Treatment of chronic granulomatous disease-related pulmonary *Aspergillus* infection in late pregnancy

Johnson JA, Pearson JC, Kubiak DW, Dionne B, Little SE, Wesemann DR

1Division of Infectious Diseases, 2Department of Pharmacy, 4Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, and 5Division of Allergy and Clinical Immunology at Brigham and Women’s Hospital, Boston, MA, USA. 3Department of Pharmacy and Health System Sciences, Northeastern University, Boston, MA, USA

Corresponding Author:

Jennifer A. Johnson, MD
Assistant Professor of Medicine, Harvard Medical School
Associate Physician, Division of Infectious Diseases, Brigham and Women’s Hospital
75 Francis Street, PBB-A4, Boston, MA 02115
Tel: (617)525-8853, Fax: (617)732-6829
Email: jjohnson30@bwh.harvard.edu

Alternate Corresponding Author:

Duane R. Wesemann, MD, PhD
Assistant Professor of Medicine, Harvard Medical School

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Associate Physician, Division of Rheumatology, Immunology and Allergy, Brigham and Women’s Hospital

NRB 77 Avenue Louis Pasteur Room 431D

Boston, MA 02115

Tel: (617)525-1295, Fax: (617)525-1310

Email: dwesemann@bwh.harvard.edu
Abstract

Chronic granulomatous disease (CGD) is a primary immunodeficiency syndrome which results in increased risk for bacterial and fungal infections, as well as inflammatory/autoimmune complications. While CGD historically was associated with early death in childhood, life expectancy and morbidity of patients with CGD have greatly improved. Many patients with CGD now survive to well into adulthood and data on adult cohorts of patients with CGD are now 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

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

She reported cough and dyspnea during 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 5-day course of prednisone 40 mg daily, though 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, BP 99/63, HR 72, RR 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 3.2g/dL and increased globulin 4.8g/dL. Blood counts were within normal range: WBC 9,560/uL, hemoglobin 13.0g/dL, platelets 159,000/uL. Nasopharyngeal swab tested negative for influenza A, influenza B and RSV by 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 jirovecii 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 2gm every 8 hours, oral oseltamivir 75mg 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 300mg (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, South Texas), where antifungal minimum inhibitory concentrations (MIC) 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 (1.32mg/dL), hyponatremia (130mmol/L), and acidosis (carbon dioxide 20mmol/L). TMP/SMX was transitioned to 320mg twice daily oral tablets, and
laboratory abnormalities improved. She was discharged to home and continued to receive IV liposomal amphotericin B.

After 16 days of liposomal amphotericin B she was noted to have new thrombocytopenia with platelets decreased from 181,000/uL to 64,000/uL. 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) 372mg by mouth every 8 hours for 6 doses, and then continued 372mg once daily. She tolerated isavuconazole without any adverse events. Isavuconazole trough level was measured twice: 1.5mcg/mL and 1.9mcg/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 post-partum the patient and the infant were healthy.

Discussion

CGD is an inherited immunodeficiency disorder which 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. 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 which 80 were diagnosed with invasive fungal infections (IFI)\(^3\). 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 one 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 one 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 and who had serial episodes of chorioamnionitis resulting in early delivery in three pregnancies, one 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 post-partum period\(^6\). At least 2 older
case reports described uneventful pregnancies in patients with CGD. 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 160/800mg daily (with augmented folate supplementation) during conception and throughout pregnancy.

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. 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. 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 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 significant increased risk of musculoskeletal abnormalities at birth with low-dose fluconazole during early pregnancy, though no increased risk of oral cleft or truncural abnormalities. A single case report documents use of voriconazole during pregnancy. 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 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.
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 prior to 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 is typical among patients with CGD and highlights the importance of early triage to imaging and invasive diagnostics. As more patients with CGD survive to adulthood improvements in pre-conception 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.
Potential Conflicts of Interest

No conflicts of interest.

Patient Consent Statement

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

1. Holland SM. Chronic granulomatous disease. Hematology Oncology Clinics of North America 2013;27:89-99

2. Dunogue B et al. Chronic granulomatous disease in patients reaching adulthood: a nationwide study in France. Clinical Infectious Diseases 2017;64(6):767-75

3. Blumenthal S et al. Invasive mold infections in chronic granulomatous disease: a 25 year retrospective survey. Clinical Infectious Diseases 2011;53(12):e159-69

4. Margolis DM et al. Trimethoprim-sulfamethoxazole prophylaxis in the management of chronic granulomatous disease. J Infect Dis 1990;162:723-6

5. Haidar ZA et al. Chronic granulomatous disease carrier with recurrent poor obstetric outcome. Obstetrics & Gynecology 2014;123(2):484-5

6. Sheikbahaei S et al. Pregnancy, child bearing and prevention of giving birth to the affected children in patients with primary immunodeficiency disease; a case-series. BMC Pregnancy and Childbirth 2018;18:299

7. Hisano M et al. Successful completion of pregnancy in a woman with chronic granulomatous disease. Obstetric Medicine 2011;4:174-6

8. King CT et al. Antifungal therapy during pregnancy. Clinical Infectious Diseases 1998;27:1151-60

9. Liu D et al. Fetal outcomes after maternal exposure to oral antifungal agents during pregnancy: a systematic review and meta-analysis. International Journal of Obstetrics & Gynecology 2020;148:6-13
10. Zhu Y et al. Oral fluconazole use in the first trimester and risk of congenital malformation: population based cohort study. BMJ 2020; 369:m1494

11. Shoai Tehrani M et al. Case report of exposure to voriconazole in the second and third trimester of pregnancy. Antimicrobial agents and chemotherapy 2013;57(2):1094-5

12. Isavuconazonium package insert:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/207500s005,207501s004lbl.pdf
Figure 1. a) Chest CT at the time of presentation with infection at 21 weeks gestational age. b) Chest CT at 1 day post-partum.
