Congenital brucellosis: a case report

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Research Article

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Abstract

Background

Brucellosis is the most common zoonotic infection worldwide, and is caused by bacterial genus Brucella. The disease is rarely transmitted via human-to-human transmission. Few cases have been reported about vertical transmission of human brucellosis. Herein, we reported a case of congenital brucellosis, with clear evidence of pathogen detected in mother's placental specimen.

Case presentation:

A 34-day-old girl was admitted to the department of pulmonology with fever for eight days. Three blood samples and one sample of cerebrospinal fluid were positive for *Brucella melitensis*. The diagnosis of brucellosis and *Brucella melitensis* meningitis were established, along with hyperbilirubinemia and liver dysfunction. Treatment of rifampicin (for six weeks) and meropenem (for two weeks) was administered. However, the disease relapsed within 18 days. Thereafter, a combination therapy of rifampicin and SMZ/TMP was administered for eight weeks. The disease relapsed again in 42 days. For chronic brucellosis, three courses of combination therapy of rifampicin and SMZ/TMP was administered. The mother had fatigue and arthralgia for two weeks, fever and membrane rupture one day before the baby was born. *Brucella melitensis* DNA was detected in the mother's placental specimen by next-generation sequencing and bacterial identification under microscope proved chorioamnionitis.

Conclusions

We reported a confirmed case of congenital brucellosis. This disease should be closely monitored even in non-epidemic areas. The treatment of brucellosis in infancy faces challenges of drug choice and disease relapse.

Introduction

Brucellosis is the most common zoonotic infection worldwide, and is caused by bacterial genus Brucella [1]. There are half a million new cases annually in some countries [2]. Zhejiang is not an endemic province, and no infection has occurred during 1983–2003. However, rare cases occurred after 2003. Symptoms of brucellosis are fever, arthralgia or arthritis, night sweats, asthenia, insomnia, anorexia and headache. Physical examination reveals hepatomegaly and splenomegaly, lymphadenopathy, osteoarticular manifestations, genitourinary complications, neurological findings, mucocutaneous manifestations, and pulmonary manifestations. The disease is transmitted via consumption of unpasteurized dairy products, direct contact with infected animals, inhalation of contaminated aerosols, and rarely human-to-human transmission [3]. Although intrauterine transmission, transmission during delivery, and transmission through breast milk are among the main routes of transmission in the

mammalian reservoirs, few cases have been reported about vertical transmission of human brucellosis [4–6]. Herein, a congenital brucellosis case was reported. This helps to provide a scientific basis for the prevention and control of brucellosis in pregnant women and their newborn babies.

Case Presentation

A 34-day-old girl was admitted to the department of pulmonology with fever from day 26. The peak body temperature was 37.6–37.7°C. She was born to a Chinese 25-year-old G1P0 at 37 weeks 4 days' gestation (3300 g birth weight without resuscitation). Her mother had visited and stayed for several periods in her parents' house, where 20 sheep were once kept. Although she had never fed or touched those sheep, the mother had fatigue and arthralgia for two weeks, fever and membrane rupture one day before the baby was born. Considering that the mother might have been experiencing chorioamnionitis, which was later confirmed by pathology, the baby was delivered by cesarean section. The baby was fed with mother's milk for four days until the mother's blood culture revealed a positive result of brucellosis. The mother was immediately started on six weeks' course of rifampicin and doxycycline. A screening of Rose Bengal plate test among her family showed that the mother's father was also positive and symptomatic, while other family members were negative. The grandfather had fatigue, arthralgia and low grade fever for four months, but did not seek medical help. He had killed and sold all the sheep because of his fatigue and arthralgia before the baby was born.

The baby's father took her to the pediatric department at another hospital on the third day of fever, where acute upper respiratory tract infection was diagnosed and she was observed for one night. Blood samples were obtained for blood culture and Rose Bengal plate test. The baby's body temperature returned to normal on the second day, so she was discharged. However, fever returned after three days of normal body temperature. This time, she was agitated and often cried. She had a peak body temperature of 37.7°C, once a day. Her father immediately brought her to our hospital. She was admitted to the department of pulmonology after a short examination at the outpatient clinic, without any laboratory test or therapy. On physical examination, the girl was febrile (37.6°C), with heart rate 144 beats/minute, respiratory rate 34/min, blood pressure 74/43 mm Hg. She appeared acutely ill but nontoxic. Her oral mucosa was normal. Her lungs were clear in auscultation. Her abdomen was not distended. Liver and spleen were not palpable below the costal margin. Her joints were all normal. Findings of neurological and dermatological examinations were normal.

