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Amniotic fluid sludge – a marker of intra-amniotic infection and histological chorioamnionitis in cervical insufficiency

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ABSTRACT

Amniotic fluid sludge is an ultrasound demonstrable hyperechogenic mass close to the uterine cervix and is an independent risk factor for preterm birth and preterm premature rupture of membranes. Cervical insufficiency represents cervical dilatation in the mid-trimester of pregnancy regardless of uterine contractions. It appears to be associated with intraamniotic infection/inflammation. Chorioamnionitis is the inflammation of the fetal membranes (chorion and amnios) and is the consequence of the inflammatory response of the maternal organism to aggression that can be infectious or non-infectious (sterile intraamniotic inflammation). The paper illustrates the association between the amniotic fluid sludge and microbial invasion of the amniotic cavity and chorioamnionitis.
Conclusion. Amniotic fluid sludge is a marker of intra-amniotic infection and histological chorioamnionitis in pregnant women with cervical insufficiency.

Keywords: amniotic fluid sludge, cervical insufficiency, chorioamnionitis, intra-amniotic infection

INTRODUCTION

Premature birth, birth before 37 weeks of pregnancy, is one of the main causes of perinatal mortality in developed countries, with an incidence between 7.6% and 12%, while in underdeveloped countries the incidence of premature births is > 15% of total births. The etiopathogenesis of premature birth is multifactorial. The main etiological factor is of infectious origin, a problem throughout pregnancy [1,2]. The most often isolated infectious agents are Ureaplasma spp., Mycoplasma spp., from the lower genital tract; they invade the amnios and chorion, causing the appearance of chorioamnionitis and intra-amniotic infection [1,2]. Microbiological studies have shown that intra-amniotic infection is responsible for 25% to 40% of preterm births, although this percentage is underestimated in terms of the conventional bacterial detection methods used. Intra-amniotic infection is most often polymicrobial [2]. Intra-amniotic inflammation following infection is associated with premature birth, it can lead to acute histological chorioamnionitis and funisitis [3]. Cervical insufficiency is a risk factor associated with premature birth. 8-52% of patients with cervical insufficiency have associated intra-amniotic infection, and 81% have associated intra-amniotic inflammation [2,3].

AIM

The article aims to bring to the foreground the importance of diagnosing intra-amniotic infection/

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inflammation in second trimester pregnancies in order to improve the maternal-fetal prognosis.

CASE PRESENTATION

A 27-year old woman, gravida 2, primipara was referred for a routine pregnancy survey at 24 1/7 gestational weeks. The patient had a previous history of spontaneous abortion at 19 weeks of gestation one year ago (preterm premature rupture of membranes). Clinical exam revealed: shortened cervix, 2 cm dilated with bulging membranes. Transvaginal ultrasound confirmed cervical length 3,4 cm, chorioamnionitis membranes bulging to the external cervical os, amniotic fluid sludge is present. (figure 1A) The scan for fetal morphology was normal.

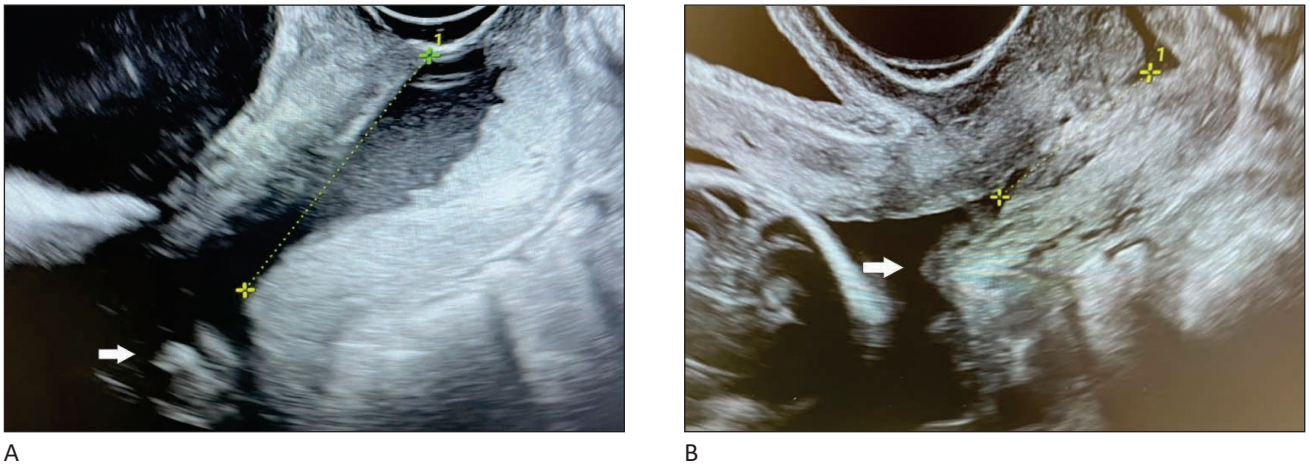
The patient was admitted for suspected preterm labor. Upon admission, she was in good general condition: afebrile, heart rate 83 bpm, and blood pressure 125/69 mmHg. She denied leakage of fluid, bleeding, or contractions (also confirmed by tocodynamometry). The local exam proved the same. The following labs were ordered at admission and during the hospital stay: complete blood count, coagulation panel, C-reactive protein. All the microbiological exams were negative during the hospital stay (genital cultures for Mycoplasma hominis and genitalium, Ureaplasma Urealyticum and Parvum using a multiplex-tandem polymerase chain reaction (MT-PCR) for the amplification of targeted DNA and RNA). The patient received triple antibiotic therapy (Ceftriaxone 1g iv every 12h, Clarithromycin 500 mg oral every 12h, Metronidazole 500mg iv every 12h) for 11 days, antenatal corticosteroids (Dexamethasone 6mg/12h for 48h). In the following days (on the fifth day of treatment and 12th day of hospitalization), the external cervical os was closed, the membranes didn't bulge, and the inflammatory tests were normal (figure 1B).

