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Case Report: Chorioamnionitis and Premature Delivery due to *Burkholderia pseudomallei* Infection in Pregnancy

Michelle C. Porter,[1]* Craig E. Pennell,[2] Patricia Woods,[3] John Dyer,[4] Adam J. Merritt,[5] and Bart J. Currie[6]

[1]*Microbiology Department, PathWest Laboratories, Perth, Australia;* [2]*Division of Obstetrics and Gynaecology, Faculty of Health and Medical Sciences, The University of Western Australia, Perth, Australia;* [3]*Neonatology Critical Care Unit, King Edward Memorial Hospital, Perth, Australia;* [4]*Infectious Diseases Department, Fiona Stanley Hospital, Perth, Australia;* [5]*Microbiology Department, PathWest Laboratories, Perth, Australia;* [6]*Global and Tropical Health Division, Menzies School of Health Research and Infectious Diseases Department, Royal Darwin Hospital, Darwin, Australia*

Abstract. We report a case of placental infection leading to preterm delivery in a mother diagnosed with septicemia and pneumonia due to *Burkholderia pseudomallei* in pregnancy. Placental infection occurred despite prolonged ceftazidime therapy.

INTRODUCTION

A 35-year-old, G_4 $P_{2\text{-}1}$ Australian woman presented with a seven-day history of shoulder pain, fevers, and chills 2 weeks after a vacation during the wet season in Phuket, Thailand. Unexpectedly, she was found to be 16 weeks pregnant. On examination, a fever of 38.3°C and tachycardia of 120 beats per minute were noted. A chest X-ray revealed signs of right upper lobe pneumonia. C-reactive protein (CRP) was elevated to 280 mg/L. Three consecutive blood cultures yielded growth of *Burkholderia pseudomallei*, confirming a diagnosis of bacteremic melioidosis with pneumonia. The patient resided in a nonendemic area for melioidosis in Perth, Western Australia. It was assumed that exposure to the organism occurred in Phuket. Initially reported susceptibilities for the isolate according to the Clinical and Laboratory Standards Institute (CLSI) guidelines were as follows: imipenem, ceftazidime, doxycycline, amoxicillin/clavulanic acid—all susceptible; meropenem minimum inhibitory concentration (MIC) 2 mg/L (no CLSI guidelines); and trimethoprim/sulfamethoxazole—resistant (MIC > 32 mg/L).

Intravenous (IV) meropenem 1 g 8 hourly was commenced, which was subsequently modified to ceftazidime 6 g/day at day 3 and administered as continuous infusion for 30 days. Symptoms resolved and CRP normalized to 1.6 mg/L at day 20 of IV therapy. Following cessation of ceftazidime, oral amoxicillin/clavulanic acid 875/125 mg twice daily (BD) was instituted with a plan to continue for 3 months as eradication therapy.

At 19 weeks and 4 days gestation, mild cerebral ventriculomegaly was noted on formal fetal anatomy scan. This persisted at the 23-week ultrasound which confirmed normal fetal growth, generous amniotic fluid volume, and a long closed cervix.

