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Severe oropharyngeal candidiasis in an anemic pregnant woman: A case report

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ABSTRACT

Hormonal fluctuations during pregnancy increase susceptibility to *Candida* infections, typically presenting as vulvovaginal candidiasis, but rarely as oropharyngeal candidiasis. We report a rare case of a woman being pregnant for 27 + 1 weeks with twins with oropharyngeal candidiasis, likely attributed to nutritional anemia and adverse reactions of amoxicillin. Following a thorough literature review and evaluation of medication safety during pregnancy regarding route, dosage, and gestational stage, we treated the patient with fluconazole and piperacillin-tazobactam. The patient fully recovered and successfully delivered two infants via cesarean section at term, with no adverse reactions noted during a six-month follow-up.

1. Introduction

Candida species are opportunistic *fungi* that typically colonize human skin, mucosal surfaces, the upper respiratory tract, the genitourinary tract, and the gastrointestinal tract. In individuals with disrupted normal flora or compromised immune systems, these organisms can become invasive and pathogenic, leading to secondary infections [1]. Hormonal fluctuations during pregnancy can potentially weaken the localized immune response in the vagina, thereby increasing susceptibility to *Candida* infections, which commonly present as vulvovaginal candidiasis (VVC). VVC affects approximately 30 % of pregnant women in the later stages of pregnancy [2]. However, severe oropharyngeal candidiasis during pregnancy is rarely reported. In non-pregnant adults, moderate to severe oropharyngeal candidiasis is primarily treated with systemic antifungal therapy using azole drugs, such as fluconazole, voriconazole, and posaconazole [3]. However, studies have reported that azole drugs may have teratogenic effects on the fetus [4]. The treatment of oropharyngeal candidiasis in pregnancy necessitates a comprehensive assessment of the severity of the fungal infection, the possibility of mixed infections, and the safety of the fetus. Therefore, we report a case of oropharyngeal candidiasis in pregnancy, which we thoroughly examine the etiology, formulate a treatment plan based on a comprehensive review of the literature and incorporating the patient's specific condition, and subsequently follow up on the outcomes for both the mother and child, to provide a reference for the clinical diagnosis and treatment of similar cases.

2. Case presentation

This is a case of an 18-year-old pregnant woman at 27 + 1 weeks of gestation, who has had regular prenatal check-ups showing no abnormalities. She presented to our facility with recurrent fever, increased oral and pharyngeal pain, and worsening dysphagia. She reported no long-term use of systemic or inhaled corticosteroids, antimicrobial drugs, or immunosuppressants. We defined "day 0" at the day of hospital admission. The patient developed headache and fever without any identifiable cause at day −4. Her body temperature was 38.5 °C. She then self-treated with amoxicillin and antipyretics, which provided slight relief from her headache symptoms after 2 days, but she continued to have recurrent fever. Her symptoms started to progress with the addition of oral and pharyngeal pain, oral ulcers, and dysphagia, which worsened upon ingestion of food or water. She was admitted to a local hospital at day −2. Physical examination revealed extensive white vesicular lesions on the buccal mucosa, along with grade III tonsillar enlargement. Laboratory findings included a white blood cell (WBC) count of 10.47 * 10^9/L(10.47 * 10^3/μL) and a hemoglobin (Hgb) level of 80 g/L(8 g/dL). Despite two days of treatment with Cefuroxime, the patient continued to experience recurrent fever, exacerbated oral and

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pharyngeal pain, and worsening dysphagia. Consequently, she was transferred to our hospital for further treatment at day 0. Physical examination revealed necrosis and ulceration of the gingival margins throughout the mouth, swollen gums, and extensive ulceration with white pseudomembranes on the dorsal surface of the tongue, resulting in a limited mouth opening of approximately one transverse finger breadth. Fig. 1 displays the gradual decrease in oral pseudomembranes in the patient during fluconazole treatment, indexed by days of administration. Laboratory tests indicated an elevated C-reactive protein (CRP) level of 86.4 mg/L (0.086 mg/dL), an elevated white blood cell count (WBC) of 11.67 * 10^9/L (11.67 * 10^3/μL), and a decreased hemoglobin level (Hgb) of 78 g/L (7.8 g/dL). Fungus were found in the vaginal discharge by microscopy, while the oral swab smear was negative for fungus. Screening for immune system diseases including antinuclear antibody profiles, TORCH (Toxoplasma, Rubella, Cytomegalovirus, and Herpes) complex, Epstein-Barr virus, HIV, and lymphocyte subsets returned negative results. Investigations for iron-deficiency anemia, hemolytic anemia, thalassemia, megaloblastic anemia, and anemia of chronic disease were all negative, and no bone marrow aspiration was performed. The patient was diagnosed with oropharyngeal candidiasis(severe disease) during pregnancy.

