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Preterm Labor Caused by Hemolysis, Elevated Liver Enzymes, Low Platelet Count (HELLP) Syndrome and Postpartum Infection Complicated with *Actinomyces* Species: A Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Female, newborn
Final Diagnosis: *Actinomyces* infection
Symptoms: Premature labor
Medication: —
Clinical Procedure: —
Specialty: Infectious Disease

Objective: Rare disease

Background: *Actinomyces* species are normal flora of the upper respiratory, female genital, and gastrointestinal tract. *Actinomyces* species are generally considered to have a low virulence potential. Here we report one case of *Actinomyces viscosus* isolated from a neonatal blood culture as a consequence of extreme prematurity in the presence of HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome.

Case Report: A 23-week gestational age female infant was born to a 32-year-old mother. The pregnancy was complicated by severe HELLP syndrome leading to cesarean section at 23-week gestation. The initial blood culture grew anaerobic gram-positive branching rods consistent with *Actinomyces* species. Due to patient instability, antibiotic was started and continued for a total of 13 days. On day of life 26, the reference laboratory identified the organism as *A. viscosus* by 16S ribosomal RNA.

Conclusions: In this case, *Actinomyces* species was a consequence of HELLP syndrome and consecutive extreme prematurity. Further research to look more closely at *Actinomyces* species isolated from neonatal blood culture will help to elucidate the true significance of these isolates.

MeSH Keywords: Actinomyces • Infant, Premature • Sepsis

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Background

Actinomyces species are normal flora of the upper respiratory, female genital, and gastrointestinal tract and are considered to have a low virulence potential [1,2]. Neonatal sepsis caused by *Actinomyces* species is a poorly known entity in the reviewed literature. Three cases of neonatal sepsis caused by *Actinomyces* species cases have been reported [3–5]. Here we report one case of *Actinomyces viscosus* isolated from a neonatal blood culture as a consequence of HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome and consecutive extreme prematurity.

Case Report

A 23-week gestational age female infant was born to a 32-year-old gravida 3, para 1-2-0-2 mother. Serology of maternal blood for human immunodeficiency virus, hepatitis, chlamydia, and syphilis were negative; group B streptococcal status was unknown. The pregnancy was complicated by severe HELLP syndrome, which led to cesarean section at 23-week gestation. Birthweight was 485 grams. Apgar scores were 3 at 1 minute and 8 at 5 minutes. The patient was intubated in the delivery room, received surfactant, and remained on mechanical ventilation when transferred to the neonatal intensive care unit. Initial laboratory data included: white blood cells (WBC) 2.1×10^9/l, hematocrit 39.6%, hemoglobin 12.6 g/100 mL, platelet 186×103 mL. The differential included 9% segmental WBC, 1% bands, 60% lymphocytes, 26% monocytes, and 603 nucleated red blood cells per 100 WBC. Initial C-reactive protein (CRP) was less than 0.3 mg/dL. Subsequent laboratory data showed persistent neutropenia, thrombocytopenia, and bandemia over 2 weeks. The patient developed hemodynamically significant hypotension requiring vasopressors. There was no definitive infection at this point; however, due to severe patient instability, the team decided to start ampicillin and gentamicin empirically for early-onset sepsis. Blood sample was sent for culture. On day of life 4, the blood culture was reported as anaerobic gram-positive branching rods consistent with *Actinomyces* species. The culture was sent to a reference laboratory (LabCorp, Columbus, Georgia) for identification. Ampicillin was switched to penicillin for possible *Actinomyces* bacteremia while awaiting the final identification. The antimicrobial course of therapy was as follows: the patient was started on ampicillin and gentamicin at birth for 7 days then penicillin for 5 days (total course of therapy was 13 days). Subsequent blood culture had no growth. On day of life 26, the reference laboratory identified the organism as *Actinomyces viscosus* by 16S ribosomal RNA gene sequencing. Matrix-assisted laser desorption ionization-time of flight spectrometry (MALD-TOF, Brucker) was unable to identify the organism.

Despite the negative repeat blood culture, the patient continued to do poorly during hospitalization. The patient demonstrated clinically significant hypotension requiring vasopressor support and stress dose corticosteroid, persistent neutropenia, thrombocytopenia, disseminated intravascular coagulation, transient hypoglycemia, electrolyte imbalance, adrenal insufficiency, and acute renal failure. On day of life 31, an endotracheal aspirate grew *Staphylococcus aureus* (oxacillin susceptible), a urine culture grew *Enterococcus faecalis*, and a central line grew *Staphylococcus epidermidis*. There was clinical evidence of infection and the patient received 7 days of vancomycin and ampicillin/sulbactam. The patient was discharged to another healthcare facility for higher level of care after 3 months of hospital admission.

Discussion

Actinomyces species are a normal flora of the oral cavity and gastrointestinal and female genital tracts [1]. Traditionally, this isolate from sterile specimens is considered significant [2]. Nowadays, there is an expansion in rapid development of diagnostic techniques, which lead to identifying a multitude of organisms from different sample types [6]. Previously, 3 cases of *Actinomyces* species causing neonatal sepsis were reported in the literature [3–5]. In all 3 cases, the mother presented with copious vaginal discharge and preterm labor. However, in all of these cases, the neonate developed a significant infection (i.e., elevated CRP and WBC) and required prolonged antibiotic therapy. However, neonatal sepsis severity demonstrated varying degree of illness ranging from mild to multi-organ failure (see Table 1).

