Candida glabrata infection of the amniotic fluid with chorioamnionitis and maternal candidemia and a negative 1,3-β-D-glucan test: A case report

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A B S T R A C T

A case is reported of *Candida glabrata* microbial invasion of the amniotic cavity and maternal candidemia with a negative 1,3-β-D-glucan test. A 28-year-old singleton pregnant woman (gravida 1, para 0) presented at 18 weeks and 3 days of gestation following *in vitro* fertilization and embryo transfer. She had suddenly experienced uterine contraction and genital bleeding with watery discharge and. After diagnosing preterm rupture of the membrane with clinical chorioamnionitis, *Candida glabrata* was detected both in the amniotic fluid and in the vaginal discharge; however, a test for 1,3-β-D-glucan in the maternal serum was negative. At 18 weeks and 5 days of gestation, the pregnancy was terminated after intensive counseling. On the eighth day of admission, *Candida glabrata* was detected in maternal blood culture. When a culture of amniotic fluid is positive for *Candida glabrata*, even if the 1,3-β-D-glucan test is negative, maternal candidemia should be suspected in the presence of features of clinical chorioamnionitis.

1. Introduction

Microbial invasion of the amniotic cavity (MIAC) is one of the causes of chorioamnionitis and preterm birth. *Mycoplasma*, *Ureaplasma*, *Gardnerella vaginalis*, and *Fusobacteria* species are well known causative organisms of MIAC [1]. In contrast, *Candida* species are unusual causes of MIAC although they are frequently detected in the vagina of pregnant women [2]. Chorioamnionitis caused by *Candida* species can lead to preterm delivery and other adverse perinatal outcomes [2].

Candidemia during pregnancy, especially infection by *Candida glabrata*, is extremely unusual [3–5]. The risk factors for candidemia by *Candida glabrata* infection include diabetes mellitus, malignancies, hematopoietic stem cell transplantation, pharmacotherapy with azole compounds, and advanced age [6]. In fact, most pregnant women do not have these risk factors.

The test to detect serum 1,3-β-D-glucan is usually performed when candidemia is suspected [7]. If a pregnant women woman manifests clinical chorioamnionitis with fever and amniotic infection with *Candida* species, the test for serum 1,3-β-D-glucan is considered. It was reported that the positive predictive value (PPV) of 1,3-β-D-glucan test for invasive fungal infections is low (51.9%), and the negative predictive value (NPV) is high (97.8%) [8]. The test of serum 1,3-β-D-glucan is very useful to exclude the possibility of candidemia because of its high NPV.

However, there is no report of a negative 1,3-β-D-glucan test in a case of *Candida* MIAC with clinical chorioamnionitis.

This report concerns a case of *Candida glabrata* MIAC, clinical chorioamnionitis, and maternal candidemia, even though the 1,3-β-D-glucan test was negative.

2. Case Presentation

A 28-year-old woman (gravida 1, para 0) with a singleton pregnancy, who had conceived through *in vitro* fertilization and embryo transfer (IVF-ET), was referred to hospital at 10 weeks of gestation. No prior chorionic villous sampling and amniocentesis was performed for a fetal chromosomal test during her pregnancy. The pregnancy was uneventful until, at 18 weeks and 3 days of gestation, she attended hospital with sudden uterine contraction and genital bleeding with watery discharge. Speculum examination showed watery discharge with a small amount of blood. Because the test for monoclonal antibodies against insulin-like growth factor-binding protein 1 was positive, premature rupture of the membrane was suspected. Moreover, the patient was diagnosed with clinical chorioamnionitis because she had a temperature over 38 °C, tachycardia, and uterine tenderness. Initial treatment with intravenous ampicillin and gentamicin was empirically started for clinical chorioamnionitis. Amniocentesis was performed to identify the cause of

Table 1
Blood results on day 1 of admission.

Parameters	Results
White blood cell count (/μl)	11,600
Hemoglobin (g/dl)	12.0
Platelet (10^4/μl)	28.4
C reactive protein (mg/dl)	4.1
Procalcitonin (ng/ml)	0.05
Aspartate aminotransferase (IU/l)	14
Alanine aminotransferase (IU/l)	10
Creatinine (mg/dl)	0.46

Table 2
Results of amniocentesis on day 1 of admission.

Parameters	Results
Gram stain smear	Yeast
Anaerobic culture	*Candida glabrata*
Glucose (mg/dl)	19
Total cell count (/μl)	1964
Mononucleocytes (/μl)	440
Polymorphonuclear granulocytes (/μl)	1524
Red blood cells (/μl)	3

clinical chorioamnionitis. Blood and vaginal discharge cultures were also examined. Early premature rupture of the membrane was diagnosed because of the blue-green vaginal discharge subsequent to the injection of indigo carmine into the amniotic fluid at amniocentesis.

Initial blood investigations revealed an elevated white blood cell count and C-reactive protein level, and amniotic fluid showed numerous inflammatory cells (Tables 1 and 2). Cultures of both the amniotic fluid and the vaginal discharge showed the presence of *Candida glabrata*. The patient's temperature persisted over 38 °C. However, a blood test for 1,3-β-D-glucan was negative (3.3 pg/mL) on the second day of admission. Candidemia was not suspected as a cause of maternal infection at this point.

