Adult-onset Invasive Haemophilus influenzae Type f Caused by Acute Lower Leg Cellulitis

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Abstract

In Japan, routine Haemophilus influenzae type b (Hib) vaccination began in 2013. Thus, similar to other countries, a strain shift is expected in the near future. We experienced a case of H. influenzae type f (Hif) bacteremia in a 66-year-old man. The primary focus of the infection was the soft tissue of the left lower leg, which is an extremely rare origin in adults. Subsequently, we conducted multilocus sequence typing and identified the strain as sequence type 124, which is the most common invasive strain of Hif worldwide. This case may mark the beginning of an Hif strain shift in Japan.

Key words: H. influenzae type b, H. influenzae type f, multilocus sequence typing, cellulitis, invasive


Introduction

Haemophilus influenzae are Gram-negative bacilli which are known to colonize the nasal cavity and upper respiratory tract. H. influenzae are classified as typeable and non-typeable (NTHi) on the basis of the presence of a polysaccharide capsule. Encapsulated H. influenzae are divided into six groups (a, b, c, d, e, and f). The capsular type, mainly H. influenzae type b (Hib), often causes systemic invasive diseases such as bacteremia. In comparison, NTHi often leads to local infections such as bronchitis and sinusitis.

Hib vaccination was introduced into the routine childhood immunization schedule in Japan in 2013, 20 years after its introduction in European countries and the US. In countries where the use of the Hib vaccine has become widespread, the incidence of invasive Hib disease has decreased. However, there has been an increase in the incidence of invasive infections caused by non-type b H. influenzae; in particular, a relative increase was seen in the incidence of invasive infections caused by H. influenzae type f (Hif) in Sweden, the United Kingdom, and the United States (1-3). There have also been reports of increased numbers of admissions to intensive care units (2), indicating the possibility that Hif may become a major cause of invasive infections in Japan after the introduction of the Hib vaccination. We herein report an adult case of Hif bacteremia resulting from a soft-tissue infection, an extremely rare origin in adults. To the best of our knowledge, this is the first case report of adult-onset invasive Hif disease of soft tissue origin to be confirmed by multilocus sequence typing (MLST) in Japan.

Case Report

The patient was a 66-year-old man, who had been diagnosed with IgG4-related disease six months previously and who had been treated with oral steroids (9 mg/day). He visited the dermatology department of our institution in the autumn of 2014 due to a contusion on the left anterior lower leg that had occurred during agricultural work. He was diagnosed with left lower leg acute cellulitis. Although blood laboratory tests were not performed at that time, azithromycin (500 mg/day) was administered orally for three days. The improvement of the patient’s lower leg cellulitis was

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observed to be poor upon subsequent visits to our hospital. We found no abnormalities in his vital signs. Two contusions of approximately 1 cm diameter on the anterior left lower leg and inflammatory findings, such as erythema, edema, and pain from the distal lower leg radiating toward the dorsum of the foot, were observed (Figure). Blood tests indicated an acute inflammatory response with an increased C-reactive protein level of 5.94 mg/dL and a white blood cell count with a high neutrophil level (12,290/L, 75.4%). The improvement of the patient’s inflammatory findings was indicated by the neutrophil level, which decreased to 6,990/L (51.7%). Serum C-reactive protein levels gradually improved and the patient was discharged after finishing treatment over a total period of 14 days. No additional antibiotic therapy was administered and the patient had no evidence of relapse.

Because *H. influenzae* is a rare cause of cellulitis in adults, we performed a detailed analysis of the *H. influenzae* isolates in this case. We identified the f serotype of *H. influenzae* by slide agglutination with antisera (*Haemophilus influenzae* Antiserum “SEIKEN” Set: Denka Seiken, Tokyo, Japan), and further confirmed this result using a polymerase chain reaction (PCR) reference method (4). Furthermore, an analysis of the microbial genome by MLST (5) identified that the Hif strain corresponded to sequence type ST 124.

