□ CASE REPORT □

Septic Arthritis Subsequent to Urosepsis Caused by Hypermucoviscous *Klebsiella pneumoniae*

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Abstract

We herein report the first case of septic arthritis caused by *rmpA*-positive hypermucoviscous community-acquired *K. pneumoniae* that followed urosepsis in a 65-year-old Japanese woman. The patient responded well to drainage of the abscesses and treatment with cefazolin. Although this virulent phenotype of *K. pneumoniae* has been primarily reported in Hong Kong, we confirmed that 18/50 isolates obtained in our hospital over the past five years displayed the hypermucoviscous phenotype. Therefore, clinicians should consider the possibility of an increasing prevalence of *rmpA*-positive hypermucoviscous *K. pneumoniae* infection in Japan and be particularly vigilant for invasive clinical manifestations, even in patients with urinary tract infections.

Key words: *Klebsiella pneumoniae*, hypermucoviscosity phenotype, *rmpA*, septic arthritis

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Introduction

Klebsiella pneumoniae, a member of the Enterobacteriaceae family, is a pathogen with a worldwide distribution. It is associated with a variety of infections, particularly urinary tract infections (UTI) and pneumonia. Over the last two decades, a distinct clinical syndrome has emerged in Southeast Asia that is characterized by bacteremia, liver abscesses and metastatic infection (1, 2). Extrahepatic complications resulting from bacteremic dissemination, including endophthalmitis, meningitis, necrotizing fasciitis and abscess formation, have been reported (1). This invasive syndrome is associated with community-acquired strains of *K. pneumoniae* exhibiting a particular hypermucoviscous phenotype. These bacteria grow in sticky colonies on agar plates, can be identified using “string tests” and express the regulator of mucoid phenotype A gene (*rmpA*) (1-4).

This strain, with its distinct phenotypic and genotypic features, has been primarily reported in Hong Kong, Singapore and South Korea. However, as it is highly invasive, this bacteria is increasingly being spread worldwide, and Japan is

no exception to this issue. We herein report the first known Japanese patient with monomicrobial septic arthritis caused by an infection with *rmpA*-positive hypermucoviscous *K. pneumoniae* following a UTI.

Case Report

A 65-year-old Japanese woman presented with a history of general malaise and appetite loss lasting for one week. She had rheumatoid arthritis and was taking 10 mg of prednisolone daily, 6 mg of methotrexate weekly and 25 mg of diclofenac as needed to manage her symptoms. She also exhibited degenerative changes in her hip associated with rheumatoid arthritis. Two days before admission, she visited her primary care doctor and was prescribed an antifatulent agent based on a diagnosis of enterocolitis; however, the drug elicited a limited clinical response. The patient subsequently developed disturbed consciousness and was taken to our hospital by ambulance. She had no history of recent hospitalization or prolonged use of antibiotics. She was born in Japan and had not travelled outside of Japan.

On admission to our hospital, her consciousness level was

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Figure 1. (a-d) Computed tomography (CT) images obtained on admission showed abnormal gas within the bladder and bladder wall (arrowheads in c), consistent with a diagnosis of emphysematous cystitis. There was evidence of swelling, particularly on the left side of the hip (arrow in b). However, we were unable to confirm the presence of abscesses on plain CT images obtained at the initial visit due to the presence of degenerative changes associated with rheumatoid arthritis.

E3V4M6 on the Glasgow Coma Scale. Her blood pressure was 107/53 mmHg, her heart rate was 112 beats/min, her oxygen saturation was 100% on 4 L/min of oxygen inhalation, her respiratory rate was 22 beats/min and her body temperature was 38.0°C. No cardiac murmurs or abnormal respiratory sounds were heard. A physical examination revealed back tenderness. Rapid blood glucose testing revealed hypoglycemia (64 mg/dL), and intravenous glucose was administered. Other laboratory findings obtained on admission were as follows: white blood cell (WBC) count, 15,800/ μ L; hemoglobin, 5.9 g/dL; platelet count, 109 $\times$ 10³/ μ L; C-reactive protein, 23.4 mg/dL; albumin, 1.4 mg/dL; blood urea nitrogen, 24 mg/dL; creatinine, 0.96 mg/dL; and lactate dehydrogenase (LDH), 283 IU/L. Other liver indices and the blood electrolyte levels were within the normal ranges. The patient had not been previously diagnosed with diabetes mellitus, and her HbA1c level was 6.1% (Japan Diabetes Society unit). A urinalysis was positive for bacteriuria and pyuria. A computed tomography (CT) scan revealed no signs of infection in the lungs or upper abdominal organs; however, gas was observed within the bladder and bladder wall, suggesting emphysematous cystitis (Fig. 1).

Considering the clinical findings of hypoglycemia and py-

uria in addition to the radiological findings, we initially diagnosed the patient with sepsis secondary to a UTI. Because her anemia was normocytic normochromic and she was negative for fecal occult blood, she was also diagnosed with anemia and chronic disorders. Gram staining of a urine sample revealed abundant Gram-negative bacilli; therefore, we empirically treated her with intravenous meropenem (1 g every eight hours) after obtaining two sets of blood cultures and a urine culture.

