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NOVEL ID CASES

Treatment of Chronic Granulomatous Disease–Related Pulmonary *Aspergillus* Infection in Late Pregnancy

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Chronic granulomatous disease (CGD) is a primary immunodeficiency syndrome that results in increased risk for bacterial and fungal infections, as well as inflammatory/autoimmune complications. While CGD historically has been associated with early death in childhood, the life expectancy and morbidity of patients with CGD have greatly improved. Many patients with CGD now survive well into adulthood, and data on adult cohorts of patients with CGD have been published. However, reports of pregnancy management, complications, and outcomes for patients with CGD are sparse. In addition, management of invasive fungal infections, including use of newer triazole antifungals, during pregnancy has not been well described. We report a case of fungal lung infection in a pregnant woman with CGD, diagnosed during her second trimester, which was treated with multiple antifungal agents, including more than 12 weeks of isavuconazole therapy, resulting in resolution of infection and delivery of a healthy newborn at term.

Keywords. *Aspergillus fumigates*; chronic granulomatous disease (CGD); isavuconazole; pregnancy.

Received 24 July 2020; editorial decision 17 September 2020; accepted 25 September 2020.

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Open Forum Infectious Diseases®

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DOI: 10.1093/ofid/ofaa447

CASE REPORT

A 37-year-old woman with chronic granulomatous disease (CGD) was admitted to the hospital while pregnant at 21 weeks gestational age (GA) with 2 weeks of progressive cough and shortness of breath. She had been diagnosed with autosomal recessive NCF1 (p47phox)–deficient CGD at age 9 years. Prior testing indicated <1% neutrophil oxidative burst activity. At age 17 years, she was treated for *Nocardia* sp. pulmonary infection followed by interferon gamma (IFNγ) intermittently for 1 year and then chronic prophylaxis with trimethoprim-sulfamethoxazole (TMP/SMX). At age 23 years, she was treated for *Aspergillus* sp. pulmonary infection and then chronic prophylaxis with itraconazole. At age 31 years, TMP/SMX and itraconazole were held during pregnancy; she had an uncomplicated pregnancy and term delivery. She began prophylactic cefdinir 300 mg twice daily. Itraconazole was not restarted due to planning for subsequent pregnancy. At age 36 years, she suffered a spontaneous abortion at 8 weeks GA. She then became pregnant again and continued on cefdinir prophylaxis.

She reported cough and dyspnea during the first trimester, which were attributed to asthma. Her inhaler regimen was modified, eventually including fluticasone/salmeterol 500 mcg/50 mcg twice daily, budesonide 90 mcg twice daily, and albuterol 90 mcg as needed. At 19 weeks GA, she reported worsening dry cough, chest tightness, and dyspnea on exertion. She was treated with prednisone 40 mg daily for 5 days. She developed worsening sinus pressure, cough, and shortness of breath. She was treated with 7 days of amoxicillin-clavulanate and a 5-day course of prednisone 40 mg daily and developed low-grade fevers. A chest radiograph showed new opacities in the right lung, prompting referral to the emergency department (ED).

In the ED, her vital signs were temperature 36.8°C, blood pressure 99/63, heart rate 72, respiratory rate 18, and oxygen saturation 96% on room air. She had decreased breath sounds at the right lung base. Results of initial blood chemistries were normal, with the exception of decreased albumin 3.2 g/dL and increased globulin 4.8g/dL. Blood counts were within normal range: white blood cell count 9560/μL, hemoglobin 13.0 g/dL, platelets 159 000/μL. Nasopharyngeal swab tested negative for influenza A, influenza B, and respiratory syncytial virus by polymerase chain reaction (PCR). Blood cultures were obtained, which had no growth after 5 days. Serum (1,3)-beta-D-glucan was 64 pg/mL, and serum galactomannan (*Aspergillus* antigen) was 0.06. Chest computed tomography (CT) showed consolidative opacity with air bronchograms within the superior segment of the right lower lobe with additional smaller nodular opacities seen within the basilar segments of the right lower lobe (Figure 1A). The patient was triaged to urgent

bronchoscopy. The bronchoalveolar lavage sample yielded positive results for influenza A by PCR, *Pneumocystis jiroveci* by methenamine silver stain, and *Aspergillus fumigatus* by fungal culture. Galactomannan from the bronchoalveolar lavage fluid was 0.14.

