Endogenous Endophthalmitis Caused by ST66-K2 Hypervirulent Klebsiella pneumoniae, United States

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We describe a case of endogenous endophthalmitis caused by sequence type 66-K2 hypervirulent Klebsiella pneumoniae in a diabetic patient with no travel history outside the United States. Genomic analysis showed the pathogen has remained highly conserved, retaining >98% genetic similarity to the original strain described in Indonesia in 1935.

Hypervirulent Klebsiella pneumoniae (hvKp) strains are mostly community-acquired and can cause invasive infections such as liver abscess with metastatic spread (1,2). The genetic determinants of hypervirulence are found on chromosomal mobile genetic elements, large plasmids, or both. The most common virulence determinants of hvKp include siderophore systems for iron acquisition, increased capsule production, K1 and K2 serotypes, and the colibactin toxin (1). In addition, these hvKp strains demonstrate hypermucoviscosity, as indicated by a positive string test, and are usually susceptible to antimicrobial drugs (1). However, multidrug-resistant hypervirulent strains have emerged in Asia, a region to which hvKp is endemic (1,3). Kp52.145 (laboratory strain B5055), which belongs to sequence type (ST) 66, is one of the most virulent and widely studied K2 strains. The ST66-K2 sublineage contains virulence genes in its chromosome and 2 large plasmids (4,5). ST66-K2 was isolated in Indonesia in 1935; since then, cases have been reported in Australia in 2002 (caused by strain AJ210), Germany in 2017 (caused by strain 18-0005) and France in 2018 (caused by strain SB5881) (6–8).

The most common hvKp infection metastatic sites are the eyes, lungs, and central nervous system (1). Endogenous endophthalmitis (EE) caused by hvKp is associated with risk factors such as diabetes mellitus, Asian ancestry, and infection with the K1 serotype (2). Although the prevalence of hvKp is increasing in the United States and Europe (1,2,9), where EE has been documented in patients of Asian and non-Asian descent (9,10), these infections are not well-recognized. Ocular prognoses and clinical outcomes for EE are usually poor and exacerbated by late or missed diagnosis (2). We describe a case of EE caused by a hvKp strain of the ST66-K2 sublineage in the United States.

The Study

A 30-year-old Caucasian man who had a history of poorly controlled type 1 diabetes mellitus and recreational use of methamphetamine and intravenous heroin sought treatment at the emergency department of a local hospital in California, USA, for progressive right eye and ear pain, which had lasted 1 week, and vision loss. Hospital staff noted substantial edema and tenderness of the right external auditory canal with otorrhea, along with suspected orbital cellulitis. Computed tomography scans revealed complete opacification of the right middle ear cavity and mastoid air cells, prominent thickening and hyperenhancement of the right posterolateral sclera, and a cystic and necrotic lesion in the left parotid region. He was prescribed vancomycin and cefepime and then transferred to Ronald Reagan UCLA Medical Center (Los Angeles, CA, USA) for ophthalmologic evaluation.

At admission, he had a perforated right tympanic membrane with external otitis media and mastoiditis, a left parotid abscess, and right endogenous endophthalmitis with subretinal abscess. A transthoracic echocardiogram showed no signs of valvular vegetations; an abdominal ultrasound showed no signs of hepatic lesions. Results of blood cultures were negative. Cultures from the parotid abscess and ear
**Table.** Single-nucleotide polymorphism matrix of 5 ST66-K2 hypervirulent *Klebsiella pneumoniae* strains

| Strain (country, year [reference]) | 18-0005 | AJ210 | Kp52.145 | SB5881 | UCLA353 |
|-----------------------------------|---------|-------|----------|--------|----------|
| 18-0005 (Germany, 2017 [7])       | 0       | 65    | 219      | 56     | 796      |
| AJ210 (Australia, 2002 [6])       | 65      | 0     | 208      | 71     | 785      |
| Kp52.145 (Indonesia, 1935 [1/1])  | 219     | 208   | 0        | 225    | 775      |
| SB5881 (France, 2018 [8])         | 56      | 71    | 225      | 0      | 802      |
| UCLA353 (United States, 2020, this study)* | 796   | 785   | 775      | 802    | 0        |