The patient's hemodynamic status improved following the administration of the antibiotic therapy and a blood transfusion, and follow-up blood cultures were negative. However, two days after admission, she experienced difficulty walking due to hip pain. Both hip joints were swollen and tender, and there was local tissue warmth. Although a repeated CT scan showed that the amount of bladder gas had decreased, contrast scans revealed abnormal synovial fluid accumulation and multiple abscesses with ring enhancement (Fig. 2). Therefore, the patient was diagnosed with septic arthritis following a UTI, prompting the immediate administration of CT-guided drainage. Aspiration of both sides of the hip yielded 20 mL of turbid and yellowish synovial fluid with a WBC count of 22,650/ μ L (92% neutrophils), an LDH con-

Figure 2. (a-d) Computed tomography images obtained two days after admission revealed multiple abscesses with ringed enhancement following the administration of contrast medium (arrow-heads) together with abnormal synovial fluid accumulation (arrows), indicating septic arthritis. The abnormal gas in the bladder and bladder wall had disappeared by that time.

Figure 3. A string test was positive for *Klebsiella pneumoniae*. Stretching of the colonies resulted in the formation of a string measuring 12 mm in length, indicating the presence of the hypermucoviscous phenotype.

concentration of 5,397 IU/L and a glucose concentration of 19 mg/dL, consistent with a diagnosis of septic arthritis.

On the same day, the cultures of all blood and urine samples showed growth of *K. pneumoniae* with positive string test results (the result is considered positive when strings measuring ≥ 5 mm are observed and the colonies generate strings measuring 12 mm), indicating the presence of a hypermucoviscous phenotype (Fig. 3). All of the isolates were

resistant to ampicillin (minimum inhibitory concentration [MIC]: >16 $\mu\text{g/mL}$) but susceptible to cephalosporins (MIC: 1-8 $\mu\text{g/mL}$), including cefazolin (MIC: <4 $\mu\text{g/mL}$). Polymerase chain reaction (PCR) assays of the isolates of the blood, urine and synovial fluids subsequently revealed the presence of *rmpA*, as previously described (5). Semiautomated, repetitive, sequence-based PCR (rep-PCR) performed on a DiversiLab microbial typing system (bioMerieux, Marcy l'Etoile, France), which amplifies the regions between the noncoding repetitive sequences in bacterial genomes (6), confirmed that the isolates belonged to the same strain. Because the patient's abscesses improved following drainage, meropenem was replaced with cefazolin (2 g every eight hours) on day 6 of admission. The synovial fluid cultures prepared at that time were negative. The concentration of cefazolin in the synovial fluid was adequate, with concentrations at C4 and C8 of 77.3 and 32.2 $\mu\text{g/mL}$, respectively.

The patient responded well to repeated arthrocentesis and treatment with intravenous cefazolin for two weeks. She was then transferred to a regional medical center where she was treated with cefazolin for an additional two weeks, after which she was discharged with a prescription for a 2-week

course of oral levofloxacin (500 mg once daily). On discharge, she had no difficulties walking.

Discussion

We herein reported a case of bacteremia and septic arthritis caused by *K. pneumoniae*, without the formation of liver abscesses, in a patient with rheumatoid arthritis. To our knowledge, no cases of monomicrobial septic arthritis caused by community-acquired hypermucoviscous *K. pneumoniae* following a UTI have been reported in Japan. The most common pathogen of septic arthritis in adults is *Staphylococcus aureus*, which is responsible for 37-65% of cases, depending on the underlying disease (7). Approximately 75% of patients with rheumatoid arthritis are reported to have septic arthritis caused by *S. aureus* (7). In contrast, Gram-negative bacilli are cultured in only 9-20% of patients with bacterial arthritis admitted to teaching hospitals, and coliform bacteria, such as *Escherichia coli*, are more frequently isolated in such cases (7, 9). Neonates, elderly individuals, intravenous drug users, patients with chronic systemic disease or underlying joint damage and immunocompromised hosts are at high risk of developing Gram-negative arthritis (7, 10). Most infections occur secondary to a UTI or skin infection with subsequent bacteremic spread to joints. *K. pneumoniae*, a highly infectious organism that is capable of achieving hematogenous spread from its primary site of infection, is the second most common causative pathogen of UTIs (11), although it rarely causes septic arthritis (7, 12). In fact, as of 2009, only 19 cases of septic arthritis caused by *K. pneumoniae* had been reported in English-language medical journals (13).

