Candida glabrata chorioamnionitis in a twin pregnancy following in vitro fertilisation: a rare cause of septic miscarriage

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SUMMARY
Candida glabrata chorioamnionitis is uncommon and associated with poor fetal outcomes. We present a case of C. glabrata chorioamnionitis of a dichorionic diamniotic pregnancy conceived by fresh embryo transfer. Despite antifungal therapy with amphotericin B, spontaneous miscarriage of both twins occurred. The mother otherwise recovered uneventfully. Our case highlights the high fetal mortality associated with C. glabrata chorioamnionitis and the challenges of antifungal treatment in pregnancy. We recommend a low threshold of suspicion for Candida infection in pregnancy, notably those involving transvaginal uterine instrumentation such as in vitro fertilisation.

BACKGROUND
Candida glabrata chorioamnionitis is reported to be associated with uterine instrumentation and assisted reproductive techniques, and may result in poor fetal outcomes. This report describes our experience with a case of culture and histology-proven C. glabrata chorioamnionitis in a dichorionic-diamniotic twin pregnancy conceived via in vitro fertilisation (IVF). We highlight our clinical dilemmas in the management of this case, particularly in counselling of the risk of continuing the pregnancy and selection of the appropriate antifungal agents and duration of therapy.

CASE PRESENTATION
Our patient was gravida 1 with dichorionic, diamniotic twins conceived via fresh embryo transfer (FET). An endometrial scratch performed prior to the FET showed no endometritis.

She presented with premature rupture of membranes (PROM) at 17+4 weeks’ gestation (Day 0). She was febrile at 38.5°C and inflammatory markers were raised with a C reactive protein (CRP) of 57.7 mg/L (0.2–9.1 mg/L) and white blood cell count (TW) of 17.5×10⁹/L (4–10×10⁹/L). Ultrasound showed two viable fetuses and oligohydramnios (AFI 2.5) of the presenting twin. Empiric intravenous antibiotics (ceftriaxone and metronidazole) were initiated.

INVESTIGATIONS
Maternal blood cultures and high vaginal swabs obtained on admission grew C. glabrata on Day 2. The patient was counselled by both the maternal-fetal medicine and infectious diseases teams regarding the suspicion of fungal chorioamnionitis resulting in PROM, and termination of pregnancy was discussed in view of the poor fetal prognosis and risk of worsening maternal sepsis. However, she elected to continue expectant management with close monitoring. Diagnostic amniocentesis was not performed due to its attendant risks. An echocardiogram to rule out cardiac seeding and a detailed ophthalmological examination to exclude endophthalmitis were both negative.

Cultures of both placentas grew C. glabrata, while histological examination showed acute chorionamnionitis (figure 1) and funisitis (figure 2), with fungal yeasts seen at the membranes and amnion of the umbilical cord. Sensitivity testing of C. glabrata showed sensitivity to anidulafungin (minimum inhibitory concentration (MIC) 0.12 µg/mL) and caspofungin (MIC 0.12 µg/mL), and dose-dependent susceptibility to fluconazole (MIC 32 µg/mL). No interpretive criteria were available for sensitivity to amphotericin B.

TREATMENT
Given maternal fungemia, fungal chorionamnionitis was suspected and intravenous amphotericin B was...
Table 1: All previously reported cases of *C. glabrata* chorioamnionitis