The patient was treated with piperacillin-tazobactam (4.5g every 8 hours via intravenous infusion) combined with fluconazole (initially 400mg daily via intravenous infusion, then reduced to 200mg daily via intravenous infusion) for anti-infective therapy, iron dextran (200mg daily via intravenous infusion) for anemia correction, and sodium bicarbonate solution for oral rinsing to alter the oral microenvironment at day 0. The patient's body temperature returned to normal at day +2. The infection indicators (complete blood count, procalcitonin, and CRP) were normal, and the oral pseudomembranes gradually decreased in size at day +3. Oral and pharyngeal pain gradually diminished, and the patient began to resume autonomous feeding and fully recovered at day +14. At 37 weeks of gestation, a cesarean section was performed, resulting in the birth of two healthy female infants. The neonatal assessments were good, and telephone follow-up until six months after birth indicated good growth and development, with no adverse reactions reported.

3. Discussion

Major risk factors for invasive *Candida* infections include: immunocompromised states (HIV/AIDS, transplantation, malignant diseases), long-term use of immunosuppressants, corticosteroids, and broad-spectrum antibiotics, prolonged use of medical devices (central vascular catheters, urinary catheters, and dentures), poorly managed chronic diseases (diabetes mellitus and renal diseases), malnutrition, and suboptimal hygiene practices [5,6]. Upon admission, a comprehensive work-up for *Candida* infection including patient interview, physical examination, and laboratory tests, was conducted to rule out potential high-risk factors. We suggest that the etiologies of the *Candida* infection in this case are anemia and an adverse drug reaction resulting from the administration of amoxicillin.

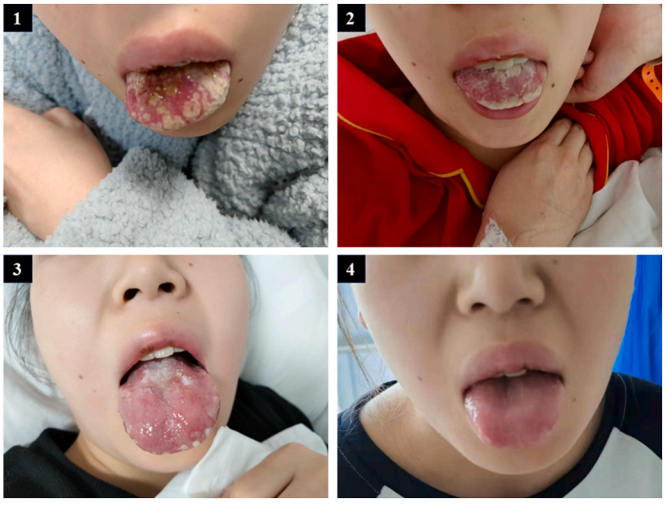

Fig. 1. The gradual decrease in oral pseudomembranes in the patient during fluconazole treatment. day 0 (1), day +3 (2), day +6 (3), day +14 (4).

Anemia can disrupt the immune system and impair the mucosal barrier, increasing the risk of *Candida* infection [7]. Studies have reported that the incidence of oral *Candida* infection in patients with iron-deficiency anemia can be as high as 85 % [8]. Another study analyzed the impact of ten risk factors, including anemia, on the proliferation of oral *Candida*, showing that the quantity of oral *Candida* increased with the severity of anemia [9]. In this case, the patient was diagnosed with moderate anemia [10], which heightens the risk of *Candida* infection. The cause of anemia in this case is most likely a nutritional deficiency, given the symptoms of nausea and vomiting in pregnancy (NVP), dysphagia, and a body mass index (BMI) of 20.19 at a gestational age of 27 + 1 weeks.

The use of broad-spectrum antibiotics, such as amoxicillin, can disrupt normal oral flora, thereby increasing the risk of *Candida* infection [5]. A meta-analysis that included 45 studies indicated that treatment with amoxicillin or amoxicillin-clavulanate was associated with an increased risk of *Candida* infection (OR: 7.77, 95 % CI 2.23–27.11) [11].

