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Disseminated "*Haemophilus quentini*" infection in a patient with multiple myeloma — a case report and review of the literature☆

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ABSTRACT

We describe a case report of a 56-year-old male with undiagnosed multiple myeloma who had severe sepsis associated with pneumonia, meningitis, polyarthritis, and osteomyelitis related to invasive "*Haemophilus quentini*" infection. The genus was misidentified as *H. influenzae* by the common bacterial identification systems including newly introduced syndromic PCR-based methods. We review the epidemiological, clinical, and laboratory aspects of this rare, cryptic species of *Haemophilus*.

1. Case report

A 56-year-old previously healthy male was seen in the emergency room with complaints of fever, chills, nausea, vomiting, and diarrhea. He had a temperature of 39.5 °C, but the results of the rest of the physical examination and chest X-ray were normal. His blood tests showed mild anemia (hemoglobin 11.9 g/dL) and leukopenia (white blood cells 3400 cell/μL). He was treated with intravenous fluids and paracetamol, and discharged home with the diagnosis of a presumed viral infection.

The fever abated, but 3e days later, he was admitted to our hospital with 1-day history of diffuse stiffness, arthralgia, and swelling of multiple joints including the right shoulder, right wrist, left ankle, and both elbows and knees. He could not walk and was extremely weak. He had a temperature of 37.3 °C, blood pressure of 130/80 mmHg, respiratory rate of 18 per minute, pulse of 100 beats per minute, and oxygen saturation of 98% breathing room air. Multiple joints were swollen and mildly erythematous. His laboratory results on admission showed

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anemia (hemoglobin of 11.1 g/dL), neutrophilia (8300 cell/μL), mild thrombocytopenia (146,000 cells/μL), acute kidney injury with creatinine of 1.3 mg/dL (previously 0.8 mg/dL), and elevated calcium (corrected of 14 mg/dL) and C-reactive protein (CRP) of 534 (normal 0–5 mg/dL).

The initial diagnosis was of reactive polyarthritis, but given his hypercalcemia, a malignancy was suspected, and a whole-body computerized tomography (CT) was performed and showed only pulmonary infiltration of the right upper and lower lobes and mild hepatomegaly. He underwent bone marrow biopsy, and he was treated with prednisone and ceftriaxone 1 g/day.

On the third day of hospitalization, he became confused and then stuporotic. A lumbar puncture was performed. The cerebrospinal fluid (CSF) was clear, with pleocytosis of 235 white blood cells (85% mononuclears), 10 red blood cells, elevated protein (72 mg/dL), and glucose of 51 mg/dL (serum glucose at the same time was 116 mg/dL). Direct Gram stain of the fluid was negative for bacteria.

An infectious diseases consultation was ordered, after which antibiotic coverage was widened to include intravenous acyclovir, ampicillin, vancomycin, and doxycycline and the ceftriaxone dosage was increased to 4 g a day.

The differential diagnosis at this point taking into consideration meningitis, pneumonia, and polyarthritis included disseminated bacterial infection with bacteria such as *Staphylococcus aureus*, beta-hemolytic streptococci, *Haemophilus influenzae*, *Listeria monocytogenes*, *Legionella pneumophila*, *Neisseria gonorrhea, Coxiella burnetii* and Nocardia spp., as well as infection with *Mycobacterium tuberculosis,* viral diseases, and *Cryptoccocus neoformans*. Other noninfectious conditions such as granulomatous diseases, acute rheumatic disease, vasculitis, and metastatic neoplasia were also considered. He was transferred to the intensive care unit.

The CSF was examined with the FilmArray® meningitis/encephalitis panel (Biofire, BioMerieux®, France) and was found positive for *H. influenzae*. Blood cultures from admission also grew Gram-negative cocobacilli that were identified as *H. influenzae* by the VITEK2 system (Biomerieux®, France) as well as by Matrix-Assisted Laser Desorption Ionization Time-of-Flight (MALDI-TOF) system VITEK® MS V3.2 with a score of 99.9%. Antibiotic susceptibility testing was performed by the disk diffusion method according to Clinical and Laboratory Standards Institute (CLSI) guidelines. The isolate was susceptible to ciprofloxacin, ampicillin, cefuroxime, chloramphenicol, azithromycin, ceftriaxone, trimethoprim/sulfamethoxazole, amoxicillin/clavulanic acid, and gentamicin.