| Case no. | Reference | Year of publication | In vitro fertilisation? | Type of twin pregnancy | Time of gestation | Mode of diagnosis | Choice of antifungal | Fetal outcomes | Fetal microbiology and pathological findings postdelivery | Subsequent pregnancy |
|----------|-----------|---------------------|-------------------------|------------------------|------------------|------------------|-------------------|---------------|-------------------------------------------------|-------------------|
| 1        | Current case | 2021 | Yes | Dichorionic diamniotic | 17 weeks | Maternal fungemia; *C. glabrata* isolated on high vaginal swab | Liposomal amphotericin B | Miscarriage of both twins at 19 weeks | Histopathological evidence of acute chorioamnionitis and funisitis in both twins, with growth of *C. glabrata* | Subsequent pregnancy |
| 2        | Tan et al | 2014 | Yes | Dichorionic diamniotic | 24 weeks | Maternal fungemia; *C. glabrata* isolated in amniocentesis fluid from twin B but not twin A | Amphotericin B | Caesarean at 28 weeks; both twins survived | Light growth of *C. glabrata* from subchorionic swab of twin B but not twin A; no histopathological evidence of acute chorioamnionitis or funisitis | Not mentioned |
| 3        | Akhanoba et al | 2014 | Yes | Dichorionic diamniotic | 18 weeks | Maternal fungemia; *C. glabrata* isolated in liquor (had premature rupture of membranes) | Liposomal amphotericin B | Miscarriage of both twins at 22 weeks | Histopathological evidence of acute chorioamnionitis and funisitis in both twins | Subsequent pregnancy |
| 4        | Lai et al | 2012 | Yes | Dichorionic diamniotic | 21 weeks | Maternal fungemia; *C. glabrata* isolated on high vaginal swab | Liposomal amphotericin B with oral 5-flucytosine | Miscarriage of both twins at 24 weeks | Histopathological evidence of acute chorioamnionitis in both twins | Not mentioned |
| 5        | Carbonnel et al | 2007 | Yes | Dichorionic diamniotic | 22 weeks | Maternal fungemia | Amphotericin B | Miscarriage of both twins at 23 weeks | Pathology reports consistent with *C. glabrata* chorioamnionitis in both twins | Not mentioned |
| 6        | Arai et al | 2002 | No | Dichorionic diamniotic | 26 weeks | *C. glabrata* isolated in amniocentesis fluid from twin B but not twin A | Fluconazole | Caesarean at 29 weeks; both twins survived | Histopathological evidence of acute chorioamnionitis in both placentae; intrauterine *C. glabrata* infection of twin B | Not mentioned |

Did not receive systemic antifungal treatment

| Case no. | Reference | Year of publication | In vitro fertilisation? | Type of twin pregnancy | Time of gestation | Mode of diagnosis | Choice of antifungal | Fetal outcomes | Fetal microbiology and pathological findings postdelivery | Subsequent pregnancy |
|----------|-----------|---------------------|-------------------------|------------------------|------------------|------------------|-------------------|---------------|-------------------------------------------------|-------------------|
| 1        | Ozer et al | 2013 | Yes | Dichorionic diamniotic | 17 weeks | Postmiscarriage | No treatment | Fetal death of twin A at 15 weeks; miscarriage of both twins at 18 weeks | Placental cultures of both twins positive for *C. glabrata* and histopathological evidence of acute chorioamnionitis in both placentae | Not mentioned |
| 2        | Asemota et al | 2010 | Yes | Dichorionic diamniotic | 16 weeks | Postmiscarriage | No treatment | Miscarriage of both twins at 16 weeks | Pathology reports consistent with *C. glabrata* chorioamnionitis in both twins | Subsequent pregnancy |
| 3        | Matsuzawa et al | 2005 | Yes | Dichorionic diamniotic | 26 weeks | Postdelivery; maternal fungemia postdelivery | No treatment prior to delivery | Caesarean at 26 weeks; twin A survived but twin B demised 13 hours after birth | Histopathological evidence of acute chorioamnionitis in both placentae; *C. glabrata* identified in the placenta of twin B but not twin A | Not mentioned |
| 4        | Ibara et al | 2004 | Yes | Dichorionic diamniotic | 34 weeks | Postdelivery | No treatment | Caesarean at 34 weeks; both twins survived | No histopathological evidence of acute chorioamnionitis in both placentae; but *C. glabrata* identified in the placenta of both twins | Not mentioned |
| 5        | Ibara et al | 2004 | Yes | Dichorionic diamniotic | 21 weeks | Maternal fungemia | No treatment | Miscarriage of both twins at 22 weeks | No histopathological evidence of acute chorioamnionitis in both placentae; but *C. glabrata* identified in the placenta of both twins | Not mentioned |
| 6        | Slameni et al | 1997 | Yes | Dichorionic diamniotic | 20 weeks | *C. glabrata* isolated on high vaginal swab | No treatment | Miscarriage of both twins at 21 weeks | Pathology reports consistent with *C. glabrata* chorioamnionitis in both twins, but not cultured | Subsequent pregnancy |
started on Day 2. The patient’s temperature decreased and she improved both clinically and biochemically with a response in her CRP levels. At Day 11, despite 9 days of appropriate antifungal therapy, the patient developed vaginal spotting. Speculum examination revealed a fully dilated cervical os and fetal head at station −1 in the vagina. This progressed to a spontaneous miscarriage of the leading twin. The couple requested to continue expectant management for the second twin; the cord of the first twin was thus tied off and the placenta was left in situ. At Day 13, recrudescence of fever occurred, accompanied by miscarriage of the second twin and both placentas.

