IDCases 21 (2020) e00893

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcr

Case report

Breakthrough and persistent bacteremia due to serotype K1 *Klebsiella pneumoniae* in an immunocompetent patient

Taketomo Maruki*, Daisuke Taniyama, Yumi Tsuchiya, Tomohide Adachi

Department of Infectious Diseases, Tokyo Saiseikai Central Hospital, Tokyo, Japan

ARTICLE INFO

Article history:
Received 20 January 2020
Received in revised form 25 June 2020
Accepted 25 June 2020

Keywords:
Klebsiella pneumoniae
Hypervirulent
Serotype K1
rmpA
Breakthrough bacteremia
String test

ABSTRACT

Herein, we report a case of breakthrough and persistent bacteremia due to serotype K1 *Klebsiella pneumoniae* in an immunocompetent 53- year-old man. He was diagnosed with pyogenic spondylitis owing to back pain and based on magnetic resonance imaging findings. On admission, several imaging studies were taken to search for other abscesses and infective endocarditis; however, there were no significant findings. Additionally, blood cultures were negative. Upon treatment with intravenous ampicillin/sulbactam, the patient's symptoms improved. However, eleven days after admission, the patient experienced a fever and worsening back pain. Blood cultures were taken again, and *K. pneumoniae* was detected, which showed sensitivity to ampicillin/sulbactam. Fourteen days after admission, *K. pneumoniae* was detected again, suggesting breakthrough and persistent bacteremia with *K. pneumoniae*. The source of the *K. pneumoniae* infection was unknown. The antimicrobial regimen was changed to a combination of ceftriaxone and gentamicin. Sixty days after admission, the patient was discharged without any sequelae. The isolated *K. pneumoniae* strains were found to carry *rmpA* and were confirmed as serotype K1; thus, detected hypervirulent *K. pneumoniae* (HvKP). HvKP is an increasingly recognized pathotype of *K. pneumoniae* characterized clinically by its ability to cause organ- or life-threatening infections in healthy persons. To the best of our knowledge, our case is the first report of spondylitis due to confirmed HvKP. Moreover, HvKP caused breakthrough and persistent bacteremia on an immunocompetent patient.

Introduction

Klebsiella pneumoniae is a gram-negative bacterium widely known to cause both community and hospital-acquired infections. There are two different groups of *K. pneumoniae*: classical and hypervirulent (HvKP). HvKP, first identified in Taiwan in 1986, has the ability to cause organ- or life-threatening infections, including liver abscesses, pneumonia, meningitis and endophthalmitis, in healthy individuals [1]. There are several virulence factors that contribute to the pathogenicity of HvKP, such as hypermucoviscosity-specific capsular serotypes, especially K1 or K2. The capsules of K1 and K2 serotypes protect the bacteria from phagocytosis. Also, the *rmpA* gene is a plasmid-mediated regulator of capsular polysaccharide synthesis. These factors are associated with the hypermucoviscosity phenotype and invasive disease [2]. We, herein, report a case of breakthrough and persistent bacteremia due to a K1 serotype *K. pneumoniae* carrying *rmpA*. We suggest that the strong pathogenicity of HvKP strains, such as the strain in our case, caused the special clinical course.

Case

A 53-year-old man presented with fever and back pain lasting for about 1 month. The patient did not have prior medical history, never used immunosuppressants, and was a businessperson and heavy drinker, consuming more than 150 g of alcohol per day. On admission, the patient had a temperature of 38.1 ℃, blood pressure 122/78 mmHg, heart rate 92 bpm, respiratory rate 16 breaths/min, and percutaneous arterial oxygen saturation of 98 % (while breathing ambient air). Physical examination revealed back tenderness to percussion and a supple neck. Cardiovascular examination was normal, lungs were clear to auscultation, abdominal examination was unremarkable, and no skin lesions were found. Neurological examination was completely unremarkable. Initial blood tests on admission showed an elevated level of C-reactive protein (CRP) (9.97 mg/dL), erythrocyte sedimentation rate (52 mm/hr), a normal leucocyte count (6300 /μL), and normal neutrophil count (3320/μL). Liver enzymes and creatine kinase were normal. Hemoglobin A1c was 5.2 %. There was no pyuria or

* Corresponding author at: Department of Infectious Diseases, Tokyo Saiseikai Central Hospital, 1-4-17 Mita, Minato-ku, Tokyo 108-0073, Japan.
E-mail address: marutakemm472@gmail.com (T. Maruki).

