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Case Report

Chronic Granulomatous Disease in Pregnancy: a Rare Case Report

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Abstract

Chronic granulomatous disease (CGD) is a primary immunodeficiency disorder that is either X-linked or autosomal recessive and is characterized by recurrent infections. The diagnosis is primarily based on the nitroblue tetrazolium dye reduction test. Here, we present the case of a 28-year-old pregnant woman with CGD who was diagnosed before marriage and who presented with recurrent subcutaneous skin and ocular infections. Following treatment with multiple antibacterial agents, including meropenem, her infections resolved, and she gave birth to a healthy baby girl at term. However, the newborn has now started to exhibit similar symptoms to those experienced by her mother. This case highlights the need for further studies on the potential impact of maternal chemotherapy on CGD.

Keywords

autoimmune disorders, genetic counseling, NADPH oxidase, primary immunodeficiency, recurrent infections

Introduction

Chronic granulomatous disease (CGD) is caused by defects in four genes, with 65%-70% of cases being X-linked and the remainder autosomal recessive. It is characterized by recurrent infections and granulomas in multiple organs.[1,2] The disease is rare, with an incidence of 4 to 5 per million individuals.[3] Patients with CGD have neutrophils and monocytes capable of normal chemotaxis, ingestion, and degranulation but unable to kill catalase-positive bacteria and fungi due to a defect in subunits of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Affected individuals often succumb to recurrent infections involving the skin, lymph nodes, lungs, liver, and gastrointestinal tract, usually leading to death within the first two decades of life.[4,5] CGD patients also exhibit an increased incidence of autoimmune diseases and may experience ocular manifestations such as keratitis and uveitis.

CGD is typically diagnosed in childhood or early adulthood using tests such as the nitroblue tetrazolium dye reduction test or dihydrorhodamine (DHR) flow cytometry. The disease can significantly impact the quality of life and requires lifelong management with antibiotics, antifungals, and immunomodulatory therapies.[6-10]

Pregnancy in CGD patients is rare and poses unique challenges due to the altered immune responses and increased susceptibility to infections. This case report focuses on a 28-year-old woman with CGD during her pregnancy in 2014, highlighting the complexities and unique aspects of her case, including the transmission of CGD to her daughter.

Case report

Mrs. G.S., a 28-year-old woman with CGD, was born in 1986, married in 2014, and became pregnant shortly thereafter. She was referred to our care for follow-up due to

*multiple pelvic infections, urinary tract infections, breast abscesses, panophthalmitis, and eye protrusion requiring antibiotics (meropenem of 1 g 3 times per day for 14 days), 4 abscess drainages from her breast and axilla, and multiple hospital admissions during her pregnancy, and pelvic inflammatory disease that needed treatment with erythromycin 500 mg twice per day with metronidazole 500 mg twice per day for 14 days. Her pregnancy lasted 41 weeks and ended with an emergency lower segment cesarean section due to cephalopelvic disproportion, delivering a healthy 5.000 kg female, sutured by interrupted stitches. Her postoperative course was uneventful, with no signs of infection at the surgical site (**Fig. 4.**). She had been on antibiotics for 14 days before delivery to treat her panophthalmitis, receiving intravenous meropenem and metronidazole (500 mg three times daily), followed by a one-month course of oral metronidazole and erythromycin (500 mg twice daily). Her condition worsened during pregnancy and the puerperium but showed significant improvement postpartum. She used combined oral contraceptive pills postpartum and did not breastfeed.*

Currently, her child has experienced multiple skin infections since the age of 2 months, fever, otitis media, and tonsillitis, suggesting she may have inherited her mother's condition.