*Isolate from a 30-year-old man in California who had endogenous endophthalmitis.*
recently described phospholipase D family protein gene (Figure) (11). In addition, UCLA353 carried 2 plasmids (with lengths of 95,157 bp and 164,217 bp) nearly identical to those present in the SB5881 isolate documented in 2018 in France (GenBank accession nos. LR792629 and LR792630), with 100% genomic coverage and 99.9% pairwise identity (Appendix Figure 2). The 95-kb plasmid I in UCLA353 was also nearly identical to the Kp52.145 plasmid I (GenBank accession no. FO834904); the 164-kb plasmid II shared 100% genome coverage with Kp52.145 plasmid II (FO834905) but had a 39-kb sequence insertion previously described in SB5881 (8) (Appendix Figure 2). SNP analysis of the chromosomal sequences of UCLA353 and the other 4 ST66-K2 strains revealed that UCLA353 was genetically distinct, with 775 SNPs compared with Kp52.145 and 785–802 compared with AJ210, 18-0005, and SB5881 (Table 1). UCLA353 did not carry any resistance genes. Similar to other ST66-K2 strains, UCLA353 did not have the blaSHV gene, and was therefore susceptible to β-lactams including ampicillin (Appendix Table 1). Further analysis showed all the ST66-K2 strains carried highly similar virulence factors (Appendix Table 2).

Conclusions

Ocular prognoses and clinical outcomes for EE are usually poor, often entailing partial or complete vision loss, enucleation or evisceration, or death (2). Late or missed diagnosis delays the initiation of specialized ocular therapy (e.g., intravitreal or source control) and can worsen outcomes. Early treatment is crucial to preserving full or partial vision (1–3,10). A pooled analysis of clinical studies revealed that most (83.2%) EE infections caused by hvKp were detected >24 hours after admission (2). These data indicate that patients at high risk for EE, especially those with underlying conditions such as diabetes mellitus or K. pneumoniae-associated pyogenic liver abscess, should be monitored closely for EE even when it is not initially apparent. Detection of K1 or K2 capsular serotypes, hypermucoviscous phenotype, and ampicillin susceptibility might suggest disseminated EE caused by hvKp. Although bacteremia is usually a prerequisite for metastatic dissemination, it may not always be detectable (1,2).

This infection probably began as otitis externa complicated by otitis media caused by perforated tympanic membrane and otomastoiditis, conditions that subsequently spread to the sinuses and right orbit. In a similar scenario, strain SB5881 also caused invasive infection including acute otitis media in a patient with type 1 diabetes mellitus and chronic alcoholism (8). Despite its emergence in or before 1935, ST66-K2 hvKp infections were not reported until 2002, probably because of the limited availability of high-resolution genomic sequencing tools in the 20th century (8,11). Thus, the prevalence of ST66-K2 hvKp might be largely underestimated.

In summary, we describe a case of EE caused by ST66-K2 hvKp in a Caucasian diabetic man with no travel history outside the United States. This lineage has remained highly conserved, preserving all of its virulence factors and >98% of its genome. Clinicians should be aware of the threat and challenges of EE caused hvKp infections.

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Appendix

**Appendix Figure 1.** Positive string test for hypermucoviscuous *Klebsiella pneumoniae* cultures grown from left parotid abscess and right ear drainage samples of a patient with endogenous endophthalmitis, United States.
Appendix Figure 2. Whole-genome alignment of *Klebsiella pneumoniae* plasmids. Values indicate base pairs. Corresponding colors indicate nearly identical sequences. A) UCLA353 plasmid I and SB5881 plasmid I (GenBank accession no. LR792630). B) UCLA353 plasmid II and SB5881 plasmid II (GenBank accession no. LR792629). C) UCLA353 plasmid I and Kp52.145 plasmid I (GenBank accession no. FO834904). D) UCLA353 plasmid II and Kp52.145 plasmid II (GenBank accession no. FO834905). Images generated by Geneious Prime (Geneious, https://www.geneious.com).
### Appendix Table 1. Antimicrobial susceptibility profile of *Klebsiella pneumoniae* strain UCLA353