https://doi.org/10.1016/j.idcr.2020.e00893

bacteriuria. Magnetic resonance imaging (MRI) showed a high intensity signal, mainly on the 10th and 11th thoracic vertebrae under short T1 inversion recovery (STIR) fat suppression conditions (Fig. 1), and he was diagnosed with pyogenic spondylitis. Whole body computed tomography (CT) and brain MRI were performed, but there were no significant findings. Transthoracic echocardiogram (TTE) and transesophageal echocardiography (TEE) were also performed, and vegetation and valve dysfunction were not confirmed. Additionally, there were no dental caries, and no findings of endophthalmitis in the eye. We consulted with an orthopedic surgeon to perform a CT-guided biopsy; however, it was difficult due to the location of the lesion. For that, the patient was administered 3 g of ampicillin/sulbactam intravenously 4 times a day (a total of 12 g per day) after blood cultures were taken. In response to treatment, his fever reduced and his other symptoms improved. Although blood cultures on admission were negative, the patient developed a fever of 40 ℃ and worsening back pain eleven days after admission. His CRP level and erythrocyte sedimentation rate that had once improved increased again. Blood cultures were taken at that time, and gram-negative rods were identified. We then considered that the bacteria was resistant to ampicillin/sulbactam, and the antibacterial treatment was changed to 1 g of meropenem 3 times per day (a total of 3 g per day). It was found that the patient was infected with *Klebsiella pneumoniae* that was sensitive to ampicillin/sulbactam. Fourteen days after admission, blood cultures were taken to investigate if the patient had persistent bacteremia and *K. pneumoniae* was detected again. From this result, it was suggested the patient had breakthrough and persistent bacteremia with *K. pneumoniae*. To determine where the strains may have originated, esophagogastroduodenoscopy (EGD), colonoscopy (CS), and magnetic resonance cholangiopancreatography (MRCP) were performed. However, there were no substantial findings. The patient was suspected of having an immunodeficiency; however, HIV screening and the HTLV-1-antibody tests were negative. Immunologic evaluation revealed the following values: IgG of 1210 mg/dL (normal range: 700–1600 mg/dL), IgA of 55 mg/dL (normal: 70–400 mg/dL), and IgM of 157 mg/dL (normal: 40–230 mg/dL). Evaluation of complement function revealed the following values: C3 of 109 mg/dL (normal: 90–180 mg/dL) and C4 of 35 mg/dL (normal: 10–40 mg/dL). $CD4^+$ T-lymphocyte count was 920 cells/μL (normal: 500–1500 cells/μL). The antimicrobial regimen was changed again to a combination of 2 g of ceftriaxone 2 times a day (a total of 4 g per day) and 1 mg/kg of body weight of gentamicin 3 times a day (a total of 3 mg/kg of body weight per day). Seventeen days after admission, blood cultures were negative, and clinical findings and inflammatory responses were also resolved. The patient remained on antimicrobial therapy for forty-two days from when blood cultures were negative. Sixty days after admission, the patient was discharged without any sequelae (Fig. 2). Since then, he has had no recurrence for more than 6 months.

When a bacterial colony was touched with a loop, a viscous rope measuring 12 mm formed (Fig. 3). Based on the cultured strain's hypermucoviscosity and the patient's aggressive clinical course, the pathogen was suspected to be hypervirulent *K. pneumoniae* (HvKP). The strain was determined to be serotype K1 and carried *rmpA* by whole genome sequencing using Illumina MiSeq.