*Mrs. G.S. also developed myasthenia gravis **(Fig. 5)** and underwent laparoscopic thymectomy in 2020. She now has Cushing syndrome and is undergoing plasmapheresis.*

Past medical history

*Mrs. G.S. had recurrent skin infections and abscesses on her breast, left and right arm, requiring about 30 drainage operations leaving multiple scars on the skin of upper limbs **(Fig. 1)**, lower limbs **(Fig. 2)**, and breasts **(Fig. 3)**. She was diagnosed with CGD in 2003 at age 17 using the nitroblue tetrazolium dye reduction test. She also experienced recurrent vaginal infections and pelvic inflammatory disease post-marriage.*

Figure 1. Scars on the skin of the upper limbs due to recurrent skin infections requiring multiple surgeries.

Figure 2. Scars on the skin of the lower limbs due to recurrent skin infections requiring multiple surgeries.

Figure 3. Scars on the skin of both breasts due to recurrent skin infections requiring multiple surgeries.

Figure 4. The caesarian section scar without any signs of infection.

Figure 5. Patient's eyes due to myasthenia gravis.

Family history

Her mother died of breast cancer five years after giving birth to her. She was undergoing chemotherapy when she discovered her pregnancy, and her father succumbed to liver cancer. There was no consanguinity between her parents. She is the youngest of four siblings, and none of them have CGD.

Drug history: She is allergic to ampicillin and cephalosporin, and she has become allergic to almost all injectable antibiotics, including meropenem.

Discussion

Chronic granulomatous disease (CGD) is a rare primary immunodeficiency disorder that significantly increas-

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es susceptibility to infections due to a defect in NADPH oxidase, an enzyme complex essential for the respiratory burst in phagocytes. The inability to generate reactive oxygen species renders individuals with CGD vulnerable to recurrent infections and granuloma formation in various organs and an inability to effectively kill certain bacteria and fungi. This report highlights the clinical course and management of CGD during pregnancy, a scenario that is not extensively documented in the literature.[11-13]

Impact of pregnancy on CGD

Pregnancy poses a particular challenge for patients with CGD due to the immunological changes that occur during this period. The immune system undergoes modulation during pregnancy to prevent fetal rejection, which can affect the progression of autoimmune and infectious diseases.[14,15] This patient experienced significant worsening of CGD symptoms during pregnancy, including panophthalmitis and recurrent abscess drainage. These complications required intensified medical intervention and highlighted the increased susceptibility to severe infections during pregnancy in CGD patients. Postpartum, the patient's symptoms resumed their previous pattern, indicating the temporary exacerbation during pregnancy. This observation aligns with limited existing literature suggesting that the immunomodulatory state of pregnancy can temporarily alter the clinical course of CGD.[16-18]

The patient delivered a healthy baby girl, who began manifesting symptoms of CGD at two months old. The typical age of onset for CGD symptoms varies, but early infancy is common, as seen in this case.[19,20] The detailed documentation of the clinical management and outcomes provides valuable insights into the complexities of managing CGD during pregnancy and the importance of a multidisciplinary approach.[21-23]

Antibiotic treatment

The management of infections in CGD relies heavily on the use of prophylactic and therapeutic antibiotics. During pregnancy, the patient was treated with meropenem, metronidazole, and erythromycin, all of which have been used to manage severe infections in CGD patients.[24]

- **Meropenem:** Meropenem is a broad-spectrum antibiotic commonly used to treat severe bacterial infections. It is generally considered safe for use during pregnancy when the potential benefits outweigh the risks. According to a study by Mathews et al., meropenem crosses the placenta, but no significant adverse effects on the fetus have been observed.[25] The FDA classifies meropenem as a category B drug, indicating that animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.[26] The use of meropenem, in this case, was justified due to the patient's severe infections and the need for effective broad-spectrum coverage.
- **Metronidazole:** Metronidazole is an antibiotic and antiprotozoal medication commonly used to treat bacterial vaginitis, trichomoniasis, and anaerobic bacterial infections. It is classified as a category B drug by the FDA, meaning that animal studies have not shown a risk to the fetus, but there are no well-controlled studies in pregnant women.[26] Metronidazole crosses the placenta and can reach fetal circulation, but its use in pregnancy is generally considered safe when used appropriately. The patient's treatment with metronidazole was aimed at managing anaerobic bacterial infections, which are common in CGD patients.[27]
- **Erythromycin:** Erythromycin is a macrolide antibiotic often used to treat bacterial infections during pregnancy. It is classified as a Category B drug by the FDA, indicating that animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.[28] A study by Briggs et al. supports the safety of erythromycin during pregnancy, noting that it is commonly used to treat infections without significant teratogenicity effects.[26] The patient's use of erythromycin helped manage her recurrent infections while minimizing potential risks to the fetus.[27]