On the second day, the girl continued to have fever. The highest body temperature was 38.2°C. Moreover, she seemed lethargic. Bacterial meningitis was suspected and lumbar puncture was performed. The cerebrospinal fluid (CSF) contained 85 leukocytes/microliter (86% mononuclear cells), with a protein level of 102.6 milligram/deciliter and a glucose level of 40 milligram/deciliter. The local hospital reported positive blood culture for *Brucella melitensis* and positive Rose Bengal plate test. Culture of two samples of blood and one sample of CSF also showed positive for *Brucella melitensis* (Fig. 1). The diagnosis of brucellosis and *Brucella melitensis* meningitis were established, along with hyperbilirubinemia and liver dysfunction. Since sulfamethoxazole/trimethiprim (SMZ/TMP) is forbidden for use in children < 2

months according to its drug directions, we stared treatment of rifampicin (for six weeks) and meropenem (for two weeks). Her body temperature returned to normal within two days of treatment but reoccurred on day 18 after discontinuing rifampicin. Laboratory tests including positive blood culture with *Brucella melitensis*, positive Rose Bengal plate test, and > 1:400 in serum agglutination test (SAT) of brucellosis suggested relapse of brucellosis. A combination therapy of rifampicin and SMZ/TMP was immediately started for eight weeks. Her body temperature returned to normal on the third day. She was normal for 42 days after which she became febrile and had positive blood culture for *Brucella melitensis.* The disease lasted for more than six months altogether, suggesting chronic brucellosis. So three courses of combination therapy of rifampicin and SMZ/TMP for six weeks each with one week's interval were started. Her body temperature returned to normal from the second day of therapy. At present, she is 10 months old, and is in the third course of chronic brucellosis therapy (Fig. 2). In the later two relapses, she also had liver dysfunction. However, besides fever, she had no other sign or symptom. Her liver function reverted to normal in 1–2 weeks after therapy every time. Results of brain magnetic resonance imaging, electroencephalogram, ultrasonic sound of heart, liver, spleen, kidneys, uterus, ovaries were normal.

Brucella melitensis DNA was detected in mother's placental wax specimen by next-generation sequencing and bacterial identification under microscope (Fig. 3) suggested that this was a congenital brucellosis case.

Discussion And Conclusions

Before first acute brucellosis case in 1983, Zhejiang kept zero in incidence for about 20 years [7]. After that, incidence and prevalence of brucellosis in Zhejiang has been increasing slightly [7, 8]. The incidence was 0.18/100,000 in Zhejiang in 2015 [9]. There are many reasons for the increase. First, the prevalence of brucellosis in humans mainly depends on the epidemic situation in animals. Prevalence increased of brucellosis both in human and animals in northern China at the same period. Second, an increasing demand of meat and milk increased introduction of northern livestock and also the risk of people's exposure to contact with raw lamb or beef. Third, insufficient quarantine immunity may also increase the epidemic intensity of the disease in Zhejiang [7, 8].

Alsaif et al [10], systematically reviewed 44 cases of congenital brucellosis dating back to 1941. Among these cases, only one infant had cord blood bacteremia, which was clearly congenital. Other cases were diagnosed mainly based on positive blood culture from one day to 3.5 months, in which seven cases had mothers infected with brucellosis during pregnancy. [10]We described a case of congenital brucellosis with clear evidence of intrauterine transmission. In our case, positive blood culture in mother suggested the mother's infection. Positive blood and CSF culture, and serological results suggested baby's infection. There is a small chance that transmission also occurred from breast milk even though the infant was only breastfed for four days. However, chorioamnionitis, bacterial identification by microscopy and *Brucella melitensis* DNA detected in the mother's placental specimen established the diagnosis of congenital brucellosis. The incubation period of brucellosis is usually between 1–3 weeks. In our case, the baby had symptom onset on day 26.

