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Haemophilus influenzae septic abortion

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Background: *Haemophilus influenzae* septic abortion is typically caused by nontypeable strains of the organism. Furthermore, nontypeable species with a special affinity for the genital tract are the most frequent isolates encountered, and an ascending vaginal or cervical infection is often the suspected route of transmission.

Case: A 39-year-old woman at 8 weeks gestation who underwent dilation, evacuation, and curettage for embryonic demise had clinical evidence for sepsis and isolation of a nontypeable, ampicillin resistant *H. influenzae* from blood cultures. Although an ascending vaginal infection was suspected, the route of transmission was not determined.

Conclusion: Nontypeable strains of. *H. influenzae* have demonstrated increased beta-lactamase activity, and ampicillin, formerly the treatment of choice, should be used only if isolate susceptibility is known.

Key words: UROGENITAL INFECTION; NONTYPEABLE; BIOTYPE IV

Haemophilus influenzae is a nonmotile, gram-negative coccobacillus. When the organism causes meningitis in children, it usually expresses the type B capsular polysaccharide – one of six antigenically distinct capsules (A–F) found on encapsulated strains. Strains of *H. influenzae* lacking a polysaccharide capsule are classified as nontypeable since they are nonreactive to the antiserum raised against polysaccharide capsular antigens. Up to 80% of healthy adults are estimated to be colonized in the pharynx with nontypeable *H. influenzae*[1]. Biotyping classifies *Haemophilus* strains based on their enzymatic and biochemical properties: indole production, urea hydrolysis, and ornithine decarboxlase activity[2]. Among the nontypeable strains of *H. influenzae*, biotypes II and III are the predominant colonizers of the upper respiratory tract and sinuses[3]. Nontypeable *H. influenzae* account for approximately 25% of the cases of acute bacterial otitis media[4]. They are also responsible for exacerbations of chronic obstructive pulmonary disease, and are an etiologic agent of community-acquired pneumonia. More recently, nontypeable *H. influenzae*, particularly biotype IV, have been recognized as obstetric and gynecologic pathogens.

CASE REPORT

A pregnant 39-year-old gravida 6, para 4 woman at 8 weeks gestation reported a several-day history of light vaginal bleeding accompanied by headaches and low-grade fever. When these symptoms persisted, the patient saw her primary care physician who prescribed a 7-day course of ampicillin. The patient did not take the prescribed medicine due to her concern for the use of an antibiotic during pregnancy. One day after the primary care visit, the patient went to her obstetrician for a previously scheduled appointment. Abdominal ultrasound

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demonstrated fetal size consistent with an 8-week gestation, however neither fetal movement nor cardiac activity were detected. The patient underwent dilation, evacuation, and curettage for embryonic demise. Shortly after completion of the procedure the patient became hypotensive, developed rigors, and had a rapid rise in temperature. Work-up of the fever included a chest x-ray that was without infiltrate. Serum hematologic values included a white blood cell count of 900 cells/mm^3 (with 30% bands) and a platelet count of 118 000/mm^3. Blood cultures were obtained, after which the patient was empirically initiated on intravenous antimicrobial therapy with gentamycin, ampicillin, and clindamycin.

The day after evacuation and curettage, the patient had several more hypotensive episodes that responded well to fluid challenges. Her white blood count had increased to 15 500 cells/mm^3, and the differential demonstrated a disappearance of the left shift. When blood cultures grew *H. influenzae*, an infectious disease consult was obtained. Gentamycin and ampicillin were discontinued, and ceftriaxone therapy started, due to concern for microbial beta-lactamase activity. As the patient complained of neck stiffness and headache, a lumbar puncture was also recommended. However, the cerebrospinal fluid revealed neither white blood cells nor organisms, and normal protein and glucose values were obtained.

The histology from the uterine evacuation demonstrated an acute chorioamnionitis, and Gram stain of the placental tissue showed microorganisms morphologically consistent with *H. influenzae*. The organism was sent to a reference laboratory were it was identified as a nontypeable, ampicillin resistant strain of *H. influenzae*. No biotyping was performed. By the fourth day of hospitalization the patient had stabilized, and her antimicrobial therapy was switched to oral levafloxicin alone. She was discharged on day five, and completed an uneventful 14-day course of the antibiotic.