The patient remained hospitalized for monitoring. At 26 6/7 gestational weeks, progressive effacement, dilatation of the cervix, and spontaneous rupture of membranes happened in the absence of uterine contractions either clinically or on NST, and increased C-reactive protein. After 12 hours, spontaneous labor started. The patient delivered a male infant, weighing 1,000 g, with Apgar 5,7 (at 1 and 5 min). The maternal postpartum evolution was normal, as she was discharged four days postpartum. The immediate neonatal course was complicated with severe sepsis. He was intubated and received antibiotic therapy. The neonate course was unfavorable and hospitalization lasted for more than nine weeks. Histopathological examination of the placenta revealed severe acute necrotizing chorioamnionitis stage III, grade II (figure2).

DISCUSSION

According to the literature, an important percentage of patients with intraamniotic inflammation will remain undiagnosed from a microbiological point of view [1]. In this patient's case, standard cultivation methods and molecular biology tests (MT-PCR detection) did not reveal any infectious agent.

Considering that the most common way of microbial invasion is the ascending one, we can classify the case in the category of those with sterile intra-amniotic inflammation [3]. Oh et al. reported a percentage of 81% of patients with cervical insufficiency associated with intra-amniotic inflammation, revealed by amniocentesis, thus emphasizing the importance of performing this investigation [4]. Amniocentesis can reveal the presence of an infectious agent in the amniotic fluid or inflammatory mediators. The importance of this maneuver resides from the unfavorable prognosis of inflamma-



A B

FIGURE 1. Transvaginal ultrasound: (A) at 24 1/7 gestational age cervix length 34mm, open on its entire length, with protrusion of the amniotic sac into the vagina, antero-posterior diameter 25 mm, sludge. (B) at at 25 5/7 gestational age scan reveals closed cervix 21mm, presence of sludge in the same amount at the level of the internal cervical orifice