The World Health Organization has not updated its recommended treatment regimens for brucellosis in more than 30 years [11]. The Ministry of Health of the People's Republic of China released a 2012 version of ‘Guidelines for diagnosis and treatment of brucellosis (Trial)’ in Chinese [12]. The clinical management of brucellosis is challenging because of high initial treatment failure and relapse rates [2]. The treatment failure and relapse rates range from 4.6–24% for the oral regimen and 5–8% for the oral/ parenteral regimen [2]. The independent predictors of relapse were temperatures of ≥ 38.3°C, positive blood cultures at baseline, and a duration of symptoms before treatments of < 10 days [13]. In this case, we had difficulty in choosing the antibiotics because of the patient's age. According to the Chinese version of guidelines [12], the recommended drugs are rifampicin plus SMZ/TMP for children aged six weeks and older. There is no guideline for children aged six weeks and younger. Moreover, SMZ/TMP is forbidden for use in children < 2 months according to its drug directions. The baby was only 34 days old. Moreover, she had positive skin tests to penicillin and cephalosporin. So in the first course, we chose rifampicin (for six weeks) and meropenem (for two weeks). Meropenem was previously used in some cases of brucellosis [14, 15]. In children, rifampicin monotherapy can be used but is not recommended, because it is associated with a high relapse rate [16]. The disease relapsed only 18 days after discontinuing rifampicin. Her parents were disappointed. She was three months old at that time. Extending the antibiotic treatment helps to prevent relapse [2]. So we administered rifampicin and SMZ/TMP for eight weeks for the second time. The disease relapsed again after 42 days. For chronic brucellosis, three courses of combination therapy of rifampicin and SMZ/TMP were administered.

In summary, we reported a confirmed case of congenital brucellosis. This disease should be closely monitored even in non-epidemic areas. The management of brucellosis in infancy faces the challenges of drug choice and disease relapse.

Declarations

Ethics approval and consent to participate

This research was conducted according to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Children’s Hospital, Zhejiang University School of Medicine (2020-IRB-152). No animal work was carried out as part of this study.

Consent for publication

Written informed consent to publish the patient’s information was obtained from the patient’s parent.

Availability of data and materials

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

DX designed the study and drafted the manuscript. XL, BC, YZ, MZ and WG collected the clinical data and participated in data analysis. YW and ZC coordinated all the work related to the study and revised the manuscript. All the authors read and approved the final manuscript.

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References

1. Hasanjani Roushan MR, Ebrahimpour S. Human brucellosis: An overview. *Caspian J Intern Med* 2015; **6**: 46–47.
2. Franco MP, Mulder M, Gilman RH, Smits HL. Human brucellosis. *Lancet Infect Dis* 2007; **7**: 775–86.
3. Hassouneh L, Quadri S, Pichilingue-Reto P, et al. An Outbreak of Brucellosis: An Adult and Pediatric Case Series. *Open Forum Infect Dis* 2019; **6**: ofz384.
4. Giannacopoulos I, Eliopoulou MI, Ziambaras T, Papanastasiou DA. Transplacentally transmitted congenital brucellosis due to Brucella abortus. *J Infect* 2002; **45**: 209–10.
5. Palanduz A, Palanduz S, Güler K, Güler N. Brucellosis in a mother and her young infant: probable transmission by breast milk. *Int J Infect Dis* 2000; **4**: 55–56.
6. Zhao M, Huang F, Zhang A, Zhang B, Zeng L, Xu J, et al. Congenital brucellosis in a Chinese preterm neonate: A case report. J Int Med Res. 2019;47(5):2296–301.

