Candida glabrata Sepsis Associated With Chorioamnionitis in an In Vitro Fertilization Pregnancy: Case Report and Review

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We report a case of Candida glabrata sepsis associated with chorioamnionitis in an in vitro fertilization–assisted pregnancy. There is a strong association between C. glabrata chorioamnionitis and assisted fertility techniques. Candida glabrata chorioamnionitis presents unique management challenges.

Keywords: glabrata; pregnancy; chorioamnionitis; Candida; fungal.

CASE REPORT

A 39-year-old woman with an in vitro fertilization (IVF)–assisted dichorionic diamniotic twin pregnancy presented at 21 weeks gestation with 24 hours of fever and rigors. On the day of presentation (day 1), she developed per vaginal bleeding and contractions. Her temperature was 38.5°C (101.3°F), blood pressure was 90/55 mm Hg, and pulse was 110 beats per minute. Suprapubic tenderness was the only abnormality detected on physical examination. Vaginal examination revealed a 2-cm-long, 1-cm-dilated cervix. Initial treatment with ampicillin, gentamicin, and metronidazole was directed at presumptive bacterial chorioamnionitis. Previous medical history included mild asthma. She had 2 previous pregnancies. The first was complicated by preeclampsia and ended with a stillbirth at 38 weeks gestation after cesarean section for placental abruption. The second resulted in a live birth at 38 weeks gestation after cesarean section for fetal distress. Prophylactic aspirin was administered during the current pregnancy. An amniocentesis was performed at 14 weeks gestation with 7 attempts on one fetal sac and 3 on the other.

Blood cultures from day 1 were negative, but both sets of cultures from days 2 and 4 after presentation grew Candida glabrata. Antibiotics were stopped on day 4 and liposomal amphotericin was commenced at 1.5 mg/kg daily, then increased to 3 mg/kg daily on day 6. Vaginal swabs from day 2 cultured pure growth of C. glabrata. Initial blood tests showed mild neutrophilia (8.9 × 10⁹/L, reference <7.7 × 10⁹/L) and C-reactive protein of 65 mg/L (reference <3.1 mg/L). The neutrophilia progressed to a peak of 15.5 × 10⁹/L and the blood film demonstrated toxic neutrophil changes with left shift and band forms of 1.3 × 10⁹/L (reference <0.7 × 10⁹/L). Liver function became deranged during the first 48 hours and peaked on day 4 with γ-glutamyl transpeptidase of 133 U/L (reference <38 U/L), alkaline phosphatase 259 U/L (reference 25–100 U/L), alanine aminotransferase 164 U/L (reference <40 U/L), and aspartate aminotransferase 281 U/L (reference <30 U/L), but normal bilirubin. Scanty per vaginal bleeding continued for several days as did periodic contractions, the latter improving with the addition of oral nifedipine.

Ultrasoundography on day 4 showed normal amniotic fluid volume and fetal parameters for both twins. Repeat ultrasonography on days 10 and 13 showed reduced amniotic fluid around twin 2, consistent with premature rupture of membranes. Ultrasoundography on day 17 revealed new oligohydramnios of twin 1 and anhydramnios of twin 2, but ongoing filling of fetal bladders. Ultrasoundography on day 20 showed some reaccumulation of fluid around twin 2. Growth and blood vessel Doppler ultrasound of both twins were normal on all scans.

Blood cultures remained negative after the initiation of anti-fungal therapy. The organism was resistant to fluconazole (minimum inhibitory concentration [MIC] >256 µg/mL) and itraconazole (MIC = 8.0), but sensitive to voriconazole (MIC = 1.0), amphotericin B (MIC = 1.0), 5-flucytosine (MIC = 0.12), and caspofungin (MIC = 0.5). On day 10, oral 5-flucytosine 150 mg/kg daily was added to liposomal amphotericin. The 5-flucytosine dose was reduced after 8 days due to mild neutropenia, then substituted by intravenous caspofungin 50 mg daily on day 20. On day 21, after 17 days of intravenous antifungal treatment, spontaneous labor began and both twins were delivered stillborn. The patient developed rigors and hypotension. However, repeat blood cultures were negative and there was no...
evidence of endophthalmitis. She was treated successfully with caspofungin for 7 days, then oral voriconazole for 7 days. The parents declined autopsy. Histopathology of the first placenta showed a small area of infarction but no evidence of inflammation or infection. The tissues of twin 2 showed profuse C. glabrata in the fetal membranes (see Supplementary Data), with fewer yeasts on the umbilical cord and fetal placental surface. There were few inflammatory cells in the areas containing yeasts, and culture of placental tissue was negative.

