pathmanathan & Waterer, 2005). Moreover, the presence of *Stenotrophomonas maltophilia* may be indication of a severely compromised host, rather than infection (Pathmanathan & Waterer, 2005). Our patient may have been more susceptible to *Stenotrophomonas maltophilia* infection due to his premature birth, ventilation and prolonged hospital stay. However, the patient’s continued deterioration while on appropriate therapy for *Stenotrophomonas maltophilia* pneumonia, and isolation of a polymicrobial picture from the respiratory specimen, with no predominance, would suggest colonization rather than infection. Unfortunately, the premature diagnosis of *Stenotrophomonas maltophilia* pneumonia may have prevented clinicians from further investigating alternative causative agents.

Although rare, coccidioidomycosis can be fatal in higherrisk individuals and should be a consideration in patients from or visiting endemic areas presenting with suspect clinical symptoms. We have presented a fatal case of disseminated coccidioidomycosis in an infant with an unclear route of infection, highlighting the importance of further investigating potential co-infection or alternative pathogens in patients who do not respond to initial therapy.

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**References**


