Case Report: Gestational Melioidosis through Perinatal Transmission

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Abstract. *Burkholderia pseudomallei* is an emerging pathogen in the Americas. Cases of mother-to-child transmission of *B. pseudomallei* are rare and probably occur by placental or perinatal infection. We report the first case of native gestational and neonatal melioidosis in the Western hemisphere. The isolated strains in the mother and newborn were confirmed by whole-genome sequencing and identified as a novel sequence type ST1748. The comparison of both genomes revealed a nucleotide similarity of 100%. Melioidosis should be considered within the differential diagnosis of febrile illness or pneumonia in pregnant women and newborns from endemic areas of the Americas.

CASE REPORT

Melioidosis is an infectious disease caused by *Burkholderia pseudomallei*, a gram-negative, saprophytic soil bacterium.¹ Reports of cases of melioidosis during pregnancy, including cases of vertical transmission, are scarce in the literature. Here, we report a case of gestational melioidosis that was vertically transmitted to a patient in Colombia.

A 21-year-old woman from a rural area of Valledupar, a city on the Colombian Caribbean coast, who was 27 weeks pregnant presented with high fever that lasted more than 24 hours and uterine activity. On admission, the patient had normal blood pressure (110/70 mmHg) with no signs of respiratory distress but was feverish (39°C); her fetus had a normal fetal heart rate of 145 bpm. Vaginal examination revealed that the posterior cervix was soft, with 10-cm dilatation and bulging integral membranes. During delivery, there was evidence of clear amniotic fluid; a moderately pre-term baby was delivered at 29.6-week gestational age according to the Ballard scale. The Apgar scores were 4, 7, and 8 out of 10 at 1, 5, and 10 minutes, respectively; the newborn was flaccid and hypotonic without respiratory effort and required vigorous stimulation and 1 minute of positive pressure ventilation.

The mother was administered antibiotic therapy with ampicillin-sulbactam 3 g intravenous dosing (IV) every 6 hours, and obstetric curettage was performed. The admission laboratory test results were as follows: leukocytes, 28,000 cells/mm³; hemoglobin, 9.5 g/dL; platelets, 446,000 cells/mL; creatinine, 0.6 mg/dL; and blood urea nitrogen 6.4 mg/dL. A chest X-ray did not show alveolar infiltrates (Figure 1A), and blood cultures (2/2) were positive for *B. pseudomallei*. Meropenem 1 gm IV every 8 hours was initiated along with trimethoprim sulfamethoxazole 320/1,600 mg IV every 8 hours for 14 days. The clinical evolution was adequate. After 19 days, the patient was discharged, and outpatient treatment continued with trimethoprim-sulfamethoxazole 160/800 mg every 8 hours for 6 months.

The newborn was transferred to the neonatal intensive care unit where he presented with signs of respiratory distress, requiring orotracheal intubation and the use of exogenous pulmonary surfactant (Figure 1B). Because of his perinatal medical history, treatment was initiated with ampicillin 98 mg IV every 12 hours (200 mg/kg/day) plus amikacin 14.7 mg IV every 48 hours (15 mg/kg/dose/48 hours). Blood and endotracheal aspirate samples were collected and cultured, with negative results on the fifth day. On the sixth day of life, the programmed extubation protocol with continuous positive airway pressure was performed; however, a few hours later, the neonate suffered an apnea episode with hemodynamic repercussions that required advanced cardiac resuscitation and orotracheal reintubation. New endotracheal aspirate and blood samples were obtained. A new X-ray of the thorax showed right apical atelectasis and right basal alveolar infiltrates (Figure 1C). Given the maternal positive blood culture, it was decided to initiate ceftazidime 44 mg IV every 12 hours (88 mg/kg/day). Blood culture reports from day 6 were positive for azole-susceptible *Candida albicans*, whereas endotracheal aspirate culture was positive for *B. pseudomallei*; thus, caspofungin 2.7 mg IV every 24 hours (25 mg/m²/day) was added. However, clinical efficacy was low. Extubation was challenging, hemodynamics were labile, fungemia persisted, and *B. pseudomallei* was detected in endotracheal aspirate culture at 12 days; thus, it was decided to remove the epicutaneous cava catheter and initiate meropenem 39 mg IV every 8 hours (40 mg/kg/8 hours). For the management of fungemia, caspofungin was initially administered for 15 days and then fluconazole was administered for 14 days. Treatment with meropenem was administered for 10 days, and then amoxicillin-clavulanate was administered for 3 months. The clinical course of the newborn was consistent with extreme prematurity complicated by sepsis. Respiratory support until 36 weeks of corrected pregnancy, multiple blood transfusions, and prolonged parenteral nutritional support were required. The newborn was discharged on 64th day of life. At the 8-month follow-up examination, there was no disease recurrence in either the mother or the child.