DISCUSSION

Candida glabrata, formerly known as Torulopsis glabrata, is a nonpseudohyphae–forming Candida species. Candida glabrata lower urogenital tract carriage rates during pregnancy range from 2% to 8%. Experimental data suggest reduced virulence compared to Candida albicans, with an absence of hyphae production and less adhesive capacity [1]. This, however, contrasts with extremely high fetal mortality with invasive C. glabrata infections during pregnancy.

There has been historical underdetection, and hence under-reporting, of C. glabrata infection. Reliable identification is possible using chromogenic culture media, newer biochemical and molecular techniques, and Gomori-Grocott or Periodic Acid-Schiff staining on histological specimens. In contrast to C. albicans, C. glabrata infections typically do not demonstrate subchorionic microabscesses or umbilical cord nodules [2].

Candida albicans chorioamnionitis involves the placentas of 0.5% of pregnancies [3]; C. glabrata chorioamnionitis is much less commonly reported. Review of the 16 published confirmed cases of C. glabrata chorioamnionitis (Table 1) reveals that 63% are associated with IVF, and 81% with some form of instrumentation. The first IVF-associated case was reported in 1997 [4]. Candida glabrata is less able than C. albicans to invade and migrate across intact chorionic membranes [5]. This provides a mechanistic hypothesis for the strong

<table>
<thead>
<tr>
<th>First Author [Ref] (Year)</th>
<th>In Vitro Fertilization</th>
<th>Foreign Body</th>
<th>Gestation at Diagnosis, wks</th>
<th>Prebirth Antifungal Treatment</th>
<th>Outcome and Delivery Gestation, wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quirke [19] (1980)</td>
<td>No</td>
<td>IUCD</td>
<td>23</td>
<td>Nil</td>
<td>Stillborn singleton (23)</td>
</tr>
<tr>
<td>Bruner [21] (1986)</td>
<td>No</td>
<td>IUCD</td>
<td>23</td>
<td>Nil</td>
<td>Rapid singleton death (23+2)a</td>
</tr>
<tr>
<td>Catanzarite [22] (1997)</td>
<td>No No</td>
<td></td>
<td>27</td>
<td>IV amphotericin for 11 d, and PV terconazole</td>
<td>Singleton survival (CS at 28+4)</td>
</tr>
<tr>
<td>Sfameni [4] (1997)</td>
<td>Yes No</td>
<td></td>
<td>20</td>
<td>Nil</td>
<td>1 twin stillborn and 1 twin rapid death (21+5)</td>
</tr>
<tr>
<td>Salem [23] (2000)b</td>
<td>Yes No</td>
<td></td>
<td>15</td>
<td>Nil</td>
<td>Stillborn triplets (15+3–16+5)</td>
</tr>
<tr>
<td>Ibara [17] (2004)</td>
<td>Yes No</td>
<td></td>
<td>34</td>
<td>Nil</td>
<td>Twin survival (CS at 34)</td>
</tr>
<tr>
<td>Freydiere [25] (2005)</td>
<td>Yes No</td>
<td></td>
<td>21a</td>
<td>Nil</td>
<td>Stillborn twins (22)</td>
</tr>
<tr>
<td>Matsuzawa [2] (2005)</td>
<td>Yes No</td>
<td></td>
<td>26</td>
<td>Nil</td>
<td>1 twin survival and 1 twin rapid death (CS at 26)</td>
</tr>
<tr>
<td>Carbonnel [18] (2007)c</td>
<td>Yes No</td>
<td></td>
<td>25</td>
<td>Nil</td>
<td>Singleton death on day 5 (25)</td>
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<tr>
<td>Asemota [16] (2011)</td>
<td>Yes No</td>
<td></td>
<td>19+5</td>
<td>IV amphotericin B for 9 d then termination of pregnancy for PPROM</td>
<td>Stillborn twins (21+5)</td>
</tr>
<tr>
<td>Jackel (current case)</td>
<td>Yes No</td>
<td></td>
<td>16</td>
<td>Nil</td>
<td>Stillborn twins (16)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>21 +5</td>
<td>IV liposomal amphotericin for 17 d with concomitant 5-flucytosine for 10 d; 1 d caspofungin</td>
<td>Stillborn twins (24)</td>
</tr>
</tbody>
</table>