Since the mid-1980s, there have been many reports of community-acquired invasive *K. pneumoniae* primary liver abscesses with sepsis followed by metastatic infections, such as endophthalmitis and meningitis, in Southeast Asian countries, particularly Taiwan (1, 2, 14, 15). The rate of metastatic infection ranges from 2.8% to 20% (16, 17). The cause of the high prevalence of this syndrome in Taiwan is unclear; however, it appears that the major factor is the microbe itself. This is because the invasive nature of some *K. pneumoniae* strains is dependent on the hypermucoviscous phenotype associated with serotypes K1 and K2 and *rmpA*, a gene that regulates capsular polysaccharide synthesis (2). The high prevalence of infectious strains in Taiwan may explain why the incidence of this severe syndrome is so high in this region (2). In addition, Lin and colleagues (11) demonstrated that hypermucoviscosity is strongly associated with the presence of *rmpA* in patients with UTIs caused by *K. pneumoniae* and that the *rmpA* gene may play an important pathogenic role in individuals with immunosuppression. It is also thought that, regardless of the capsular serotype, *rmpA*-associated hypermucoviscosity is the most common predictor of extrahepatic abscess formation and that the hypermucoviscous phenotype is an independent risk factor for *K. pneumoniae*-mediated invasive syndrome (2-4). CT scans

and abdominal ultrasound did not reveal any liver abscesses in our case. Based on these findings, we think that *rmpA*-positive hypermucoviscous *K. pneumoniae* is likely to induce septic arthritis following UTIs. In terms of host factors, underlying degenerative changes associated with rheumatoid arthritis and the long-term use of prednisolone and methotrexate most likely aided the invasiveness observed in our case.

More crucially, this highly invasive strain appears to be spreading worldwide due to increasing globalization (2), and Japan and Western countries are no exception to this issue (18-20). Therefore, clinicians should be cautious because the geographic distribution of this invasive strain is very different now compared with that observed in the last two decades. In fact, at our hospital, *K. pneumoniae* strains were detected in 50 blood samples between 2007 and 2011. Among these samples, 18 (36%) exhibited the hypermucoviscous phenotype, and 13 (72%) of the hypermucoviscous strains expressed *rmpA*. These results suggest that *rmpA*-positive hypermucoviscous *K. pneumoniae* is likely to induce the development of invasive syndrome and that its prevalence may be increasing, even in our hospital; therefore, clinicians must focus on the future trends of this organism. Because bacterial cultures are required to identify hypermucoviscosity or the *rmpA* expression, the presence of these factors can be determined only after the initiation of treatment. If an isolate obtained from a UTI sample expresses these factors, the presence of abscesses should be assessed by conducting a thorough physical examination and appropriate imaging tests. In this context, positive string test results may be the first clinical clue. It is also important to consider that only one-third of metastatic infections are found on admission (2, 17). Indeed, even when we retrospectively reevaluated our patient's swollen left hip joint, we were unable to reach a definitive diagnosis of septic arthritis. Because most metastatic infections appear within three days of presentation, clinicians should be cautious when trying to diagnose these infections during this time window. Making a definitive diagnosis of bacterial arthritis requires identification of bacteria in the synovial fluid. Moreover, due to the diverse number of possible organisms and the need for prolonged courses of pathogen-specific antimicrobial therapy (7), performing arthrocentesis and appropriate diagnostic cultures is essential in suspected cases of septic arthritis. Repeated arthrocentesis is as effective as joint drainage. Although the selection of empiric therapy is dictated by the results of synovial fluid Gram staining, antimicrobials with activity against Gram-negative bacilli should be chosen, especially in patients with chronic systemic diseases or underlying joint damage, as in our case.

Although hypermucoviscous *K. pneumoniae* has a negative impact on clinical manifestations, it does not express extended-spectrum β -lactamase (ESBL) and is susceptible to most antibiotics, except aminopenicillins (4). In patients with abscesses, optimal management includes the prompt administration of cephalosporins and percutaneous drainage

of the abscess; however, there is much controversy surrounding the treatment options, particularly the use of first- or third-generation cephalosporins. Chen et al. (16) reported higher rates of metastatic infection among patients treated with first-generation cephalosporins than in those treated with later generation cephalosporins. However, Lee et al. (17) described the controversy regarding the choice of late-generation cephalosporins and suggested that first-generation cephalosporins can be used instead due to their efficacy and relatively low cost. It has been suggested that the inoculum effect, a significant increase in the MIC associated with an increase in inoculum size, has an important predictive value for assessing *in vivo* efficacy, while the concentrations of extended-spectrum cephalosporins in the serum greatly exceed the MIC, even when the MIC is determined using a large inoculum (16). Therefore, until comparative trials are completed, we suggest that extended-spectrum cephalosporins can be administered until a decrease in the bacterial count in the abscess is achieved via drainage. In our patient, the synovial fluid concentration of cefazolin was adequate following the administration of 2 g of the drug every eight hours. Because the standard duration of treatment for septic arthritis accompanied by multiple abscesses is approximately six weeks, providing de-escalation therapy is essential. Little is known about synovial fluid therapeutic drug monitoring of relatively high doses of cefazolin; therefore, our data may provide useful information to help clinicians treat *rmpA*-positive *K. pneumoniae* septic arthritis.

In conclusion, clinicians should consider the possibility that the prevalence of hypermucoviscous *K. pneumoniae* infection is increasing in Japan and be aware of the disease's invasive clinical manifestations, even in patients with UTIs that accompany bacteremia. Further studies are urgently needed to assess the epidemiology of this infection and its optimal therapeutic strategies in Japan and other countries.

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

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