DISCUSSION

Septic abortion caused by *H. influenzae* infection was initially reported in 1973[5]. Wallace and colleagues were among the first to recognize that the nontypeable strains of *H. influenzae* are the predominant isolates found in cases of septic abortion[6]. It is thought that the immunosuppressive effects of pregnancy increase host susceptibility to *H. influenzae* infection. In 1992, the annual incidence of invasive *H. influenzae* disease was 1.7/100 000 adults, but increased to 4.9/100 000 when only pregnant women were considered[7]. This same prospective study found a six-fold increased risk for *H. influenzae* bacteremia in pregnant women aged 18–39 years compared with other adults of the same age, and that over one-half of the bacteremias associated with pregnancy resulted in fetal death. Septic abortion caused by *H. influenzae* is often characterized by a mild maternal course, but a more severe, life-threatening course is also possible[8].

Two possible mechanisms of transmission of *H. influenzae* to the fetus during pregnancy are hematogenous spread with subsequent infection of the placenta or amniotic fluid or an ascending infection from the cervix and vagina. When a nontypeable *H. influenzae* bacteremia is present, the respiratory tract is the usual source of infection. In studies of pregnant asymptomatic females, the isolation rate of *H. influenzae* from the genital tract was typically less than 1%[9,10]. Because of this low genital carriage rate, hematogenous spread from another source of infection was considered a more likely route of transmission. However, more recent evidence has demonstrated that the *H. influenzae* isolates that cause maternal infections are often the result of an ascending infection by nontypeable strains that possess a specific tropism for the genital tract[11]. Nontypeable biotype IV isolates are seldom recovered from most body sites: less than 2% of all nontypeable *H. influenzae* encountered in clinical specimens are biotype IV[2,3,12]. However, in cases of *H. influenzae* septic abortion, biotype IV is frequently identified from blood and genital cultures[13]. This suggests that the genital isolates of nontypeable *H. influenzae* are distinct from the species that typically colonize the upper respiratory tract. Furthermore, identification of the urogenital-specific biotype IV isolates decreases the likelihood that either orogenital contact or hematogenous spread from pneumonia or sinusitis represents the route of transmission. In our case report, hematologic spread of an *H. influenzae*

infection cannot be dismissed. However, the failure to identify another source of infection does argue against it. Biotyping of the isolate would have helped clarify if an ascending cervical or vaginal infection was indeed the more likely route of transmission.

Molecular biological studies have further elucidated the role of nontypeable *H. influenzae* in obstetric infections. Characterization of the electrophoretic mobilities of multiple metabolic enzymes has demonstrated that the chromosomal genotypes of the nontypeable biotype IV isolates are sufficiently different from other *H. influenzae* isolates as to represent a different species[14]. Subsequent genome hybridization experiments have shown about 60% relatedness of biotype IV isolates to the type strain, a dissimilarity that further supports this proposal. These strains are thought to form a monophyletic unit with *H. influenzae* and *H. haemolyticus*; with a distant separation from these two species[15]. Biotype IV isolates are known to have peritrichous fimbriation. This may confer an increased ability to survive in the genital tract environment[16]. In addition, biotype IV strains express a variant P6 outer membrane protein molecule[17]. The P6 molecule is highly conserved among *H. influenzae* strains, and antibody to P6 is bactericidal for most nontypeable isolates. The variant P6 molecule of biotype IV is consistent with the observation that this strain is genetically distinct from the type strain, and the alteration may be important in its pathogenicity.

Due to rapidly shifting antimicrobial resistance patterns, treatment guidelines for *H. influenzae* have changed. Ampicillin was previously considered the treatment of choice for *H. influenzae* infections. However, over 30% of nontypeable *Haemophilus* sp. strains causing invasive disease are ampicillin resistant, and this incidence is expected to increase. Therefore, ampicillin should be used only if the susceptibility of the infecting isolate is known. There is evidence that urogenital *H. influenzae* biotype IV strains are also distinguished from other nontypeable isolates by their increased susceptibility to the quinolone antimicrobials[19]. Hence, the development of genomic probes that allow the rapid identification of the urogenital strains of *Haemophilus* sp. could facilitate appropriate antibiotic selection. Prospective studies of maternal vaginal flora using selective culture media could help clarify the prevalence, transmission, and potential morbidity of *H. influenzae* in pregnant women. Prospective studies that help determine how accurately genital colonization with *H. influenzae* predicts subsequent chorioamnionitis or septic abortion would also be invaluable for future treatment guidelines.

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