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Neonatal bacteremia and oligoarthritis caused by *Rhodococcus corynebacterioides/Rhodococcus kroppenstedtii*☆,☆☆

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1. Case Report

A 16-day-old female newborn was admitted to Cincinnati Children's Hospital Medical Center (CCHMC) in September of 2018 with a four-day history of worsening swelling of multiple digits. On admission, she was found to have swelling, induration and erythema of the proximal interphalangeal joints of the fourth digit of the right hand, the third digit of the right foot, and the second digit of the left hand without evidence of abscess or discharge. The digits were warm to the touch and mildly tender to palpation, with range of motion mildly limited by edema (Fig. 1).

There was no history of fever or other symptoms. She was born at 40 + 2 weeks gestation by spontaneous vaginal delivery, weighing 3150 g. Routine newborn work-up was normal, with the exception of a ventricular septal defect noted on fetal echocardiogram.

The mother of the patient reported a history of sickle cell trait and was hospitalized approximately a week after delivery for a postpartum uterine infection. Unfortunately, per mother's report, no organism was identified at that time. There was no history of infections before or during pregnancy and no zoonotic or soil exposures. The mother had received adequate prenatal care during pregnancy. Group B *Streptococcus* and HIV screens were negative.

The patient was afebrile, but given her unusual presentation of symptoms, a complete septic work-up was performed. The patient's CSF and urine cultures, *Neisseria gonorrhoeae* and *Chlamydia trachomatis* urine nucleic acid amplification, and rapid plasma reagin test were negative. On admission, C-reactive protein was elevated to 14.4 mg/dL (reference range ≤0.40 mg/dL) and white blood cell count was increased (24.2×10^3μL, reference range 5.0–20 $\times 10^3$μL) with 43% neutrophils. Infant newborn screen was positive for sickle cell trait.

Radiographs of the fingers and toes demonstrated soft tissue swelling without evidence of bony involvement. Multiple ultrasounds of the affected digits revealed soft tissue swelling without fluid collections or joint effusions.

One set of blood cultures was collected via venipuncture on admission, prior to the administration of antimicrobial agents. Gram-positive bacilli were observed in the pediatric bottle of one set of blood cultures after 76 h of incubation in VirtuO BACT/ALERT. No targets were detected when the positive blood culture was tested with the Verigene BC-GP panel. After 36 h of incubation, orange-pink colonies were visible on 5% sheep blood agar and chocolate agar (Fig. 2a). The isolate was catalase positive, and a Gram stain of the colony showed thin Gram-positive bacilli (Fig. 2b). The isolate could not be identified using MALDI-ToF (database version 3.0) spectrometry (Vitek MS, bioMeriuex, Leone, France). DNA was extracted using the NucliSENS EasyMAG (Powell, 2019). Following amplification of the 16S gene, DNA was sequenced using the ABI 3730xl sequencer which resulted in a 1368 base pair fragment. After analysis using BLAST 2.8.1 (Table 1), the isolate was identified as *Rhodococcus* species. Species-level identification was not possible, as the isolate had 99% sequence homology to both *Rhodococcus corynebacterioides* and *Rhodococcus kroppenstedtii*.

She was treated empirically with vancomycin for 24 h and then ceftriaxone for 14 days with slow clinical improvement. At the time of discharge, the affected digits became less swollen and less erythematous, and had improvement in range of motion. Susceptibility testing was not performed as there is no standardized reference available. Since *Rhodococcus* is typically susceptible to macrolides in vitro, the patient was transitioned to treatment with oral azithromycin for 3 weeks with close outpatient follow up. The patient was seen in the infectious disease clinic in the following month after discharge, with near-complete resolution of her symptoms before being lost to follow up.

2. Discussion

There are at least 15 *Rhodococcus* species of which *Rhodococcus equi* is the most described human pathogen. Infections by other species are less common (Cherry et al., 2019). The genus *Rhodococcus* is described as Gram-positive, catalase-positive, facultative, intracellular, non-spore-forming, weakly acid-fast bacilli (Cherry et al., 2019; Goodfellow and Alderson, 1977; Kedlaya et al., 2001). Rhodococci can be isolated from various sources of the environment including rocks, groundwater, soil, marine sediment, insects, or from sick and healthy animals and plants (Majidzadeh and Fatahi-Bafghi, 2018). PCR and DNA sequencing, in combination with phenotypic testing, has made it possible to accurately identify *Rhodococcus* species (Deurenberg et al., 2017).

Our patient's infection was most likely caused by *Rhodococcus corynebacterioides* as there is one human case of *R. corynebacterioides* infection that has been previously reported. This was described in 2012 by

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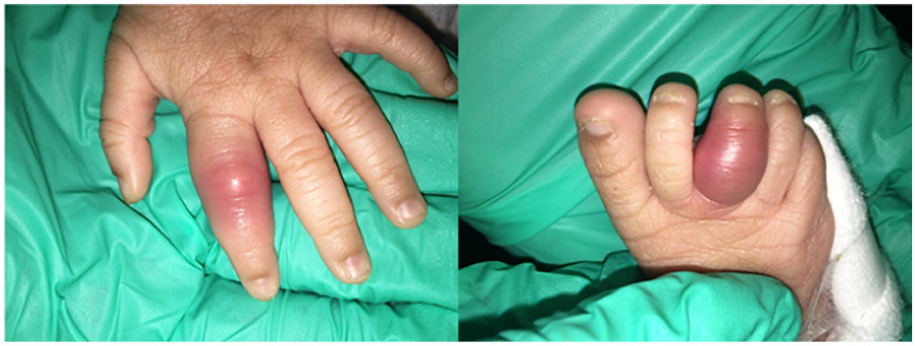

Fig. 1. Swelling of a) fourth digit of the right hand, b) the third digit of the right foot.