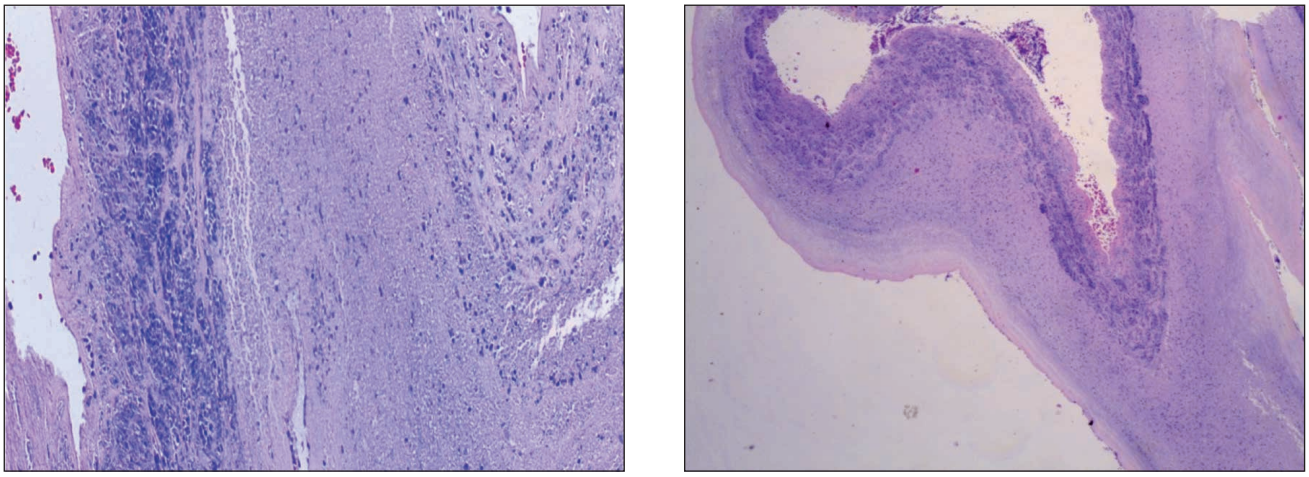


FIGURE 2. Histopathological examination of the placenta reveals mature, vascularized, slightly hyperplasic chorionic villi, fibrinoid deposition and rare dystrophic microcalcifications; amniotic membranes with abundant acute inflammatory infiltrate with extensive necrobiosis; edematous diagnosis of severe acute necrotizing chorioamnionitis stage III, grade II

tion/infection – in 50% of cases the birth took place in less than seven days. The same authors reported that 95% of patients with intra-amniotic inflammation and negative cultures gave birth prematurely and associated a perinatal mortality rate of 63% [4]. A diagnostic protocol is needed to perform amniocentesis to determine the microbial status of the amniotic cavity when an ultrasound scan reveals shortened cervix and sludge in asymptomatic patients [5]. At the same time, the investigation is useful in the case of patients who are candidates for cervical cerclage.

According to studies, there is a strong association between the presence of sludge and the microbial invasion of the amniotic cavity with premature birth and histological chorioamnionitis [6]. Prolonged exposure to the infectious agent is associated with an intense inflammatory response and probably the combination between proinflammatory cells and microorganism leads to sludge formation. In many of the cases with intra-amniotic infection – sludge association, the presence of biofilms was also detected. Thus organized, the microorganisms acquire resistance to antimicrobial agents and to host's defense reactions [6]. The lack of sludge visualization at a second time does not necessarily correlate with its disappearance, because there are situations in which the result may be false-negative. The presented case associated the presence of sludge with cervical insufficiency and histological chorioamnionitis. This association has been also reported in several recent scientific papers [7,8,9].

A particularity of the case is represented by spontaneous abortion in the patient's pathological antecedents. According to literature, patients with a history of miscarriage or premature birth are at increased risk of chronic endometritis [8,9].

As regards the treatment in patients with intra-amniotic infection and/or intra-amniotic inflammation associated with cervical insufficiency, this is considered largely ineffective, most often the birth being imminent [4]. In the case of the presented patient, the clinical diagnosis corroborated with the ultrasound examination (the presence of sludge) suggested, from the very beginning, a reserved prognosis regarding the prolongation of the gestation period. It was decided to combine three antibiotics (Ceftriaxone, Clarithromycin, Metronidazole) which led to the prolongation of the gestation period from 24 to 27 weeks. Yeo et al. described in their study similar cases that associate cervical insufficiency with intra-amniotic infection/inflammation, which were treated with the same treatment scheme [7]. In our situation, it is not possible to discuss with certainty the absence of intra-amniotic infection because the amniotic fluid was not analyzed either before or after the initiation of treatment. The following aspects were considered when choosing the therapeutic scheme: Ureaplasma spp. is the most common microorganism detected in amniotic fluid and placenta, in women with chorioamnionitis, funisitis, and premature birth and can cause chronic, asymptomatic intrauterine infections and can modulate the host's immune response leading to delaying the initiation of antibiotic treatment, thus increasing the risk of maternal-fetal complications [1]. Moreover, studies have shown that Clarithromycin has to be more effective in eradicating intra-amniotic infections, not only those caused by Ureaplasma spp., by high transplacental bioavailability and by modulating the intensity of the inflammatory intra-amniotic response in patients with premature rupture of membranes and in those with intra-amniotic infection/inflammation [2]. The mechanism by which antibiotics act on intra-amniotic inflammation has not been fully elucidated [7]. Positive results may also occur due to the therapeutic success of antibiotic treatment on microorgan-

isms that are not detected in routine tests [10,11]. The only marker that can support a diagnosis of intra-amniotic infection/inflammation is the evolution in the dynamics of PCR value after antibiotic treatment, in the sense of its normalization and maintaining a period within normal limits in the absence of treatment.

CONCLUSIONS

Monitoring these cases is difficult because they require complex modalities of microbiological diagnosis, and the presence of amniotic sludge is equivalent to a marker of intra-amniotic infection and chorionic-amniotic infection, and even possible amniotic fluid in patients with cervical insufficiency. Amniotic sludge must be reported after ultrasound examination and considered in establishing therapeutic management in such cases.

The cases that associate inflammation/intra-amniotic infection and cervical insufficiency have a reserved prognosis. Thus, in these cases, it is useful to perform amniocentesis to establish a correct and complete microbiological diagnosis. The lack of this investigation represents one of the major limitations in the management of the presented case.

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