In our case, the cause of preterm labor and immunological deficiency was HELLP syndrome, and infection by *Actinomyces* was just a consequence of the prematurity complicated with the preterm illness of the mother. Our patient demonstrated significant pulmonary hypertension, cardiac hypertension on cardiogenic pressor and stress dose corticosteroid, persistent anemia, thrombocytopenia, disseminated intravascular coagulation, transient hypoglycemia, electrolyte imbalance, adrenal insufficiency, and acute renal failure. All of these complications were not a consequence of the *Actinomyces* infection but the consequences of HELLP syndrome and consecutive extreme prematurity [7,8]. Interestingly, the patient continued to have persistent neutropenia, thrombocytopenia, and bandemia over 2 weeks while the patient was on antibiotics. However, because the patient was clinically unstable and there was no published data to guide this challenging decision, clinical judgment was the only guide available and the antibiotics were initiated and continued for 2 weeks. At this point, it is unknown if the patient developed a significant *Actinomyces* infection that required a prolonged antibiotic therapy, or all of these abnormalities were simply due to extreme prematurity in the presence of HELLP syndrome.

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Table 1. Clinical characteristics, treatment strategies and outcomes of the 4 cases of neonatal sepsis caused by *Actinomyces* species.

Case	Mother characteristics				Neonate characteristics			Organism			Antibiotics	Outcome
	Age (Y)	Copious vaginal discharge	EGA (wk)	Vaginal delivery	Sex	Wt (g)	Clinical	Species	Identification method	Time (days)		
Our 1st case	32	Yes	23	No	F	485	Respiratory distress requiring mechanical ventilation and sepsis at birth	*A. viscosus*	16S ribosomal	26	AMP + GEN for 7 days then PEN for 5 days	Cured
Mann et al., 2002 [2]	21	Yes	27	Yes	F	1120	Mild respiratory distress and sepsis 2 hour after birth	*A. neuii*	Biochemical analysis*	NA	AMP + GEN for 2 weeks then PEN for 4 weeks	Cured
Knee et al., 2004 [3]	26	Yes	29	No	F	NA	Respiratory distress requiring mechanical ventilation and severe sepsis with multi-organ failure	Unspecified	Unspecified (sent to reference lab)	15	AMP + CFT then AMP + GEN patient continued to receive multiple antibiotic (started PEN on day 19)	Died
Alsohime et al., 2017 [4]	26	Yes	25	Yes	F	1090	Respiratory distress requiring mechanical ventilation	*A. neuii*	NA#	NA	AMP and GEN for 5 days then PEN for 6 weeks	Cured

EGA – estimated gestational age; F – Female; Y – year; Wk – week; Wt – weight; AMP – ampicillin; GEN – gentamicin; PEN – penicillin; CFT – cefotaxime. * Biochemical analysis using Api Coryne system; # morphologic features and staining properties were consistent with those of Actinomyces.

A review study including 60 patients (11 from pediatric and neonatology) from whom *Actinomyces* species were isolated from 61 blood cultures showed that only 10 of the 60 patients were considered to have a significant infection and required antibiotic therapy. The main difference between the patients who require treatment and who did not require treatment was the presence of clinically recognized risk factors [9]. This highlights the fact that this isolate could be a contamination in neonatal blood culture especially in the era of rapid development of diagnostic techniques. In a study by Jeffery-Smith et al., they noticed an increase of *Actinomyces* species after the introduction of MALDI-TOF MS and 16S ribosomal RNA gene PCR techniques and they hypothesized that these organisms would have been dismissed as contaminants such as *Corynebacterium* species or *Propionibacterium* prior to the introduction of these new diagnostic technologies [9]. This expansion of diagnostic technologies needs to be matched with an understanding of the clinical significance, to ensure appropriate antibiotic therapy for patients. The need for further research to identify the significance of this isolate in premature neonatal blood could be warranted to minimize the risk of prolonged antibiotic exposure and disruption of normal flora.

In our case, MALDI-TOF (Brucker) failed to identify this isolate. In 2011, a study was published to compare the accuracy of the identification of areo-tolerant *Actinomyces* species. and found out that MALDI-TOF MS was able to identify 97% (29 out of 30) of *Actinomyces* species. However, 3% were considered unreliable identifications [10]. Although MALDI-TOF is a promising tool for identification, 16S ribosomal RNA gene sequencing should be used when MALDI-TOF does not provide the answer.

Our patient developed a secondary infection at 30 days of life (different site and different organism). The risk of using antibiotics in neonates has been discussed in several studies. These risks include increasing antibiotic resistance as well as altering the microbiota and impairing the neutrophils, leaving the newborn vulnerable [11,12]. There might be an opportunity to reduce unnecessary antibiotic exposure by carefully evaluating the patient clinically as *Actinomyces* species. could represent

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contamination in premature neonatal blood that may not require antibiotic treatment.

Conclusions

Actinomyces species was isolated from the blood culture of a preterm neonate as a consequence of extreme prematurity in the presence of HELLP syndrome. Further research to look more closely at *Actinomyces* species isolated from neonatal blood culture will help to elucidate the true significance of these isolates.

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