| Antimicrobial drug                      | Minimal inhibitory concentration, µg/mL | Interpretation |
|----------------------------------------|----------------------------------------|----------------|
| Piperacillin/tazobactam                | ≤8                                     | Susceptible    |
| Cefazolin                              | 2                                      | Susceptible    |
| Ceftriaxone                            | ≤1                                     | Susceptible    |
| Ceftazidime                            | ≤0.5                                   | Susceptible    |
| Ceftolozane/tazobactam                | ≤0.5                                   | Susceptible    |
| Cefepime                               | ≤0.5                                   | Susceptible    |
| Imipenem                               | ≤0.25                                  | Susceptible    |
| Meropenem                              | ≤0.25                                  | Susceptible    |
| Gentamicin                             | ≤1                                     | Susceptible    |
| Tobramycin                             | ≤1                                     | Susceptible    |
| Amikacin                               | ≤4                                     | Susceptible    |
| Ceftazidime/avibactam                 | ≤2                                     | Susceptible    |
| Ertapenem                              | ≤0.25                                  | Susceptible    |
| Trimethoprim/sulfamethoxazole          | ≤1/20                                   | Susceptible    |
| Ciprofloxacin                          | ≤0.25                                  | Susceptible    |
| Levofloxacin                           | ≤0.5                                   | Susceptible    |
| Ampicillin                             | 2                                      | Susceptible    |
| Colistin                               | ≤2                                     | Wildtype       |

### Appendix Table 2. Chromosomal virulence factors in *Klebsiella pneumoniae* strains UCLA353, AJ210, SB5881, and 18-0005.

| Virulence factor    | Locus | UCLA353 | AJ210 | SB5881 | 18-0005 | Alleles |
|---------------------|-------|---------|-------|--------|---------|---------|
| Colibactin          | clbA  | 1       | 1     | 1      | 1       | 1       |
|                     | clbB  | –       | –     | 4      | 4       | 4       |
|                     | clbC  | 1       | –     | 1      | 1       | 1       |
|                     | clbD  | 1       | –     | 1      | 1       | 1       |
|                     | clbE  | –       | 1     | 1      | 1       | 1       |
|                     | clbF  | 1       | –     | 1      | 1       | 1       |
|                     | clbG  | 1       | 1     | 1      | 1       | 1       |
|                     | clbH  | 5       | –     | 5      | 5       | 5       |
|                     | clbl  | 1       | –     | –      | 1       | 1       |
|                     | clbL  | 1       | –     | 1      | 1       | 1       |
|                     | clbM  | 1       | 1     | 1      | 1       | 1       |
|                     | clbN  | 1       | –     | 1      | 1       | 1       |
|                     | clbO  | 1       | 1     | 1      | 1       | 1       |
|                     | clbP  | 1       | 1     | 1      | 1       | 1       |
|                     | clbQ  | 1       | 1     | 1      | 1       | 1       |
|                     | clbR  | 1       | –     | 1      | 1       | 1       |
| Type 3 fibriae      | mrkA  | 2       | 2     | 2      | 2       | 2       |
|                     | mrkJ  | 87      | 87    | 87     | 87      | 87      |
|                     | mrkA  | 9       | –     | 9      | 9       | 9       |
|                     | mrkK  | 10      | –     | –      | –       | –       |
|                     | mrkC  | 302     | 302   | 302    | 302     | 302     |
|                     | mrkD  | 8       | –     | 8      | 8       | 8       |
|                     | mrkF  | 2       | 2     | 2      | 2       | 2       |
|                     | mrkI  | 3       | 3     | 3      | 3       | 3       |
|                     | mrkJ  | 6       | 6     | 6      | 6       | 6       |
| Yersiniabactin      | ybtA  | –       | –     | 1      | 1       | 1       |
|                     | ybtA  | –       | 39    | 39     | 39      | 39      |
|                     | ybtE  | 1       | 1     | 1      | 1       | 1       |
|                     | ybtP  | 1       | 1     | 1      | 1       | 1       |
|                     | ybtQ  | 1       | –     | 1      | 1       | 1       |
|                     | ybtS  | 1       | 7     | –      | 7       | 7       |
|                     | ybtU  | 1       | 1     | 1      | 1       | 1       |
|                     | ybtX  | 1       | –     | 1      | 1       | 1       |
|                     | irp1  | –       | –     | 16     | 16      | 16      |
|                     | irp2  | –       | –     | 3      | 3       | 3       |
|                     | fyuA  | 1       | –     | 1      | 1       | 1       |