The antibiotic coverage was narrowed to include only high-dose ceftriaxone with rapid improvement of the neurological status. Both knees were aspirated to yield 40–60 mL of frank pus containing 90,540 white blood cells (64% polymorphonuclear cells). The synovial fluid culture was negative, but the FilmArray® blood culture panel was positive for *H. influenzae.* Needle aspirates of both knees were performed 3 more times, and 5 mL of purulent fluid was also aspirated from the left ankle. An arthroscopy was planned but was not carried out because the surgeon thought that there was not enough intra-articular fluid.

After 13 days of conservative treatment, he was afebrile, but the knees were still swollen and very tender, and arthritis of the sternoclavicular joint developed (Fig. 1). The leukocytosis was not resolved and thrombocytosis of over 1,000,000 cells/μL gradually appeared as well. CRP levels remained over 100 mg/dL.

Magnetic resonance imaging of the right knee showed soft tissue collections within the gastrocnemius muscles, osteomyelitis of the tibial plateau, and diffuse severe sinovitis. Eventually, he underwent arthroscopy with complete sinovectomy and multiple rinsing of both knees, after which the knees improved clinically. Cultures from the operation were negative, but PCR from tissues taken during the operation were still positive for *H. influenzae* using the FilmArray® blood culture panel.

Echocardiography preformed twice during the hospitalization did not show evidence of endocarditis.

At that time, the pathology of the bone marrow biopsy returned and showed hypercellular marrow with over 50% plasma cells and monoclonality to lambda light chain, compatible with multiple myeloma. He completed 6 weeks of antibiotic therapy (4 of ceftriaxone and 2 of penicillin G) and began treatment with bortezomib, dexamethasone, and intravenous immunoglobulins.

Since *H. influenzae*–related infection is a notifiable disease in Israel, all isolates are sent to the Israeli national reference laboratory for verification and typing. The isolate cultivated from the blood of this patient was sent to the reference laboratory. There, it was subcultured on chocolate agar plates and incubated for 18 h at 35 °C in 5% CO2, and a DNA lysate was prepared by suspension of the culture in 200 mL 10 mM Tris–HCl and 1 mM EDTA and incubation at 100 °C for 10 min. *H. influenzae* confirmation and molecular serotyping were performed by multiplex polymerase chain reaction (Gonin et al., 2000), with primer pairs for detection of the ompP2 specific *H. influenzae* gene (Hobson et al., 1995), primers for detecting the *bexA* gene (van Ketel et al., 1990), and specific primers for each capsular type: a, b, c, d, e, f (Falla et al., 1994). The isolate was negative for *ompP2*, which indicated that it was not *H. influenzae*. The identity of the pathogen was further determined by 16S rRNA gene sequencing. PCR was performed according to CLSI guidelines (Petti and Clinical and Laboratory Standards Institute (CLSI), 2008), with the following modifications: primers 16S-F (TGGAGAGTTTGATCCTGGCTCAG) and 16S-R(TATTACCGCGGCTGC TGGCA). The PCR conditions were as follows: initial denaturation at 95 °C for 2 min followed by 28 cycles of 95 °C for 15 s, 65 °C for 15 s, and 73 °C for 30 s. Sequencing of the 16S rRNA gene revealed that the