The primary clinical manifestations of this case include fever, oral and pharyngeal pain, extensive mucosal ulceration and pseudomembrane. According to the "China Expert Consensus on the Diagnosis and Treatment of Candidiasis in Adult Patients", the clinical diagnosis was gestational candidiasis, with potential sites of infection including the oral cavity and pharynx [13]. Laboratory test results showed elevated CRP, PCT, WBC and neutrophil percentage (NEUT%). According to the " Expert Consensus on Clinical Significance of Infection-Related Markers", bacterial infection cannot be ruled out [12]. Therefore, systemic antifungal and antibacterial drugs are indicated. The first-line antifungal treatment was fluconazole (400 mg orally or intravenously on the first day, followed by 200–400 mg daily for 14–21 days, extended to 28 days for refractory diseases) [3]. Due to the patient's dysphagia, intravenous administration was required. A limited number of studies have suggested that azole drugs may have potentially teratogenic effects [4]. Consequently, we performed a comprehensive literature search and evaluated the safety of these drugs during pregnancy regarding various factors, including route of administration, dosage, and stage of gestation.

The existing literature has reported on the safety of oral fluconazole during pregnancy, but no literature has reported on the safety of intravenous fluconazole [14–17]. Oral fluconazole is well absorbed, with an oral bioavailability greater than 90 % [18]. Therefore, existing literature on oral fluconazole was used to assess intravenous fluconazole safety. A cohort study showed that the incidence of musculoskeletal malformations in early pregnancy using oral fluconazole was 0.52 % (196/37649), higher than the control group (RR: 1.30, 95 % CI 1.09–1.56), and in the high cumulative dosage group (>450mg), the incidence was 0.85 % (18/2109), higher than the control group (RR: 1.98, 95 % CI 1.23–3.17) [14]. A nested case-control study showed that the incidence of cardiac septal defects during pregnancy with more than 150mg of oral fluconazole was 1.5 % (3282/226599), higher than the control group (OR: 1.81, 95 % CI 1.04–3.14) [15]. A Swedish cohort study found no association between fluconazole use during pregnancy and the risk of stillbirth or neonatal death [16]. In this case, the patient developed oropharyngeal candidiasis at 27 + 1 weeks of gestation, with a cumulative dose of fluconazole of 3000mg. We informed the patient of the potential increased risk of musculoskeletal malformations and cardiac septal defects, which is less than 2 %. After obtaining informed consent, intravenous fluconazole was administered for antifungal treatment. Additionally, studies have shown that low salivary pH can

increase the proliferation of *Candida* in the oral cavity [9]. Sodium bicarbonate can increase oral pH and reduce fungal proliferation, hence an oral rinse solution of 2 %–4 % sodium bicarbonate was used for adjunctive treatment.

4. Conclusion

This is a rare case of oropharyngeal candidiasis during pregnancy. We suggest that the possible etiologies were nutritional anemia and use of amoxicillin. Through literature review, we conducted a comprehensive assessment of medication safety during pregnancy regarding the route of administration, dosage, and gestational stage. The patient was treated with a combination of fluconazole for antifungal therapy and piperacillin-tazobactam for antibacterial treatment, resulting in a full recovery. The patient delivered twins via cesarean section at term, and no adverse reactions were observed during the six-month follow-up. Clinicians should be vigilant regarding the correlation between gestational anemia and the development of candidiasis, as pregnancy itself is a predisposing factor for mucocutaneous candidiasis. Additionally, the utilization of amoxicillin in clinical practice may increase the susceptibility of patients to opportunistic Candida infections. Anti-infective treatment during pregnancy should consider factors including the route of administration, dosage, and gestational stage to ensure the safety of both mother and fetus.

CRediT authorship contribution statement

Shuyan Quan: Writing – review & editing, Writing – original draft, Conceptualization. **Hong Li:** Writing – review & editing, Writing – original draft, Conceptualization. **Kailing Li:** Writing – review & editing, Writing – original draft, Conceptualization. **Xuan Wang:** Data curation. **Yang Xu:** Data curation. **Peng Gu:** Writing – review & editing, Supervision, Funding acquisition, Formal analysis.

Conflict of interest

There are none.

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