OUTCOME AND FOLLOW-UP

Postdelivery, intravenous amphotericin B was switched to intravenous anidulafungin to reduce the risk of nephrotoxicity. Our patient improved clinically and her TW and CRP counts rapidly normalised. She completed a 2-week course of intravenous antifungals from her first negative blood culture.

DISCUSSION

C. glabrata is generally considered to be an innocuous vaginal commensal and rarely associated with pathogenicity in healthy, non-immunocompromised individuals. This reduced virulence is mainly due to the inability of C. glabrata to produce hyphae and its less adhesive capacity, thereby reducing its capability to invade across intact chorionic membranes. C. glabrata chorioamnionitis is a rare entity; in a 2015 review, only 20 cases were identified in the literature.3 There is, however, a strong link between C. glabrata chorioamnionitis and IVF and invasive uterine instrumentation,2 supporting a possible iatrogenic mechanism of pathogenesis, in which C. glabrata chorioamnionitis and subsequently sepsis are facilitated by direct uterine inoculation via antenatal instrumentation. Given the association with IVF, most reported cases of C. glabrata chorioamnionitis have involved twin pregnancies.2,3 To identify all previously reported cases in the medical literature of C. glabrata chorioamnionitis in twin pregnancies, we searched (without language restrictions) the following computerised databases using the terms ‘Candida’, ‘Torulopsis’, ‘glabrata’, ‘chorioamnionitis’, ‘congenital’, ‘perinatal’ and ‘infection’: MEDLINE and PubMed from January 1980 to December 2021. After excluding all cases involving singleton pregnancies, our search strategy identified 10 papers included by abstract evaluation. Of the 10 papers identified, some included two case reports, and the number of cases eventually analysed was 12 (including the case reported in our institution). Cases were reported between 1997 and 2021 (table 1).4–12

Notably, almost all cases occurred in the second trimester, suggesting a possible latent incubation phase between antenatal instrumentation and presentation of frank infection.4 Our case presented at 17+4 weeks, which posed a therapeutic dilemma in management at the point of presentation—to advocate for termination of pregnancy given the significant fetal mortality for presumed fungal chorioamnionitis, or to continue treating the presumptive chorioamnionitis by administering systemic maternal antifungal treatment with their attendant potential drug toxicities, till fetal viability could be attained.4,4

In the case of C. glabrata chorioamnionitis, administering systemic maternal antifungal treatment is a non-trivial undertaking, as the optimal choice and duration of antenatal antifungal therapy for this unusual organism is yet to be clearly defined. Fetal considerations also further complicate antimicrobial choice. As C. glabrata commonly exhibits inherent resistance to azoles such as fluconazole, higher doses are required for effective treatment. However, high doses of azoles in pregnancy (400–600 mg/day) are contraindicated due to potential fetotoxicity (FDA Category D).13 The echinocandin class of antifungals which include anidulafungin have limited human data regarding safety in pregnancy, with teratogenic effects reported in animal studies (FDA Category C).13 Polynenes such as amphotericin B are generally considered the safest for the treatment of C. glabrata sepsis in pregnancy (Category B).14 However, use of amphotericin B is associated with significant side effects such as nephrotoxicity and electrolyte imbalances.15 In our review of the literature, 50.0% (6/12) of the cases received systemic maternal antifungal treatment,14 16 with the majority treated with amphotericin B.4–6 Maternal candidaemia, such as occurred in our case, was an additional indication for systemic antifungal treatment. The majority of cases with maternal candidaemia were treated with amphotericin B4–6 as well. In the two cases of untreated maternal candidaemia, candidaemia occurred shortly before or just after delivery.10,11 No cases of maternal mortality were reported.

Unfortunately, C. glabrata chorioamnionitis remains associated with poor fetal outcomes and substantial fetal mortality. In the literature, only one-third (4/12) of cases had successful outcomes, with equal numbers in both treated and untreated groups.4,7,10,11 In both cases that reported fetal survival post-treatment with systemic maternal antifungal treatment, caesarean delivery was performed soon after diagnosis at 287 and 29 weeks. One case was successfully treated with amphotericin B4 and the other with fluconazole.6 Furthermore, in both cases, C. glabrata was only isolated in amniocentesis fluid from a solitary fetus but not the other,4 suggesting a potential association between survival and lower burden of disease. Unfortunately, in our case, amniocentesis could not be performed for prognostication due to presentation with PROM resulting in oligohydramnios of the presenting twin. The extensive burden of fungal infection was only confirmed on histopathological examination after miscarriage.