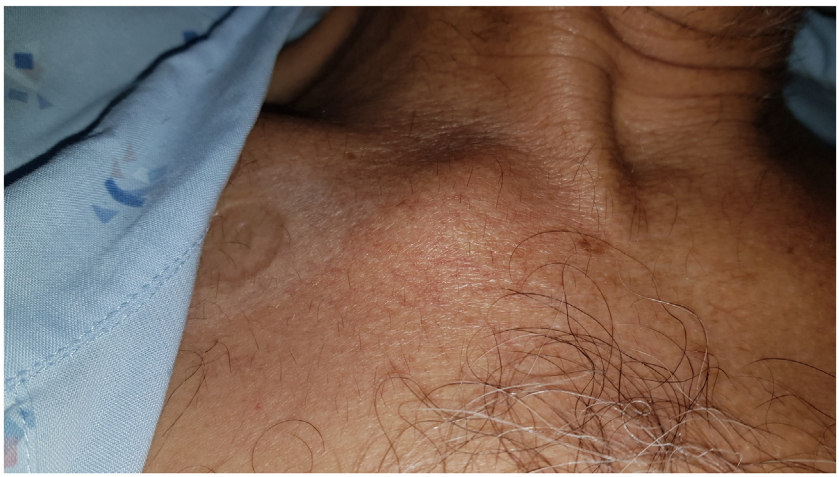

Fig. 1. Right sternoclavicular joint arthritis.

strain is "*Haemophilus quentini*" with 100% identity to accession number JF433944 (Glover et al., 2011). This was confirmed by 100% identity in sequencing using 16S rRNA gene PCR in another laboratory (Mak et al., 2005). The 16S forward and reverse sequences were submitted to Genbank under accession numbers MK169212 and MK169213. In addition, biochemical testing (Jorgensen et al., 2015) indicated the isolate was negative for indole and positive for urease and ornithine decarboxylase (biotype IV), as was previously described for "*H. quentini*" (Quentin et al., 1993).

2. Discussion

For many years, encapsulated species of *Haemophilus influenzae* (especially type b, Hib) caused a variety of invasive diseases including meningitis, epiglottitis, and bacteremic pneumonia, while nonencapsulated (nontypeable) *H. influenzae* (NTHi) species were traditionally linked to noninvasive infections, such as otitis, sinusitis, conjunctivitis, and nonbacteremic pneumonia (Van Eldere et al., 2014). During the last decades, probably related to the introduction of Hib vaccine during the 1990s, NTHi has emerged as a significant cause of invasive disease, primarily among patients at the extremes of age and among those with underlying comorbidities (Ladhani et al., 2010; Resman et al., 2011; Whittaker et al., 2017). NTHi is devoid of a polysaccharide capsule; hence, the species identification cannot rely on capsule serotyping, and molecular typing is the preferred method for accurate identification of NTHi, while multilocus sequence typing (MLST) is best for NTHi subtyping (Van Eldere et al., 2014). Quentin et al. (1990) described a cryptic genospecies of NTHi (biotype IV) commonly isolated from the genitourinary tract of females and causing neonatal invasive disease, and the name "*H. quentini*" was suggested. Invasive neonatal infections with this strain were repeatedly reported (Eshaghi et al., 2016; Giufre et al., 2015; Hubbard et al., 2016; Mak et al., 2005; Naito et al., 2018; Wallace et al., 1983), and it was also isolated from urethral samples of males (Horie et al., 2018). Phylogenetic analyses based on DNA–DNA hybridization (Quentin et al., 1993), restriction fragment length polymorphism (Quentin et al., 1993), and 16S rRNA sequencing (Quentin et al., 1996) indicated "*H. quentini*" formed a distinct clade. A recent study based on whole-genome comparison and MLST confirmed these previous analyses and indicated "*H. quentini*" is phylogenetically distinct from other *Haemophilus* species (Hubbard et al., 2018) and is more closely related to *H. haemolyticus* than to *H. influenzae*.

To the best of our knowledge, our report is the second to describe invasive disease caused by "*H. quentini*" in an adult patient (Eshaghi et al., 2016). Resman et al. reviewed 410 cases of *H. influenzae* during 12 years in Sweden and showed a significant increase in invasive NTHi disease, but although multiplex PCR was used to type 250 isolates, "*H. quentini*" was not reported among them (Resman et al., 2011).

Our experience indicates a cross-reaction of "*H. quentini*" with the *H. influenzae* targets in both the BioFire FilmArray® panels used: meningitis/encephalitis and blood culture identification. The user manuals of these assays report a cross-reaction of the *H. influenzae* target with *H. haemolyticus* only, and no cross-reactivity with the species *H. paraheamolyticus*, *H. parainfluenzae*, *H. parasuis*, and *H. somnus*. Due to its proven clinical significance, "*H. quentini*" is a relevant target in both assays. Regarding the MALDI-TOF misidentification, there is no "*H. quentini*" in the database probably since this is not an official species designation. However, there are 6 *Haemophilus* species, and the system should be capable, whenever there's a species that is not in the database, to report it as unknown and not to issue a mistaken diagnosis.