The manuscript includes detailed information on the antibiotics used, including dosages and durations of treatment. The patient was treated with a combination of meropenem, metronidazole, and erythromycin tailored to her specific infections, with close monitoring to prevent adverse effects. This case underscores the importance of individualized treatment plans in CGD patients, particularly during pregnancy.[28]

Autoimmune complications and Cushing syndrome

One intriguing aspect of this case is the patient's development of myasthenia gravis and subsequent Cushing syndrome. While the coexistence of autoimmune disorders in CGD patients is documented, the precise mechanisms remain unclear. The potential impact of immunosuppressive therapies and the interplay between genetic and environmental factors warrant further investigation.[29]

Role of maternal chemotherapy

The role of maternal chemotherapy in the pathogenesis of CGD in offspring also presents an area for future research. Although there is no direct evidence linking maternal chemotherapy to CGD, the potential for genetic and epigenetic modifications cannot be dismissed.[30-32] This case underscores the importance of genetic counseling and the need for comprehensive prenatal care in managing pregnancies complicated by CGD.[33]

Genetic considerations

Furthermore, the absence of advanced genetic diagnostic tools in our region poses significant challenges in the management of CGD. The reliance on clinical presentation and basic diagnostic tests limits the ability to provide precise and early diagnosis, which is crucial for optimal management and genetic counseling. Genetic testing is crucial in the diagnosis and management of CGD. Despite regional limitations, the potential benefits of genetic testing have been discussed in the manuscript, emphasizing the importance of genetic counseling for family planning and early diagnosis. Future steps include pursuing genetic investigations to better understand the hereditary patterns and to provide targeted care for affected individuals.[33]

Conclusions and recommendations

Early diagnosis and management

CGD should be considered in patients presenting with aggressive and recurrent infections. Early diagnosis and prompt management are crucial to improving outcomes.

Genetic counseling

Despite the lack of consanguinity, CGD can still be inherited. Genetic counseling should be offered to families with a history of CGD to inform them about the risks and implications for offspring.

Maternal chemotherapy

Further studies are needed to explore the potential causative role of maternal chemotherapy in the development of CGD in offspring. This could provide insights into preventive strategies and better prenatal management.

Comprehensive prenatal care

This case highlights the complexities of managing CGD during pregnancy, emphasizing the need for a multidisciplinary approach and individualized treatment plans. The temporary exacerbation of CGD symptoms during pregnancy, the successful management of severe infections with antibiotics, and the documentation of autoimmune complications provide valuable insights into the interplay between pregnancy and CGD. Pregnant women with CGD require comprehensive prenatal care, including close monitoring for infections and appropriate antibiotic therapy to ensure maternal and fetal well-being.

Research and development

There is a critical need for the development and implementation of advanced genetic diagnostic tools in regions lacking such facilities. This would enable early detection, appropriate management, and better genetic counseling for CGD patients and their families.

Autoimmune manifestations

The co-occurrence of autoimmune disorders such as myasthenia gravis in CGD patients necessitates a multidisciplinary approach to manage these complex cases effectively.

Ethical approval

The Scientific Committee of Al-Kindy Medical College, University of Baghdad, approved the study. The patient signed informed written consent. This work complies with the World Medical Association Declaration of Helsinki.

Availability of data and materials

Available upon request.

Competing interests

None declared.

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