Notably, cases with fetal survival generally presented at a more advanced stage of pregnancy (24–34 weeks).4,7,10,11 In our case, despite continuation of systemic maternal antifungals for ≥1 week and clearance of fungemia in maternal blood cultures, septic miscarriage of both twins still occurred. This may be attributed to presentation at an earlier phase of gestation, as well as extensive burden of fungal infection. Histopathological examination revealed evidence of acute chorioamnionitis and funisitis in both twins, with growth of C. glabrata. In the literature, either histopathological evidence of chorioamnionitis or growth of C. glabrata was reported in both twins in a majority (8/12) of cases.6–12 Our case was one of only two in the literature that reported both histopathological evidence of chorioamnionitis as well as retrieval of the causative organism (C. glabrata) from both twins.6

Screening and treatment of Candida infection prior to embryo transfer and during antenatal visits may be considered for IVF pregnancies,4 given the association with C. glabrata infections and the high financial and emotional cost of losing an IVF pregnancy. This should be undertaken on an individualised basis considering patient factors, extent of infection as well as risks associated with antifungal therapy. Women with C. glabrata chorioamnionitis should be managed by a multidisciplinary team to determine the optimal dose regime of antifungals and advise on timing of delivery. Even with early recognition and institution of appropriate antifungals, our case highlights the high fetal

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mortality associated with this uncommon infection, especially during the previable period. In our case, despite institution of treatment, fetal mortality was likely inevitable given presentation in an earlier phase of gestation, as well as an extensive burden of fungal infection.

Case report

In pregnancies involving in vitro fertilisation (IVF) or invasive antenatal procedures, a low threshold for suspicion of Candida infection should be considered. Routine screening for Candida infection may be considered for IVF pregnancies, given the high emotional and financial cost of losing an IVF pregnancy.

Candida glabrata infections in pregnancy pose a unique challenge to treatment, as higher azole doses are typically required for effective treatment due to inherent resistance, yet high doses of azoles are also contraindicated in pregnancy due to potential fetotoxicity. Amphotericin B has the best safety profile among antifungals, but its efficacy for improving fetal outcomes is not proven.

A multidisciplinary approach is crucial in the management of C. glabrata infections in pregnancy to determine the optimal dose and duration of antifungals, as well as the timing of delivery. Careful counselling and monitoring are particularly important in cases of systemic Candida, where prolongation of the pregnancy should not come at the expense of worsening maternal sepsis.

C. glabrata chorioamnionitis is associated with poor fetal outcomes and substantial fetal mortality, particularly with infection at early gestation. In this case of C. glabrata chorioamnionitis in a twin pregnancy, fetal mortality was likely inevitable despite treatment, given presentation earlier in gestation as well as extensive fungal infection that was only diagnosed on histopathological examination subsequent to miscarriage.

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Learning points

► In pregnancies involving in vitro fertilisation (IVF) or invasive antenatal procedures, a low threshold for suspicion of Candida infection should be considered. Routine screening for Candida infection may be considered for IVF pregnancies, given the high emotional and financial cost of losing an IVF pregnancy.

► Candida glabrata infections in pregnancy pose a unique challenge to treatment, as higher azole doses are typically required for effective treatment due to inherent resistance, yet high doses of azoles are also contraindicated in pregnancy due to potential fetotoxicity. Amphotericin B has the best safety profile among antifungals, but its efficacy for improving fetal outcomes is not proven.

► A multidisciplinary approach is crucial in the management of C. glabrata infections in pregnancy to determine the optimal dose and duration of antifungals, as well as the timing of delivery. Careful counselling and monitoring are particularly important in cases of systemic Candida, where prolongation of the pregnancy should not come at the expense of worsening maternal sepsis.

► C. glabrata chorioamnionitis is associated with poor fetal outcomes and substantial fetal mortality, particularly with infection at early gestation. In this case of C. glabrata chorioamnionitis in a twin pregnancy, fetal mortality was likely inevitable despite treatment, given presentation earlier in gestation as well as extensive fungal infection that was only diagnosed on histopathological examination subsequent to miscarriage.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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