7. Xu W, Shi S, Yang Y, Jin X, Wang H. Epidemic situation and exploration of the prevention and control strategies on Brucellosis in Zhejiang Province. Chinese rural health service administration. 2007;27(3):209–11.
8. Yang H, Zhang S, Wang T, Zhao C, Zhang X, Hu J, et al. Epidemiological Characteristics and Spatiotemporal Trend Analysis of Human Brucellosis in China, 1950–2018. Int J Environ Res Public Health. 2020;17(7).
9. Shi X, Sun J, Ling F. Surveillance of human brucellosis in Zhejiang Province in 2015. Disease surveillance. 2017;32(3):203–5.
10. Alsaif M, Dabelah K, Girim H, Featherstone R, Robinson JL. Congenital Brucellosis: A Systematic Review of the Literature. *Vector Borne Zoonotic Dis* 2018; **18**: 393–403.
11. Joint FAO/WHO expert committee on brucellosis. *World Health Organ Tech Rep Ser* 1986; **740**: 1–132.
12. Ministry of Health of the People's Republic of China. Guidelines for diagnosis and treatment of brucellosis (Trial). *Infectious disease information* 2012; **25**: 323–24,359.
13. Solera J, Martínez-Alfaro E, Espinosa A, Castillejos ML, Geijo P, Rodríguez-Zapata M. Multivariate model for predicting relapse in human brucellosis. *J Infect* 1998; **36**: 85–92.
14. Ay N, Kaya S, Anil M, et al. Pulmonary Involvement in Brucellosis, a Rare Complication of Renal Transplant: Case Report and Brief Review. Exp Clin Transplant. 2018. 16(6): 757–760.
15. Mohzari YA, Alshuraim RA, Asdaq S, et al. Congenital brucellosis: A case report. J Int Med Res. 2020. 48(12): 300060520975576.
16. Khuri-Bulos NA, Daoud AH, Azab SM. Treatment of childhood brucellosis: results of a prospective trial on 113 children. *Pediatr Infect Dis J* 1993; **12**: 377–81.