Kitamura et al. (2012) in an adult immunocompromised patient with sepsis. No prior *R. corynebacterioides* infection has been documented in immunocompetent patients or in the pediatric population. It seems less likely that the symptoms were secondary to *Rhodococcus kroppenstedtii* infection as this organism has only been isolated in the cold desert of the Himalayas, India and has not been previously described to be a human pathogen (Mayilraj, 2006). In our case, the mother of the patient denied any travel, soil exposure or animal exposure. The mother had a uterine infection that required hospitalization and possibly had a role in our patient's presentation.

There is one previously reported case of *R. equi* infection in a male newborn with joint swelling similar to our patient (Devi et al., 2011). *R. equi* is the most common cause of *Rhodococcus* infections and usually occurs in immunocompromised patients, especially those with HIV/AIDS (Bennett et al., 2014). Only 19 confirmed cases of *R. equi* have been reported in immunocompetent patients (Bildik et al., 2013; Devi et al., 2011). *R. equi* infection most commonly manifests as localized infection in immunocompetent patients (Devi et al., 2011), in contrast to necrotizing pneumonia in immunocompromised patients (Scott et al., 1995). Other reported Rhodococcus human pathogens include *R. erythropolis* (Baba et al., 2009), *R. fascians* (Austin et al., 2016), *R. ruber* (Lalitha et al., 2006), and *R. globerulus* (Ramanan et al., 2014).

There is limited data available regarding antimicrobial susceptibility testing results for *Rhodococcus* species. *R. equi* has shown susceptibility to macrolides, clindamycin, vancomycin, rifampin, aminoglycosides, fluoroquinolones and imipenem (Bennett et al., 2014; Cherry et al., 2019; Yamshchikov et al., 2010). While this species has occasionally been reported as susceptible in-vitro to beta-lactams, these antibiotics are avoided due to the rapid development of resistance. The organism is commonly resistant to penicillin and cephalosporins. However, several authors recommend the use of combination antimicrobial therapy that include bactericidal and intracellularly active agents (Devi et al., 2011; Kedlaya et al., 2001; Nordmann and Ronco, 1992). Surgical treatment should be considered in those who fail to respond with antibiotic therapy alone (Kedlaya et al., 2001).

There is no consensus on duration of therapy to treat *Rhodococcus* species infections due to insufficient data. Several reports recommend treating pulmonary infections in immunocompromised hosts for at least 2 months (Kedlaya et al., 2001) and up to 6 months (Bildik et al., 2013), while clinical success with a shorter duration of therapy has been demonstrated in immunocompetent patients (Bildik et al., 2013;

Table 1
16S gene analysis using BLAST database.

Top matches	Accession number	Species provided	Query cover	Sequence homology
1	CP015219.1	*Rhodococcus* species	99%	100%
2	KU995335.1	*Rhodococcus corynebacterioides*	99%	100%
3	KU560402.1	*Rhodococcus* species	99%	100%
4	AB685427.1	*Rhodococcus corynebacterioides*	99%	100%
5	HQ860791.1	*Rhodococcus* kroppenstedtii	99%	100%

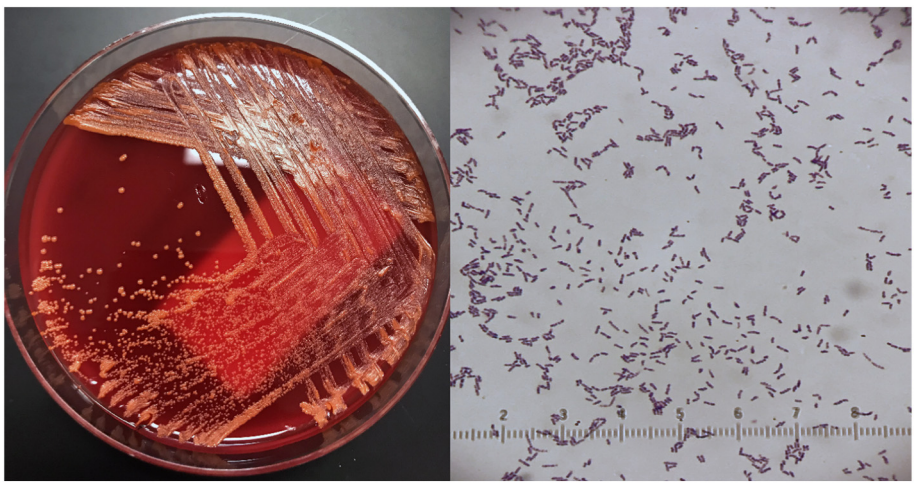

Fig. 2. a) Growth on Blood agar plate after 48 h of incubation at 35°C, b) Gram Stain showing long, thin Gram positive rods at 1000× magnification.

Devi et al., 2011; Kedlaya et al., 2001). Other factors to consider when determining treatment duration include site of infection and degree of tissue involvement (Bildik et al., 2013). Our patient's symptoms improved slowly with IV ceftriaxone followed by oral azithromycin.

To our knowledge, this is the first case of infection caused by *R. corynebacterioides* or *R. kroppenstedtii* in a pediatric or immunocompetent patient. The diagnosis was made possible with 16S RNA sequencing, which was unable to further differentiate between the two species. With the assistance of modern diagnostic modalities, *Rhodococcus* species may become increasingly recognized as the causative organism in infection.

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