Six days after cessation of IV antibiotics, the patient developed fevers, night sweats, suprapubic pain, and threatened premature labor. The gestational age, calculated from the 16-week ultrasound scan, was 23 weeks and 4 days (±7 days), on the cusp of viability. A repeat ultrasound confirmed fetal ventriculomegaly (12 mm atrial width), polyhydramnios, and cervical shortening. Contractions settled initially with nifedipine tocolysis. Maternal corticosteroids were administered to enhance fetal maturation. The CRP was elevated at 131 mg/L. After obtaining blood, vaginal, and urine isolates for culture, 1 g 8 hourly administration of meropenem was commenced. Twelve hours later, uterine contractions returned and premature labor progressed. Magnesium sulfate was administered for fetal neuroprotection. Two doses of meropenem were given to the mother before the infant was born. A live 750 g female infant was delivered vaginally with Apgar scores of 4, 7, and 8 at 1, 5 and 10 minutes, respectively. The infant was intubated, admitted to the neonatal intensive care unit, and commenced on meropenem and gentamicin therapy. Maternal blood, vaginal, urine, and placental cultures all subsequently yielded growth of *B. pseudomallei*. The following antimicrobials were reported to be susceptible by CLSI guidelines: ceftazidime MIC 2 mg/L, trimethoprim/sulfamethoxazole MIC 0.12 mg/L, doxycycline MIC 2 mg/L, and amoxycillin/clavulanic acid 2 mg/L. Meropenem MIC was 1 mg/L (no interpretative CLSI guidelines). Review of susceptibility testing and repeat testing of a stored initial isolate established that the initially reported MIC > 32 to trimethoprim/sulfamethoxazole was erroneous because of misinterpretation of trailing end points. Placental histology confirmed the presence of acute chorioamnionitis with features of an early fetal inflammatory reaction. Postpartum the mother continued to experience fevers up to 38.9°C. Doxycycline 100 mg BD was added until the fevers ceased. Three days later, repeat blood cultures were negative (day 5 of meropenem therapy). The infant received human donor breast milk until the maternal milk was confirmed to be culture negative for *B. pseudomallei.* Cultures from the infant yielded *B. pseudomallei* from a gastric aspirate only. Blood cultures and an endotracheal aspirate yielded no pathogens. Polymerase chain reaction (PCR) for *B. pseudomallei* was negative on both blood and endotracheal tube secretions. A CRP rise to 26 mg/L at day 1 of life prompted the performance of a lumbar puncture. Cerebrospinal fluid parameters were not suggestive of infection and yielded no bacterial growth. Given the presence of maternal chorioamnionitis, perinatal exposure to infected vaginal secretions, and extreme prematurity of the infant, the infant was treated pre-emptively with 17 days of meropenem at 20 mg/kg 12 hourly from birth. When gut function allowed oral administration, trimethoprim/sulfamethoxazole initially at 4/20 mg/kg BD and then escalating to 6/30 mg/kg BD at 6 weeks of age (supplemented with folic acid) was prescribed to complete a further 3 months of therapy.

*Address correspondence to Michelle C. Porter, Microbiology Department, PathWest Laboratories, Perth, Australia. E-mail: michelle.porter@health.wa.gov.au

The mother completed a 6-week course of meropenem 3 g/day via outpatient parenteral therapy. Her intermittent night sweats resolved. The CRP measurement normalized to 10 mg/L at day 22 post reinstitution of IV antibiotics. A CT scan of chest, abdomen, and pelvis did not reveal any ongoing foci of infection. After clarification of susceptibilities, oral trimethoprim/sulfamethoxazole was commenced at a dose of 320/1600 mg BD with folic acid supplementation. A cutaneous delayed-type hypersensitivity reaction prompted a change in maternal therapy to doxycycline at day 12, during which time breast milk was discarded (with the infant receiving donated breast milk) until completion of 3 months of oral therapy.

The infant's clinical course was consistent with that of extreme prematurity complicated by suspected sepsis, including prolonged respiratory support until 36 weeks corrected gestation and administration of 2 courses of postnatal steroids, multiple blood products, and nutritional support. Neonatal MRI demonstrated brain morphology consistent with extreme prematurity, grade 2 intraventricular hemorrhage, and features of periventricular leukomalacia. The infant was discharged from the NICU at day 135 of life. Neurodevelopmental assessment at 12 months corrected gestational age confirmed normal developmental progress. *Burkholderia pseudomallei* infection did not recur in the mother or infant.

MICROBIOLOGY METHODS

Identification procedures, PCR, and MLST were performed as previously described on blood culture isolates obtained during the original and recrudescent bacteremic episodes and on a placental isolate.[1] MICs were derived by Etest® (Biomérieux). All isolates were of the same previously unreported sequence type (ST) assigned by the database curators as type 1503 (https://pubmlst.org/bpseudomallei). The closest related ST was the single locus variant ST97 which comprised a single human clinical isolate from the Netherlands in 1985, strain 2002721103. Expanding the comparison to include double locus variants returned matches to strains mostly of South-east Asian origin.