Immediately after bronchoscopy, treatment was initiated with intravenous cefepime 2 g every 8 hours, oral oseltamivir 75 mg twice daily, and intravenous TMP/SMX 15 mg/kg daily divided every 8 hours. Voriconazole was initiated at 6 mg/kg intravenously every 12 hours for 2 doses, followed by 300 mg (4 mg/kg) orally twice daily. Cefepime was discontinued after 48 hours. After 48 hours of voriconazole therapy, the patient reported severe visual and sleep disturbances. Voriconazole trough was 2.3 mcg/mL. Voriconazole was discontinued, and intravenous liposomal amphotericin 5 mg/kg once daily was initiated. The *Aspergillus fumigatus* isolate was sent to a reference lab (UT Health San Antonio, San Antonio, TX, USA), where antifungal minimal inhibitory concentrations (MICs) were fluconazole >64 mcg/mL, itraconazole 0.25 mcg/mL, posaconazole 0.06 mcg/mL, and voriconazole 0.5 mcg/mL. After 6 days of treatment, laboratory abnormalities developed: elevated serum creatinine (1.32 mg/dL), hyponatremia (130 mmol/L), and acidosis (carbon dioxide 20 mmol/L). TMP/SMX was transitioned to 320-mg twice-daily oral tablets, and laboratory abnormalities improved. She was discharged to home and continued to receive intravenous liposomal amphotericin B.

After 16 days of liposomal amphotericin B, she was noted to have new thrombocytopenia, with platelets decreased from 181 000/μL to 64 000/μL. Liposomal amphotericin B was discontinued, and TMP/SMX dosing was further decreased to 160 mg once daily. At this point (24 weeks GA), therapy was initiated with isavuconazonium sulfate (prodrug of isavuconazole) 372 mg by mouth every 8 hours for 6 doses, and then continued 372 mg once daily. She tolerated isavuconazole without any adverse events. Isavuconazole trough level was measured twice: 1.5 mcg/mL and 1.9 mcg/mL. At 36 weeks GA, there were no signs of infection, and the patient expressed concern about continuing isavuconazole through planned breastfeeding. Isavuconazole was discontinued, completing 12 weeks of isavuconazole therapy and more than 14 weeks of antifungal therapy. At 39 weeks GA, she underwent planned cesarean section due to breech presentation, delivering a healthy infant without complications. Chest CT obtained after delivery documented complete resolution of the prior multifocal opacities (Figure 1b). In follow-up at 6 months postpartum, the patient and the infant were healthy.

DISCUSSION

CGD is an inherited immunodeficiency disorder that results in defective phagocyte killing, leading to recurrent bacterial and fungal infections. Historically CGD was associated with universal childhood mortality, but improvements in diagnostics and therapeutics for infectious and inflammatory complications have led to marked improvement in prognosis [1]. A retrospective analysis of adult patients with CGD diagnosed in childhood in France identified pulmonary as the most common infection site (31%), and the most common pathogens were *Aspergillus* sp. (17%) and *Staphylococcus aureus* (10.7%) [2]. Infections with gram-negative bacteria and mycobacteria were reported, but infections with *Burkholderia* sp. and *Nocardia* sp. were uncommon [2]. Only 38% of patients with infection presented with fever. Another analysis identified 155 patients with CGD, of whom 80 were diagnosed with invasive fungal infections (IFIs) [3]. Only 27% of cases of proven invasive aspergillosis had positive *Aspergillus* serologic testing (serum galactomannan). No infections with *Pneumocystis* sp. were reported in these cohort studies—in our case report, the patient may have been predisposed to *Pneumocystis* infection due to treatment with systemic and inhaled corticosteroids, as well as immune system alterations during pregnancy. It is not clear which of the concurrently diagnosed infections (influenza, *Pneumocystis jiroveci,* and *Aspergillus fumigatus*) in this case may have developed first, and to what degree 1 infection may have predisposed to the development of the other infections. Prior studies have documented benefit with TMP/SMX prophylaxis to prevent bacterial infections and itraconazole prophylaxis to prevent fungal infections in patients with CGD [1, 3, 4]. However, 54% of patients in 1 CGD cohort who developed IFI were receiving itraconazole prophylaxis at the time of infection diagnosis [3]. These cohort studies highlight the challenges and importance of efficient diagnosis and early effective treatment of pulmonary infections in CGD, which may otherwise be fatal. Use of empiric antimicrobial therapy is often insufficient due to the variety of atypical pathogens; however, routine diagnostic tests, such as sputum culture, often do not reveal the causative pathogen. Rapid triage to invasive diagnostics such as bronchoalveolar lavage or biopsy is crucial to achieve early microbiologic diagnosis and initiation of targeted, often life-saving, antibiotic therapy in CGD patients with pulmonary infections.