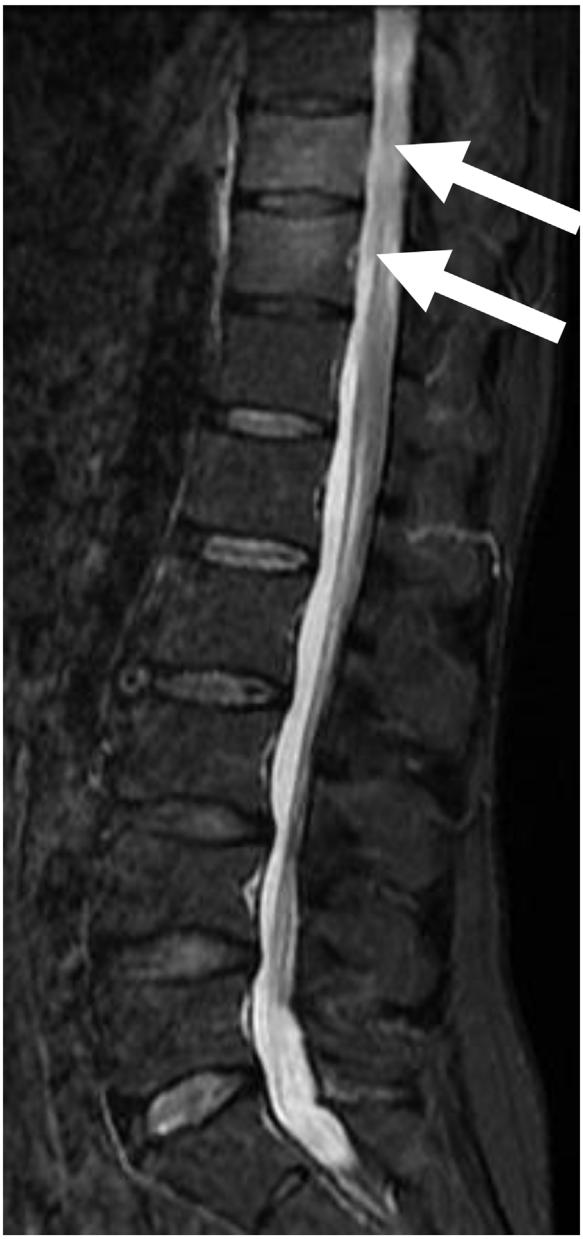

Fig. 1. Spinal short tau inversion recovery (STIR) magnetic resonance imaging on admission showed high signal intensity at the level of Th10-11 (white arrow) suggestive of a disk space infection and spondylitis.

Discussion

In our case, *K. pneumoniae* was responsible for breakthrough and persistent bacteremia during treatment of pyogenic spondylitis. Typically, breakthrough bacteremia is revealed as positive blood cultures despite appropriate antimicrobial therapy [3]. There are several cases of *K. pneumoniae* breakthrough bacteremia that have been reported. Most of them were due to an acquired bacterial resistance, such as a represented carbapenemase [4], or an extended-spectrum-β-lactamase (ESBL) [5]. On the other hand,

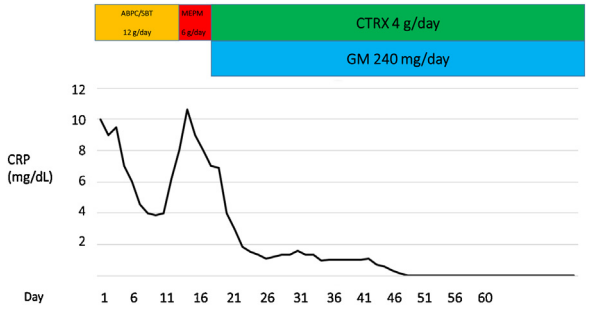

Fig. 2. The patient's clinical course. ABPC/SBT: ampicillin/sulbactam, MEPM: meropenem, CTRX: ceftriaxone, GM: gentamicin.

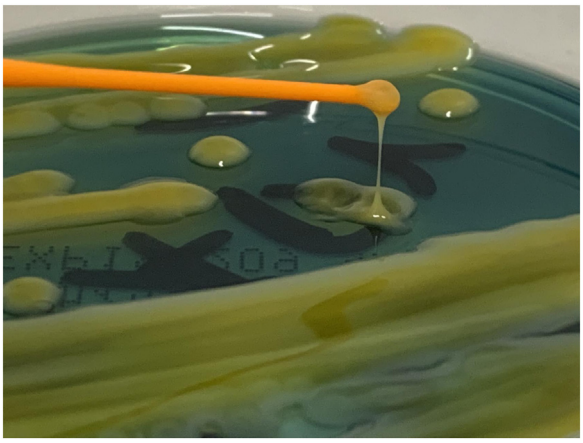

Fig. 3. The string test confirming the hypermucoviscosity of *Klebsiella pneumoniae*. The formation of a viscous rope was 12 mm when a bacterial colony was touched with a loop on a B.T.B. Lactose Agar plate. A positive result is defined as string formation greater than 5 mm.