**Discussion**

We experienced a rare case of adult-onset invasive Hif disease originating from the soft tissue of the lower leg. There are three important points in this case:

First, *H. influenzae* soft tissue infections are common in young children (6) and are located mainly in the facial region. However, the present case was an adult with acute cellulitis of the lower extremity caused by Hif, not Hib. Adult-onset invasive Hif disease from cellulitis is a remarkably rare occurrence. In fact, we were able to find only two previously reported cases (7, 8). The cases involved 64- and 86-year-old patients with cellulitis affecting the left arm and right leg respectively. These reports suggest that age-related immune dysfunction may contribute to an increased risk of Hif infection. In the present case, in addition to advanced age, daily oral steroid use and IgG4-related disease may have been additional risk factors for invasive Hif disease. It is well known that patients with chronic hypocomplementemia are at particular risk of developing serious infections with encapsulated organisms in systemic lupus erythematosus (9). IgG4-related disease is often accompanied by hypocomplementemia, which may have predisposed our patient to infection with *H. influenzae*.

Second, after the introduction of the Hib vaccine, the incidence of non-type-b *H. influenzae*, particularly Hif and NTHi, has increased globally (1, 3, 10). In the US, invasive Hif disease increased from 0.06 cases in 1989 to 0.25 cases/100,000 population in 2008 (11). Likewise, in Sweden, the incidence increased by 2.3% annually between 1997 and 2009 (2). Furthermore, in England and Wales, there was an 11.0% year-on-year increase in Hif between 2001 and 2010, and 7.8% of the 1,275 cases of invasive *H. influenzae* that occurred in England and Wales between 2009 and 2010 were reportedly caused by Hif (1). These reports indicate that a strain shift has occurred since the introduction of the Hib vaccine in many countries. In Japan, the Hib vaccine was introduced in 2008. Since the initiation of the publicly-funded Hib vaccination program in 2011, there has been a dramatic decrease in the number of Hib isolates from cases of invasive *H. influenzae* disease (12).
cidence of capsular non-type b H. influenzae may also increase in Japan in the future. In fact, there have already been a number of reported cases of invasive Hif disease in Japanese children (13).

In elderly patients in the UK, the mortality rate of invasive Hif disease has been reported to be as high as 42% (1). One of the major pathogenic features of H. influenzae infection is the presence of a polysaccharide capsule. Polysaccharide capsules can inhibit complement activity and resist phagocytosis, indicating that humoral immunity against the capsules plays a particularly important role in defense against H. influenzae. H. influenzae can cause systemic infections in immunodeficient individuals. Thus, invasive disease associated with Hif appears to disproportionately affect individuals with underlying comorbidities, including adults suffering from chronic obstructive pulmonary disease, ethanol abuse, chronic renal disease, and immunodeficiency (14). Another pathogenetic feature of H. influenzae is the prevalence of β-lactamase expression (reportedly between 7.7% and 24.5%) (14). However, in keeping with the present case, the literature on β-lactamase non-producing ampicillin-resistant strains (BLNAR) and β-lactamase-producing amoxicillin-clavulanate-resistant (BLPACR) isolates includes few reported cases of Hif.

Third, this is the first case report in which genome typing by MLST was conducted for adult-onset invasive Hif disease originating from a soft tissue infection in Japan. In recent years, H. influenzae has been globally classified by MLST in addition to the serotyping of the capsule. Using the determination of phenotypic and genotypic diversities, it is possible to pursue detailed epidemiological investigations. Thus, MLST has become the gold standard for population analyses of bacterial pathogens. In the present case, MLST determined the H. influenzae strain to be ST 124; the same strain as that in the majority of reports of invasive Hif disease in the UK and North America. A previous study of the molecular epidemiology of adult-onset invasive H. influenzae disease reported that capsulated strains were clonal and belonged to clonal complexes 6 (serotype b), 18 (serotype e), and 124 (serotype f, if formed by ST 124), whereas NTHi strains were genetically diverse (10). Although, the biological differences between Hif ST 124 and other strains of H. influenzae remain unclear, ST 124 appears to have a number of virulence factors, including iron-utilization proteins and kanamycin nucleotidyltransferase (15).

We reported a case of adult-onset invasive Hif disease caused by a soft tissue infection. In the future, non-type b H. influenzae, particularly Hif, is expected to become a major cause of invasive disease in elderly adults and children. Thus, epidemiological studies of invasive H. influenzae are important for increasing the understanding of the trends in the prevalence of this virulent strain. This report contributes to our knowledge on Hif disease by reporting a case of adult-onset invasive ST 124-type Hif disease after the introduction of the Hib vaccination in Japan.

The authors state that they have no Conflict of Interest (COI).

References