The two isolated strains were identified as *B. pseudomallei* by a VITEK Compact 2 (BioMérieux, Marcy l'Etoile, France) and MicroScan WalkAway (Beckman Coulter, Brea, CA) system. Minimum inhibitory concentration (MIC) testing was performed using the MicroScan WalkAway system. According

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FIGURE 1. (A) Normal chest X-ray. (B) Normal chest X-ray. (C) Anteroposterior chest X-ray showing atelectasis at the apex of the right lung; the minor fissure is displaced upward and medially.

to published cutoff points for *B. pseudomallei*, the isolates were susceptible to trimethoprim/sulfamethoxazole (MIC < 2/38 µg/mL), meropenem (MIC < 1 µg/mL), and ceftazidime (MIC 4 µg/mL). Whole-genome sequencing confirmed both isolates as *B. pseudomallei* (StrainSeeker v.1.5, Tartu, Estonia) ST1748, a newly designated sequence type (ST). The detection of acquired antibiotic resistance genes revealed the presence of the β -lactamase OXA-57 in both genomes; no other genes were detected. In addition, we explored the presence of genes encoding virulence factors. Both genomes harbored the same genes, including those encoding secretion systems types III, IV, and VI; capsular polysaccharides; and flagellar machinery. Finally, the comparison of both genomes revealed a nucleotide similarity of 100%. Only four single nucleotide polymorphisms and 10 indels were found, confirming close genetic relatedness between the two isolates.

DISCUSSION

Melioidosis is an emerging and life-threatening disease caused by *B. pseudomallei*. It requires prolonged antibiotic treatment and is characterized by a wide range of clinical presentations. Colombia has reported the second highest number of cases in South America following Brazil.^{1,2} Melioidosis cases have been described in residents of the Colombian Caribbean coast³; however, there are no previous reports of gestational melioidosis. Although the first case of neonatal melioidosis in the Americas was described in the United States in 1971,⁴ there is no previous evidence of perinatal transmission in the Americas.

Pregnancy is not a risk factor for the development of melioidosis. The clinical presentation of gestational infection is not different from that in nonpregnant women.^{5,6} Placental infection can occur through bacteremia or through the genitourinary tract.^{7,8}

In the literature, there are few neonatal melioidosis reports.^{4,9–12} Newborns can be infected through vertical transmission (transplacentally or in the birth canal), during breastfeeding¹³ and by postpartum exposure,^{6,10,14} especially in cases of contamination of the umbilical cord due to unsterile instruments.¹⁵ In this case, given that the samples collected at birth were negative, we consider that vertical transmission occurred through the birth canal. Infection in neonates usually

presents as pneumonia, bacteremia, or meningitis and less frequently as abscesses in multiple organs or intracranial hemorrhage.^{10,11,16,17} Neonatal melioidosis has a high mortality rate that can reach 70%.^{18–20} Every mother of a child with melioidosis should be evaluated for the presence of *B. pseudomallei*. Although in this case, the presence of *B. pseudomallei* in the newborn's blood was not reported, the finding of highly related isolate in the mother's blood and the newborn's endotracheal aspirate cultures confirms perinatal transmission, and there was no apparent evidence of placental infection. Although there was also concomitant infection with *C. albicans*, we hypothesize that the pulmonary findings were attributable to the presence of *B. pseudomallei* and not to the fungal infection.