in our case, the *K. pneumoniae* strain from the patient had not gained resistance to ampicillin/sulbactam. Persistent bacteremia is defined as at least two positive blood cultures obtained on different calendar days during the same infectious episode [6]. Persistent bacteremia is a characteristic of infective endocarditis and other intravascular infections, such as vascular graft infection, a mycotic aneurysm, or an infected thrombus [7]. In contrast, it has been proposed that intermittent bacteremia may occur in patients with spondylodiscitis [7]. In our case, we excluded infective endocarditis and other lesions except spondylitis by CT, TTE, TEE, and brain MRI on admission. In addition, we searched for the site that may have been the source for the persistent *K. pneumoniae*. A previous study showed that the focal source of *Klebsiella* bacteremia was the genitourinary tract in 25 % of cases, the biliary tract in 19 % of cases, and intra-abdominal in 10 % of cases [8]. We performed EGD, CS, and MRCP and we observed no abnormal findings. Despite previous reports of periodontitis as a portal of entry for *K. pneumoniae* [9], our patient's oral cavity was clean and there were no dental caries. Therefore, the entry site of the *K. pneumoniae* in our case remained unknown. Consequently, we suspected the cause of the *K. pneumoniae* breakthrough and persistent bacteremia was the pyogenic spondylitis lesion.

Furthermore, in our case, the patient was immunocompetent. There are several known risk factors for *K. pneumoniae* bacteremia including dialysis, chronic liver diseases, organ transplantation, cancer, and diabetes mellitius [8]. It has been reported that alcoholism is related to the mortality of *K. pneumoniae* bacteremia but has not been a proven risk factor of *K. pneumoniae* infection [8]. Although the patient was a heavy drinker, laboratory findings and images did not reveal any findings suggesting cirrhosis. The risk factor for *K. pneumoniae* bacteremia remained unknown in our case.

We suspected that the cause of the special conditions in our case was the strong pathogenicity of HvKP. HvKP has been increasingly recognized as a pathotype of *K. pneumoniae* and has been characterized clinically by its ability to cause organ or life-threatening infections in healthy hosts. HvKP exhibits hypermucoviscosity, causing various severe infections in immunocompetent and young healthy individuals [10]. Previously published molecular epidemiologic data led us to hypothesize that HvKP produced more siderophores than other strains and that this trait enhanced HvKP virulence [11]. The string test has been useful in identifying HvKP strains in the clinical setting [12]. However, recent reports have suggested that identifying HvKP by the string test alone is not sufficient [10]. Regarding pathogenicity, serotypes K1 and K2, along with *magA*, *rmpA*, and *rmpA2* genes are strongly associated with HvKP [10]. In our case, after we suspected that our strain was HvKP from the positive string test, genetic testing confirmed our *K. pneumoniae* was serotype K1 which carried *rmpA*.

Several cases of spondylitis with *K. pneumoniae* have been reported to date [13–16]. However, there have been no cases of spondylitis due to HvKP. Moreover, the previous cases of spondylitis with *K. pneumoniae* were not accompanied by breakthrough or persistent bacteremia. To the best of our knowledge, our case is the first report of spondylitis due to confirmed HvKP, including the special clinical course caused by the strong pathogenicity of a HvKP strain.

To date, most HvKP strains have been very susceptible to antimicrobials except ampicillin [1]. Similarly, in our case, HvKP showed sensitivity to ampicillin/sulbactam. In situations of breakthrough and persistent bacteremia that occur during treatment with sensitive antimicrobials, as in our case, a combination of a third-generation cephalosporin and an aminoglycoside may be recommended in accordance with *Klebsiella* infective endocarditis [17]. Our case was not infective endocarditis, but the patient's symptoms resolved once changed to this regimen. Further investigation is required to determine the best antimicrobial regimen for HvKP infection.

We have reported the case of a healthy 53-year-old man with pyogenic spondylitis and breakthrough bacteremia caused by serotype K1 *K. pneumoniae* that finally resulted in a complete cure with antibacterials. In conclusion, HvKP strains may cause breakthrough and persistent bacteremia, even in an immunocompetent adult. Therefore, determining an adequate treatment course is of considerable clinical importance.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Informed consent

The patient provided informed consent before this article was written.

Author contribution

Taketomo Maruki and Daisuke Taniyama contributed to the report concept and design.

Taketomo Maruki, Daisuke Taniyama, Yumi Tsuchiya, and Tomohide Adachi performed the acquisition of patient's data.