Multiple myeloma predisposes patients to infections with encapsulated bacteria, probably as a result of the humoral immune deficiency and hypogammaglobulinemia, and *H. influenzae* infections, including meningoencephalitis (Wagener et al., 1981), lobar pneumonia (Maritz and Joubert, 1980), septic arthritis (Berthaud et al., 1993), and endocarditis (*H. parainfluenzae)* (Menacker and Scher, 1988), were occasionally reported in these patients. Invasive NTHi disease in adults was reported mainly among patients over the age of 60 and among those with underlying comorbidities, including chronic pulmonary disease and patients with humoral immunity defects (as seen in chronic lymphatic leukemia and multiple myeloma (Resman et al., 2011)). Indeed, our patient had undiagnosed multiple myeloma at the time of the infection, in accordance with this review. In 1 of these cases (Berthaud et al., 1993), the underlying multiple myeloma was suspected and diagnosed as a result from this infection, as in our case.

The typical clinical presentations of invasive NTHi infection in adults consist of pneumonia, meningitis, or cholecystitis, while other presentations (typical of invasive Hib, such as cellulitis and epiglottitis) are uncommon (Giufre et al., 2011; Resman et al., 2011). Our patient's presentation was unique: he had multiorgan involvement appearing almost concurrently that included bacteremic pneumonia, meningitis, and polyarthritis that developed to osteomyelitis (although the latter may be related to inadequate source control of the articular infection). The bacterial meningitis in our case was highly unusual and diagnostically challenging, presenting with mild mononuclear pleocytosis, as usually seen in aseptic meningitis. Although this phenomenon could be evident early in the course of bacterial meningitis, in our case, the lumbar puncture was performed 5 days after the onset of the sepsis. The CSF glucose and protein levels were also only mildly disturbed.

Septic arthritis caused by *H. influenzae* is very rare, causing 1% of cases of bacterial arthritis. Most cases are caused by Gram-positive cocci (*S. aureus* or streptococci) and usually presented with a single inflamed joint. Polyarticular involvement occurs in 20% of septic joint infection and is seen among patients with preexisting connective tissue disorders or in patients with overwhelming sepsis. Two reviews of *H. influenzae* septic arthritis in adults (Borenstein and Simon, 1986; Ho et al., 1983) describe higher rates of polyarticular arthritis (24–37% of patients). Extra-articular focus of infection was described commonly in *H. influenzae* septic arthritis cases, occurring in 60–65% of cases (Borenstein and Simon, 1986; Ho et al., 1983). Another interesting feature may be that axial joints are more frequently reported (5/29, 17%) (Borenstein and Simon, 1986), with the sacroiliac and sternoclavicular joints involved in both reviews. Contrary to these reviews, when regarding NTHi, we located scarce case reports of NTHi-related mono- or oligoarthritis (Chien et al., 2010; Hawkins et al., 1991; Le Quellec et al., 2013; Turner et al., 2006), and only 3 case reports of NTHi-related polyarthritis (Kim et al., 2011; Melhus and Svernell, 1998; Saba et al., 1979). One case was a patient with multiple myeloma (Saba et al., 1979), and neither of these reports involved "*H. quentini.*" The articular infection of our case, caused by "*H. quentini,*" resembled the reported *H. influenzae* cases, as this patient also had polyarticular infection with axial involvement of the sternoclavicular joint as well as extensive extraarticular manifestations.

To conclude, we describe invasive infection caused by "*H. quentini*" in an immunocompromised adult, until now described mainly in neonates. The clinical presentation resembled more of *H. influenzae* than NTHi infection, causing disseminated disease including bacterial meningitis and pulmonary and septic arthritis. The polyarticular and axial joint involvement was also unique and typical more of *H. influenzae*. The frequently used diagnostic methods failed to identify the genus, which may indicate that "*H. quentini*" may have a much larger role in causing infections among immunocompromised hosts thought to be infected with *H. influenzae*.

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Conflicts of interest

None of the authors reported any conflict of interests regarding this manuscript.

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