Our sequencing analyses of *B. pseudomallei* indicate a new ST, ST1748. In Colombia, different STs have been reported (ST1456, ST349, ST92, and ST518),²¹ suggesting genetic diversity among *B. pseudomallei* isolates. This observation correlates with the high rates of recombination and genomic plasticity observed in this bacterium.^{22,23}

The *B. pseudomallei* genome contains several genes that encode multiple resistance mechanisms (ambler class A, B, and D β -lactamases; outer membrane porins; and efflux pumps; among others). Similar to results reported by other authors, although both isolates were carrying the OXA-57 gene, a class D β -lactamase, they were susceptible to ceftazidime and carbapenem.^{24,25}

This disease requires a long treatment course because of the risk of recurrence that includes two phases. In the intensive phase, induction involves ceftazidime, imipenem, or meropenem IV for 10–14 days. However, antimicrobial stewardship recommends that carbapenems should be used in only the most compromised patients. During the eradication phase, trimethoprim-sulfamethoxazole is orally administered for 3–6 months. Doxycycline and amoxicillin-clavulanate are used for the management of patients with contraindications or isolated trimethoprim-sulfamethoxazole-resistant microorganisms.²⁶ There is little evidence regarding the treatment of melioidosis in pregnant women and newborns. There are two issues that make the treatment of this condition challenging. First, there may be a persistent infection in the placenta, which would increase the risk of recurrence of melioidosis in pregnant women; this is why some authors recommend prolonging

parenteral therapy and close monitoring once therapy is suspended. On the other hand, the use of trimethoprim-sulfamethoxazole is contraindicated during the first and third trimesters of pregnancy and in newborns. Amoxicillin-clavulanate therapy (the therapy of choice during the eradication phase) is associated with an increased relapse risk. There is a case report of the successful use of trimethoprim-sulfamethoxazole in a neonate during the eradication phase.²⁷

In conclusion, although gestational and neonatal melioidosis are uncommon clinical presentations, this first-ever case report in the Americas makes it necessary to consider when determining a differential diagnosis in women from endemic areas of the Americas and in women returning from endemic areas. The report of the complete genome sequence of *B. pseudomallei* in Colombia provides new knowledge about the molecular epidemiology of this microorganism in the country.