Taketomo Maruki and Daisuke Taniyama prepared and wrote the manuscript.

Declaration of Competing Interest

The authors disclose no conflicts of interest.

Acknowledgements

The authors wish to thank Dr. Kotaro Aoki (Department of Microbiology and Infectious Diseases, Toho University School of Medicine) for gene identification of strains.

References

[1] Shon AS, Bajwa RP, Russo TA. Hypervirulent (hypermucoviscous) *Klebsiella pneumoniae*: a new and dangerous breed. Virulence 2013;4:107–18.

[2] Poothakuzhiyil R, Mariappan S, Uma S. Occurrence and characterization of hyperviscous K1 and K2 serotype in *Klebsiella pneumoniae*. J Lab Phys 2018;10:283–8.

[3] López Dupla M, Martinez JA, Vidal F, et al. Clinical characterization of breakthrough bacteraemia: a survey of 392 episodes. J Intern Med 2005;258:172–80.
[4] Stone Nr, Woodford N, Livermore Dm, et al. Breakthrough bacteraemia due to tigecycline-resistant *Escherichia coli* with New Delhi metallo-β-lactamase (NDM)-1 successfully treated with colistin in a patient with calciphylaxis. J Antimicrob Chemother 2011;66:2677–8.
[5] Cho SY, Kang CI, Chung DR, Peck KR, Song JH, Jang JH. Breakthrough bacteremia due to extended-spectrum-β-lactamase-producing *Klebsiella pneumoniae* during combination therapy with colistin and tigecycline. Antimicrob Agents Chemother 2012;56:4994–5.
[6] Chowers MY, Gottesman B, Paul M, Weinberger M, Pitlik S, Leibovici L. Persistent bacteremia in the absence of defined intravascular foci: clinical significance and risk factors. Eur J Clin Microbiol Infect Dis 2003;22:592–6.
[7] Seifert H. The clinical importance of microbiological findings in the diagnosis and management of bloodstream infections. Clin Infect Dis 2009;48:238–45.
[8] Meatheral L, Gregson D, Ross T, Pitout JD, Laupland KB. Incidence, risk factors, and outcomes of *Klebsiella pneumoniae* bacteremia. Am J Med 2009;122:866–73.
[9] Kouroussis C, Georgoulias V, Souglakos J, Simvoulakis E, Karabekios S, Samonis G. Spontaneous spondylodiscitis caused by *Klebsiella pneumonia*. Infection 1999;27:368–9.
[10] Chao L, Jun G. Hypervirulent *Klebsiella pneumoniae* (hypermucoviscous and aerobactin positive) infection over 6 years in the elderly in China: antimicrobial resistance patterns, molecular epidemiology and risk factor. Ann Clin Microbiol Antimicrob 2019;18:4.
[11] Russo TA, Olson R, Macdonald U, et al. Aerobactin mediates virulence and accounts for increased siderophore production under iron-limiting conditions by hypervirulent (hypermucoviscous) *Klebsiella pneumoniae*. Infect Immun 2014;82:2356–67.
[12] Lee HC, Chuang YC, Yu WL, et al. Clinical implications of hypermucoviscosity phenotype in *Klebsiella pneumoniae* isolates: association with invasive syndrome in patients with community acquired bacteraemia. J Intern Med 2006;259:606–14.
[13] Inagaki A, Moriyama Y, Morioka S, Wakimoto Y, Shida Y, Ohmagari N. A case of *Klebsiella pneumoniae* spondylitis and bacteremia potentially due to inflammation around a fecalith. J Infect Chemother 2019;25:470–2.
[14] Kosai K, Seki M, Yanagihara K, et al. Spontaneous pyogenic spondylitis caused by *Klebsiella pneumoniae*. Intern Med 2008;47:1121–4.
[15] Barton E, Flanagan P, Hill S. Spinal infection caused by ESBL-producing *Klebsiella pneumoniae* treated with temocillin. J Infect 2008;57:347–9.
[16] Hsieh MJ, Lu TC, Ma MH, Wang HP, Chen SC. Unrecognized cervical spinal epidural abscess associated with metastatic *Klebsiella pneumoniae* bacteremia and liver abscess in nondiabetic patients. Diagn Microbiol Infect Dis 2009;65:65–8.
[17] Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American heart association. Circulation 2015;132:1462–3.