Abbreviations: CS, cesarean section; IUCD, intrauterine contraceptive device; IV, intravenous; PPROM, preterm premature rupture of membranes; PV, per vaginal.

a Day of gestation within gestation week.

b Published in Spanish.
c Published in French.
association with assisted fertility and the rarity of C. glabrata chorioamnionitis without some form of instrumentation.

Because C. glabrata has difficulty penetrating intact membranes, it benefits from direct inoculation into the uterus. This can occur through IVF techniques, coexisting intrauterine contraceptive device, cervical stitch, rupture of membranes, and with amniocentesis or chorionic villous sampling. The process of IVF allows potential C. glabrata uterine contamination at several points. Transvaginal embryo harvest enables inoculation by the mother’s cervicovaginal Candida. Candida glabrata contamination of IVF tissue for implantation, via infected semen, is also reported [6]. Transvaginal embryo transfer provides another critical opportunity for inoculation. Despite the association between C. glabrata and IVF techniques, little formal experimental work investigating these particular etiological mechanisms in detail has been published.

Historically, invasive C. glabrata infection was thought to be exclusively endogenously acquired. However, studies have shown the capacity for nosocomial acquisition of C. glabrata [7]. Hence, amniocentesis may theoretically provide a route of transfer. Similarly, chorionic villous sampling, particularly transvaginal, risks inoculation of vaginal flora [8].

Chorioamnionitis due to C. glabrata usually becomes clinically apparent in the second trimester. It has high lethality with only 31% of the published affected pregnancies having any neonatal survival. To our knowledge, our case is only the fourth report of systemic maternal antifungal treatment for C. glabrata chorioamnionitis prior to delivery, and reflects the longest period of intrauterine antifungal treatment to date.

Candida glabrata has increased resistance to azoles, particularly fluconazole, but is typically sensitive to amphotericin B. Amphotericin B penetrates into all fetal tissues with a long persistence period [9]. However, amphotericin has rarely been utilized for invasive candidal disease in pregnancy, having predominantly been used for treatment of pregnant women with cryptococcal disease, coccidioidomycosis, and blastomycosis [10]. It has been used successfully as an intra-amniotic infusion for C. albicans chorioamnionitis [11], and for intravenous line–associated C. glabrata sepsis in neonates [12]. Liposomal amphotericin appears equivalent in efficacy and safety during pregnancy.

The echinocandin group of antifungals are recommended by the Infectious Diseases Society of America for disseminated C. glabrata infection [13]. Caspofungin and anidulafungin cross the placenta, but pharmaceutical company data have demonstrated embroyotoxicity in animals with early pregnancy use. However, caspofungin has been used very successfully in premature neonates in the context of fluconazole- and amphotericin-resistant Candida parapsilosis sepsis [14].

Adequate C. glabrata carriage and vulvovaginitis eradication rates are reported using intravaginal boric acid, amphotericin, or flucytosine in women with azole-resistant C. glabrata, or in recalcitrant cases of C. glabrata vulvovaginitis [15]. Asemota et al achieved a successful IVF pregnancy after topical boric acid treatment in a woman whose previous IVF-assisted pregnancy ended in C. glabrata sepsis and fetal loss [16].

Seventeen days of liposomal amphotericin, with concomitant 5-flucytosine for 10 days, did not eradicate the infection in our patient, despite proven susceptibilities. Given the strength of the relationship between IVF techniques and C. glabrata chorioamnionitis, and the extremely high mortality rate historically, the potential role for screening prior to assisted fertility attempts involving embryo harvest or transfer is raised, as it has been by previous authors [4, 17, 18]. However, a comprehensive screening program may not be justified owing to the rarity of invasive disease despite widespread and increasing use of IVF technologies and the relatively high rates of C. glabrata carriage among pregnant women.

Supplementary Data
Supplementary materials are available at Clinical Infectious Diseases online (http://www.oxfordjournals.org/our_journals/cid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes
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References