The woman and her husband decided on termination of pregnancy after intensive counseling. The fever resolved immediately after delivery at 18 weeks and 5 days of gestation. Because on the eighth day of admission, *Candida glabrata* was detected in the blood culture from the first admission (sensitive to fluconazole, minimal inhibitory concentration of ≤0.125 μg/mL), the patient was re-admitted. Despite the absence of fever, uterine tenderness, elevated inflammatory markers in the blood, and systemic candidiasis (especially candida endophthalmitis), intravenous fluconazole was administered.

Chorioamnionitis was confirmed by histological examination of the placenta, although there was no evidence of funisitis. According to the criteria proposed by Redline et al. [9], maternal inflammatory response (stage II, grade I) and fetal inflammatory response (stage I, grade I) were noted. *Candida spp.* was identified by Grocott-Gomori methenamine silver stain on the chorion (Fig. 1).

3. Discussion

This report concerns a case of MIAC caused by *Candida glabrata* along with chorioamnionitis and maternal candidemia with a negative 1,3-β-D-glucan test. The patient had *Candida glabrata* MIAC and clinical chorioamnionitis with maternal candidemia. There are several reports of chorioamnionitis, MIAC, and maternal sepsis caused by *Candida* species [2–5,10–12]. Maki et al. [2] reported that 20–65% of cases of chorioamnionitis with *Candida* species were associated with IVF-ET. In the present case, the patient underwent IVF-ET; however, the association of perinatal *Candida* species infection with IVF-ET remains unknown.

In the present case, amniocentesis, maternal blood culture, and vaginal discharge culture at the time of the diagnosis of clinical chorioamnionitis and preterm rupture of the membrane were performed. Appropriate timing of blood culture led to the diagnosis of maternal candidemia caused by *Candida glabrata*. The mortality rate of patients with candidemia in intensive care units and tertiary care centers has been reported to be 37–38% in Europe [13]. However, there are no detailed data on the mortality and morbidity rates of low-risk pregnant women with candidemia. Urgent detailed examinations, including amniocentesis, might be useful to prevent the diagnosis of candidemia and other serious infections being missed in patients with chorioamnionitis during early gestation.

The patient reported here had a negative 1,3-β-D-glucan test. As mentioned, the PPV of the 1,3-β-D-glucan test for invasive fungal infections is low and the NPV is high (51.9% and 97.8%, respectively) [8]. Previous reports [3–5] have said that the results of blood culture were obtained two or three days after sampling. In this case, the results of blood culture were available eight days after admission. The probable cause of the false-negative result of the 1,3-β-D-glucan test in this case was that the load of *Candida glabrata* in the blood was low. Thus, caution is required in interpreting false-negative 1,3-β-D-glucan test results until the final blood culture report is available.

This report presents a case of *Candida glabrata* MIAC, clinical chorioamnionitis, and maternal candidemia with a negative 1,3-β-D-glucan test result. Amniocentesis, maternal blood, and vaginal discharge culture at the time of the diagnosis of clinical chorioamnionitis are important for the diagnosis of *Candida* species causing MIAC and maternal candidemia. The serum test for 1,3-β-D-glucan is useful for differentiating fungal species causing infections, including *Candida* species, when candidaemia is suspected. However, there is a possibility of maternal candidemia even when the 1,3-β-D-glucan test is negative.

Contributors

Michihisa Shiro drafted, reviewed and edited the manuscript, and provided patient care.

Ryo Yamamoto reviewed and edited the manuscript, and provided patient care.

Kaori Moriuchi reviewed and edited the manuscript, and provided patient care.
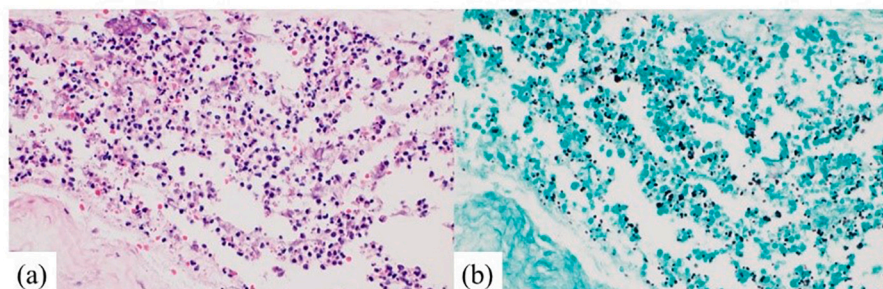

Fig. 1. Histopathological picture showing chorion in the placenta. (a) Neutrophilic infiltration in the chorion (hematoxylin and eosin stain). (b) Spores, suggested as *Candida spp.*, detected by Grocott-Gomori Methenamine Silver stain.

Keisuke Ishii drafted, reviewed and edited the manuscript.
All authors approved the final submitted manuscript.

Patient consent

Obtained.

Provenance and peer review

This article was not commissioned and was peer reviewed.

Conflict of interest statement

The authors declare that they have no conflict of interest regarding the publication of this case report.

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