There are few published data on pregnancy in patients with CGD. A case report described an X-linked carrier of CGD who

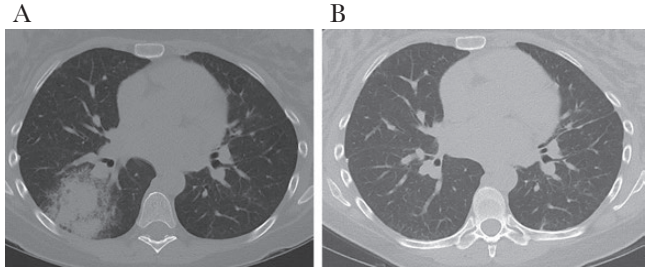

Figure 1. A, Chest computed tomography (CT) at the time of presentation with infection at 21 weeks gestational age. B, Chest CT at 1 day postpartum.

had serial episodes of chorioamnionitis resulting in early delivery in 3 pregnancies, 1 of which resulted in neonatal death due to sepsis [5]. Another report documented an uncomplicated pregnancy of a woman with CGD, but the patient developed *Aspergillus fumigatus* lumbosacral osteomyelitis in the early postpartum period [6]. At least 2 older case reports have described uneventful pregnancies in patients with CGD [5]. Hisano et al. described successful completion of pregnancy with term delivery in a woman with CGD who had been carefully monitored and treated with TMP/SMX 160/800 mg daily (with augmented folate supplementation) during conception and throughout pregnancy [7].

When fungal infections develop in pregnancy, there are limited data to guide management. Amphotericin B deoxycholate is the antifungal agent with the most data on safety in pregnancy. Although teratogenicity has not been reported with this agent, there are frequent toxicities including azotemia, fever, nephrotoxicity, thrombophlebitis, electrolyte disorders, and anemia [8]. The safety of fluconazole and itraconazole during pregnancy was examined in a meta-analysis of cohort studies including more than 1 million women in total [9]. Itraconazole use in pregnancy was not associated with significant increased risk overall, but the incidence of fetal eye defects was slightly higher among itraconazole-exposed patients. There were no data on exposure to voriconazole, posaconazole, or isavuconazole in the meta-analysis. Fluconazole use in pregnancy was not associated with significant increased risk overall, but the incidence rates of congenital heart defects and limb defects were slightly higher among fluconazole-exposed patients. First trimester exposure to fluconazole was associated with increased risk of cleft lip and cleft palate and dextro-transposition of the great arteries. Another cohort study recently documented a small but significantly increased risk of musculoskeletal abnormalities at birth with low-dose fluconazole during early pregnancy, though no increased risk of oral cleft or contruncal abnormalities was noted [10]. A single case report documents use of voriconazole during pregnancy [11]. A 28-year-old pregnant woman developed invasive aspergillosis of the sinuses initially treated with surgery and liposomal amphotericin. Voriconazole was initiated at 19 weeks GA and continued for 5 months through infection resolution and delivery of a healthy infant at 35 weeks GA, without complications. The prescribing information for isavuconazonium states that it may cause fetal harm when used in pregnancy and describes increased skeletal abnormalities and perinatal mortality in the offspring of rats with pregnancy exposure, and systemic isavuconazole is transmitted to breastmilk [12].

This is a novel case report of an invasive fungal lung infection developing during pregnancy in a woman with CGD, treated with antifungal agents including isavuconazole, without adverse events, and with cessation of antifungal treatment before delivery and breastfeeding. The absence of high-grade fevers or severe symptoms and the negative serum fungal markers at the time of presentation in this case are typical among patients with CGD and highlight the importance of early triage to imaging and invasive diagnostics. As more patients with CGD survive into adulthood, improvements in preconception and perinatal counseling and management will be required to improve pregnancy outcomes. Further data are needed on the safety and efficacy of triazole antifungal agents during pregnancy, including isavuconazole.

Acknowledgments

Potential conflicts of interest. All 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.

Patient consent. The patient in the reported case gave permission for her de-identified information to be included in this manuscript. All other cases referred to in the "Discussion" section of the manuscript are from previously published literature.

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