Figures

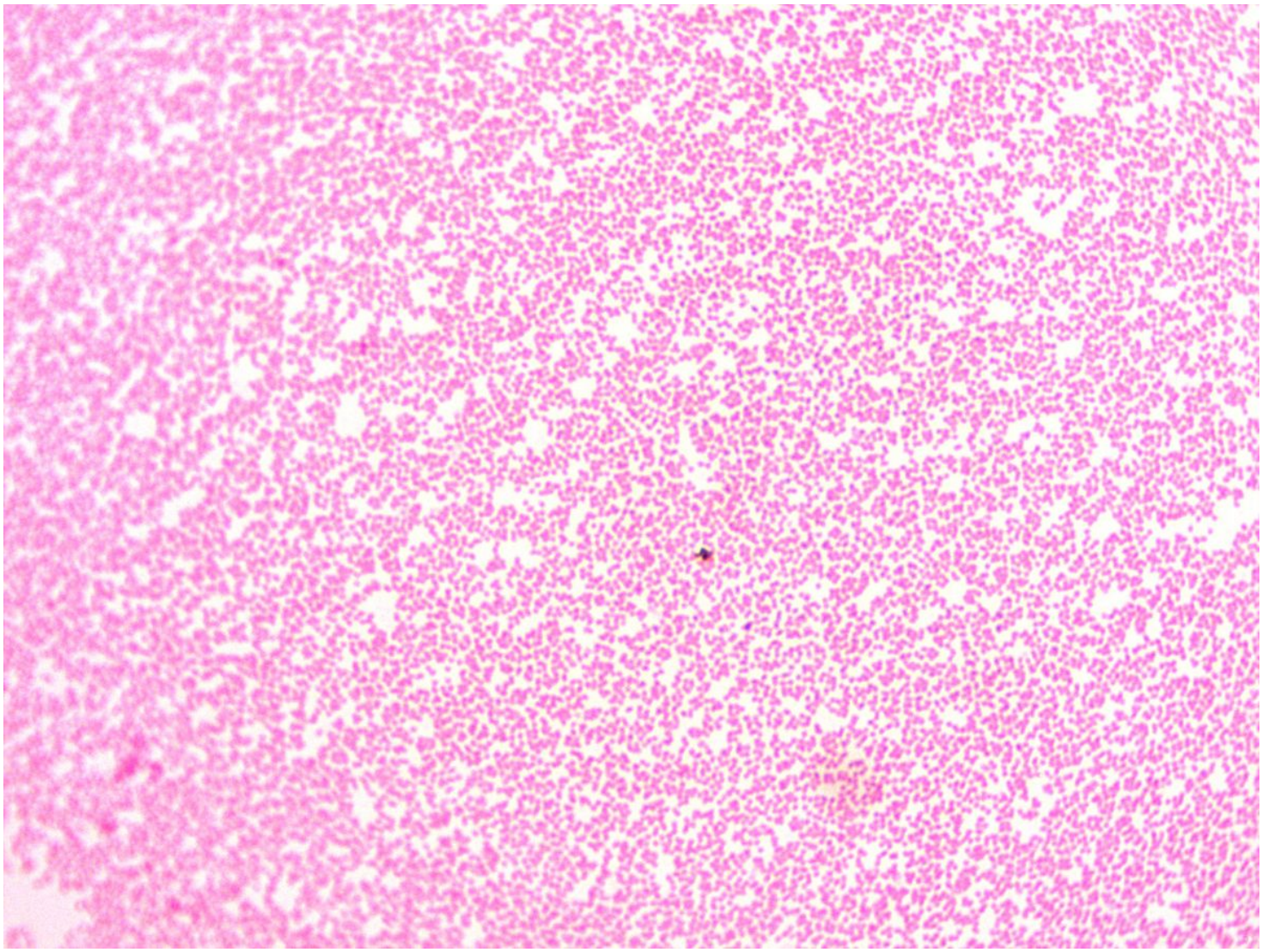

Figure 1

Blood culture showed positive for Brucella melitensis (Gram stain, × 1000).

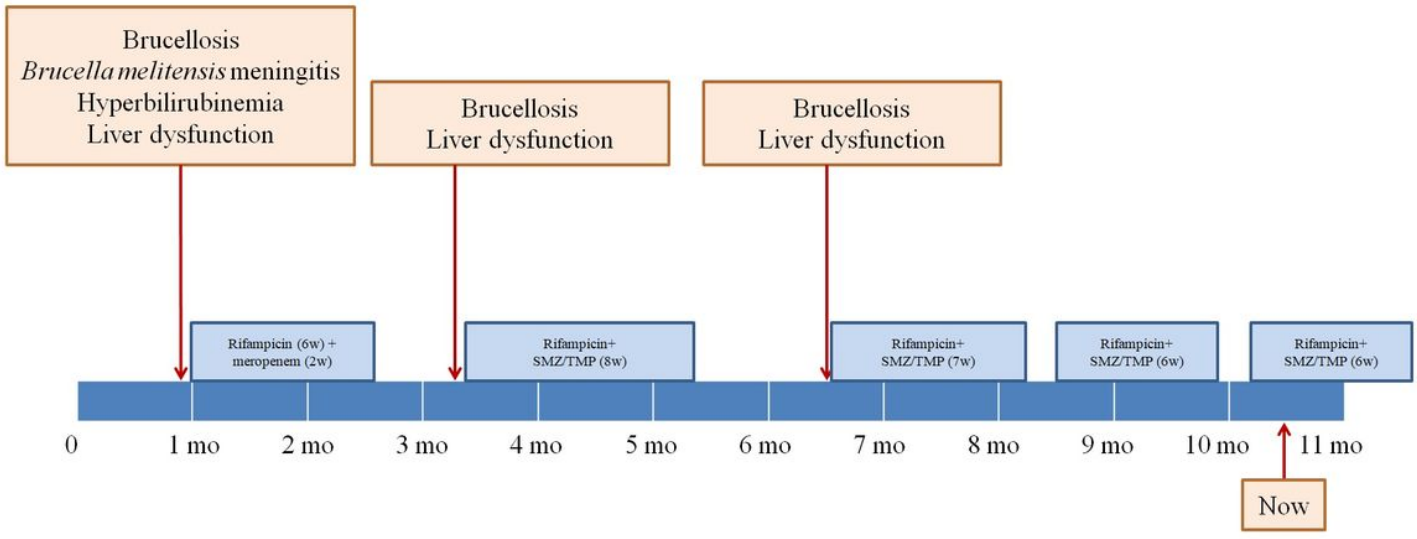

Figure 2

The timelines of diagnosis and management.