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REFERENCES

1. Benoit TJ et al., 2015. A review of melioidosis cases in the Americas. *Am J Trop Med Hyg* 93: 1134–1139.
2. Limmathurotsakul D et al., 2016. Predicted global distribution of *Burkholderia pseudomallei* and burden of melioidosis. *Nat Microbiol* 1: 15008.
3. Rodríguez JY, Morales-Lopez SE, Rodríguez GJ, Álvarez-Moreno CA, Esquea K, Pinzon H, Ramirez LR, Moreno L, Ocampo W, Cepeda ML, 2019. Case series study of melioidosis, Colombia. *Emerg Infect Dis* 25: 1531–1534.
4. Osteraas GR, Hardman JM, Bass JW, Wilson C, 1971. Neonatal melioidosis. *Am J Dis Child* 122: 446–448.
5. Watson AK, Ellington S, Nelson C, Treadwell T, Jamieson DJ, Meaney-Delman DM, 2017. Preparing for biological threats: addressing the needs of pregnant women. *Birth Defects Res* 109: 391–398.
6. Abbink FC, Orendi JM, de Beaufort AJ, 2001. Mother-to-child transmission of *Burkholderia pseudomallei*. *N Engl J Med* 344: 1171–1172.
7. Nernsai P, Sophonsritsuk A, Lertvikool S, Jinawath A, Chitasombat MN, 2018. A case report of Tubo-ovarian abscess caused by *Burkholderia pseudomallei*. *BMC Infect Dis* 18: 73.
8. Webling DD, 1980. Genito-urinary infections with *Pseudomonas pseudomallei* in Australian Aborigines. *Trans R Soc Trop Med Hyg* 74: 138–139.
9. Razmi TM, Shivaprakash MR, Saikia UN, De D, Handa S, 2017. All that necroses is not toxic epidermal necrolysis. *J Cutan Med Surg* 21: 172–173.
10. Thatrimontrichai A, 2011. Neonatal melioidosis: a case report and literature review. *Songkla Med J* 29: 235–243.
11. Halder D, Zainal N, Wah CM, Haq JA, 1998. Neonatal meningitis and septicaemia caused by *Burkholderia pseudomallei*. *Ann Trop Paediatr* 18: 161–164.
12. Daim S, Barnad E, Johnny V, Suleiman M, Jikal M, Chua TH, Rundt C, 2019. Neonatal melioidosis case reports—lessons learned. *Clin Case Rep* 8: 1–5.
13. Ralph A, McBride J, Currie BJ, 2004. Transmission of *Burkholderia pseudomallei* via breast milk in northern Australia. *Pediatr Infect Dis J* 23: 1169–1171.
14. Fang Y, Chen H, Zhu X, Mao X, 2016. Fatal melioidosis in a newborn from Hainan, China. *Am J Trop Med Hyg* 95: 444–446.
15. Ang YM, 2005. Neonatal melioidosis: very rare but be aware. *Med J Malaysia* 60: 99–102.
16. Lumbiganon P, Pengsaa K, Puapernpoonsiri S, Puapairoj A, 1988. Neonatal melioidosis: a report of 5 cases. *Pediatr Infect Dis J* 7: 634–636.
17. Noyal MJC, Harish BN, Bhat V, Parija SC, 2009. Neonatal melioidosis: a case report from India. *Indian J Med Microbiol* 27: 260–263.
18. Thatrimontrichai A, Maneenil G, 2012. Neonatal melioidosis: systematic review of the literature. *Pediatr Infect Dis J* 31: 1195–1197.
19. Nivedhana S, Rajendran S, 2016. Neonatal melioidosis with pneumatoceles. *Indian Pediatr* 53: 352.
20. Halder D, Abdullah WA, Johari MR, Choo KE, 1993. Neonatal melioidosis. *Singapore Med J* 34: 85–86.
21. Sanchez Y, Montufar F, Moreno J, Rodriguez J, Torres A, Huertas M, Morales S, Blaney D, Gee J, 2018. Búsqueda de melioidosis en Colombia (2016–2017). *Infectio* 22 (Suppl): 61.
22. Kamthan A, Shaw T, Mukhopadhyay C, Kumar S, 2018. Molecular analysis of clinical *Burkholderia pseudomallei* isolates from southwestern coastal region of India, using multi-locus sequence typing. *PLoS Negl Trop Dis* 12: e0006915.
23. Holden MTG et al., 2004. Genomic plasticity of the causative agent of melioidosis, *Burkholderia pseudomallei*. *Proc Natl Acad Sci USA* 101: 14240–14245.
24. Amladi A, Devanga Ragupathi NK, Vasudevan K, Venkatesan M, Anandan S, Veeraraghavan B, 2019. First report of *Burkholderia pseudomallei* ST412 and ST734 clones harbouring blaOXA-57 but susceptible to imipenem in India. *New Microbes New Infect* 32: 100613.
25. Panya M, Thirat S, Wanram S, Panomket P, Nilsakul J, 2016. Prevalence of bla (PenA) and bla (OXA) in *Burkholderia pseudomallei* isolated from patients at Sappasitthiprasong Hospital and their susceptibility to ceftazidime and carbapenems. *J Med Assoc Thai* 99 (Suppl 1): S12–S16.
26. Dance D, 2014. Treatment and prophylaxis of melioidosis. *Int J Antimicrob Agents* 43: 310–318.
27. Porter MC, Pennell CE, Woods P, Dyer J, Merritt AJ, Currie BJ, 2018. Case report: chorioamnionitis and premature delivery due to *Burkholderia pseudomallei* infection in pregnancy. *Am J Trop Med Hyg* 98: 797–799.