DISCUSSION

Pregnancy is not a recognized risk factor for acquisition of *B. pseudomallei* infection and neonatal infection with this organism, especially in the very preterm, has been seldom reported. Reported cases in pregnancy include a case of perinatal transmission at 32 weeks from a mother who was diagnosed with infection postpartum and a case of septicemia with spontaneous abortion at 16 weeks' gestation complicated by death from septicemic shock.[2,3] Prospective studies of pediatric melioidosis in the Northern Territory of Australia and in Sarawak, Malaysia, both known endemic areas, identified no neonatal cases and 2 of 42 cases, respectively.[4,5] A 2012 systemic review of the global literature regarding neonatal melioidosis identified 22 published cases since 1966 meeting the author's criteria, of which 4 had very low birthweight.

The commonest clinical syndromes described with *B. pseudomallei* infection in neonates are pneumonia, bacteremic infection and meningitis. Proven or hypothesized routes of infection include vertical transmission, breast feeding, community-acquired postpartum exposure, and healthcare-associated exposure. The reported mortality rate of neonatal melioidosis (clearly subject to publication bias) is 73%.[6,7]

In this case, the fetal cerebral ventriculomegaly and polyhydramnios detected on antenatal ultrasound suggest the possibility of vertical transmission with fetal effects due to infection during pregnancy.[8] Transplacental melioidosis has also been described in animals.[9,10] Despite in utero and peripartum exposure to *B. pseudomallei* and extreme prematurity, the infant survived and did not develop a microbiologically confirmed invasive infection. We speculate this outcome may be because of prompt institution of meropenem therapy in the mother prior to birth of the infant, immediate access to high-level obstetric and neonatal care, and preemptive antimicrobial treatment in the neonate.

Recrudescence of *B. pseudomallei* infection is uncommon after the intensive eradication phase, occurring in 5.1% of patients at a median time of 24 days.[11] Recrudescence of bacteremic infection in the mother was likely due to placental infection which was suppressed rather than cured by initial therapy. Placental infection may have occurred through bacteremic or ascending routes. Erroneous initial reporting of trimethoprim/sulfamethoxazole susceptibilities due to misinterpretation of trailing end points influenced prescribing decisions. The technical difficulties of determining trimethoprim/sulfamethoxazole MICs are well recognized.[12,13] Amoxicillin/clavulanic acid is known to be associated with higher risks of relapse but is an often recommended "step-down" therapy in pregnancy.[14] A dose regimen of 20/5 mg/kg 8 hourly may have been more efficacious.[15]

The isolates had a unique MLST type shared by the initial and latter isolates of the mother and the single neonatal isolate, confirming recrudescent maternal infection.

This case demonstrates the potential for recrudescence of *B. pseudomallei* infection due to placental infection in pregnant women, despite the receipt of prolonged parenteral treatment, with the consequence of preterm labor. To our knowledge, this has not been previously reported. Treatment of *B. pseudomallei*–infected pregnant women may require modification of standard therapy recommendations with consideration of extended parenteral therapy and close clinical follow-up, especially when IV therapy is ceased. Trimethoprim/sulfamethoxazole is known to be a more effective oral therapy than amoxicillin/clavulanic acid and the risk–benefit of use during pregnancy needs to be carefully considered. When amoxicillin/clavulanic acid is used, the higher dose recommendations for melioidosis should be followed. Intrapartum antibiotic therapy may improve neonatal outcome where perinatal exposure to *B. pseudomallei* has occurred.

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Authors' addresses: Michelle C. Porter, Department of Microbiology, PathWest, Nedlands, Australia, E-mail: michelle.porter@health.wa.gov.au. Craig E. Pennell, Division of Obstetrics and Gynaecology, University of Western Australia, Perth, Australia, E-mail: craig.pennell@uwa.edu.au. Patricia Woods, Neonatology Critical Care Unit, King Edward Memorial Hospital for Women Perth, Subiaco,

Australia, E-mail: patricia.woods@health.wa.gov.au. John Dyer, Infectious Diseases Service, Fremantle Hospital, Fremantle, Australia, E-mail: john.dyer@health.wa.gov.au. Adam J. Merritt, Department of Microbiology, PathWest Laboratory Medicine WA, Nedlands, Australia, E-mail: adam.merritt@health.wa.gov.au. Bart J. Currie, Menzies School of Health Research, Royal Darwin Hospital, Darwin, Australia, E-mail: bart.currie@menzies.edu.au.

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