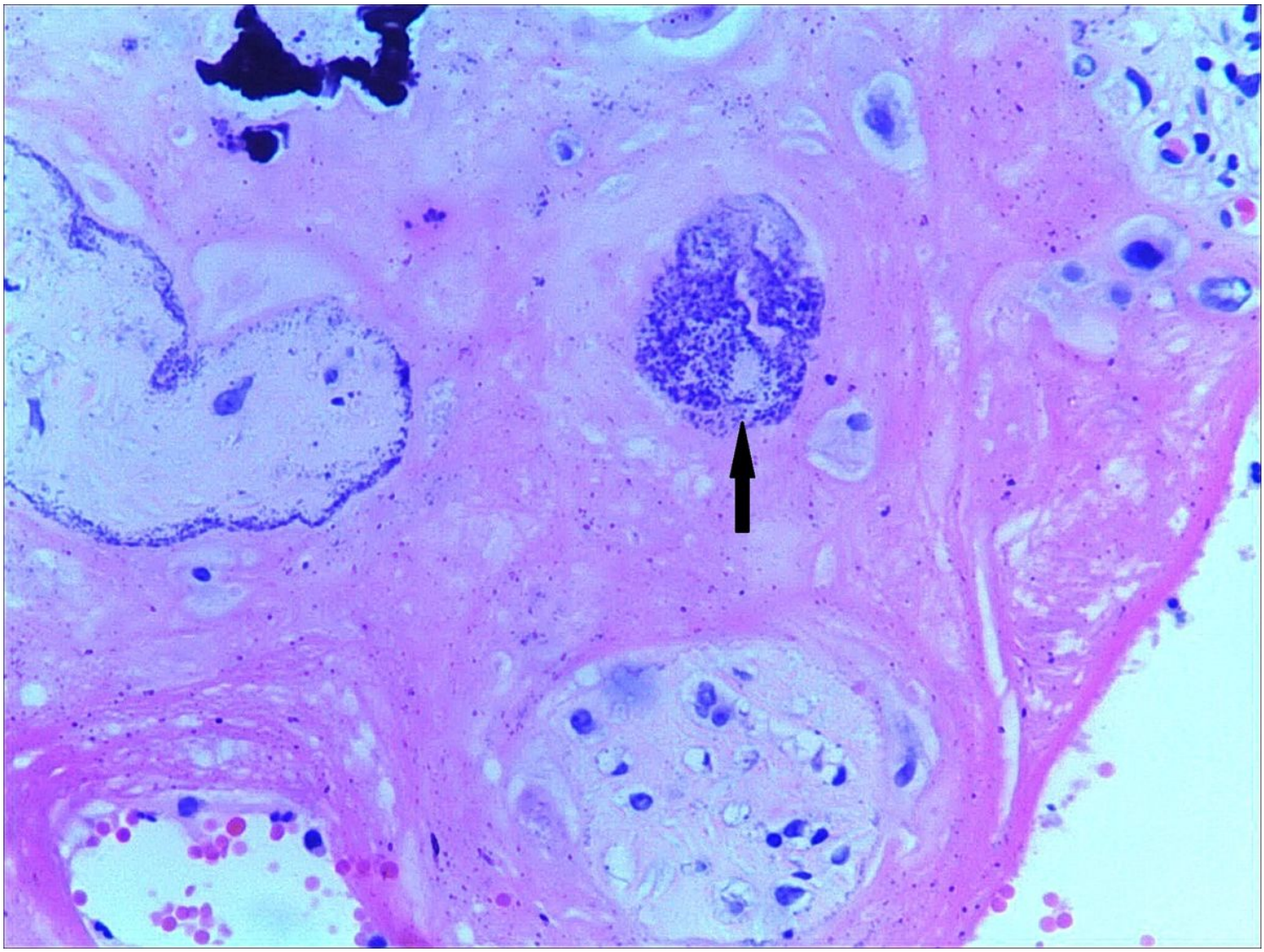

Figure 3

HE staining (× 400) shows clusters of coccobacilli in the connective tissue of chorioamnion (arrow).