Invasive Klebsiella pneumoniae Syndrome in North America

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Invasive liver abscess syndrome, which is caused by hypervirulent Klebsiella pneumoniae subtypes, has been emerging worldwide over the past 2 decades. The syndrome is associated with the hypermucoviscosity phenotype of K. pneumoniae strains and with the magA and rmpA genes. We provide the first laboratory evidence of the presence of rmpA-positive K. pneumoniae in North America.

Klebsiella pneumoniae, a member of the Enterobacteriaceae family, is a pathogen with worldwide distribution. For the past 2 decades, a distinct clinical syndrome has been emerging in Southeast Asia that is characterized by bacteremia, liver abscesses, and metastatic infections [1–4]. A common and often devastating complication is endophthalmitis [5, 6]. Involvement of the CNS can also occur, causing suppurative meningitis or brain abscess [7]. Other reported manifestations include abscesses in the lungs, prostate, and soft tissue; necrotizing fasciitis; and osteomyelitis. This disease is community acquired, and patients are usually immunocompetent and have no underlying intestinal or hepatobiliary problems. The invasive nature of certain K. pneumoniae strains appears to correlate with an extreme “stickiness” of these colonies on agar plates: this is known as the hypermucoviscosity phenotype [8]. The role of various genetic determinants of K. pneumoniae in the generation of the hypermucoviscosity phenotype and of the invasive syndrome is the subject of ongoing research. Two of the most commonly studied genes associated with this syndrome are mucoviscosity-associated gene A (magA) and regulator of mucoid phenotype A (rmpA).

The magA gene was first described by in 2004 Fang et al. [9], who reported that hypermucoviscosity and magA were more prevalent in invasive strains of K. pneumoniae and that magA-negative mutant strains lost their exopolysaccharide web and became susceptible to serum and phagocytosis. However, a significantly lower frequency of magA was found in a study by Yu et al. [10]. Their study involved patients from a different region in Taiwan and included many persons with fulminant abscesses at extra-hepatic sites. It is now known that magA is restricted to the gene cluster of K. pneumoniae capsule serotype K1 [11, 12], and the operon that contains magA is responsible for the serotype K1 [13]. Therefore, the variation in the prevalence of magA among studies may reflect geographic differences in the prevalence of the K1 serotype.

The rmpA gene is a plasmid-mediated regulator of the extracapsular polysaccharide synthesis. It was first described by Nassif et al. [14] in 1989. Nassif and colleagues showed that the mucoid phenotype, a virulence factor, is distinct from capsule synthesis and is positively controlled by the plasmid gene rmpA. Despite this early report, the relationship between rmpA and K. pneumoniae clinical syndromes remained uncharacterized for more than a decade. Yu et al. [10] recently demonstrated that rmpA-carrying strains were associated with the hypermucoviscosity phenotype, as well as with the invasive clinical syndrome.

We describe the clinical course and laboratory diagnosis for a patient with invasive K. pneumoniae syndrome. To our knowledge, this is the first clinical report from North America that describes testing for rmpA, along with testing for magA and for the hypermucoviscosity phenotype [15].

Case report. A 49 year-old Asian American man with uncontrolled type 2 diabetes mellitus presented with a 1-week history of sore throat and neck pain, fever, vomiting, abdominal pain, and progressive lethargy. One week earlier, he had received a diagnosis of acute pharyngitis and was prescribed amoxicillin, with no clinical response. The patient denied any recent travel or having sick contacts. His family is originally from China, and he was born and raised in Vietnam. He had moved to the United States 25 years before presentation. His last visit to Asia was a trip to Vietnam 5 years before presentation. He worked in a restaurant before he became ill.

Evaluation revealed that the patient had a neck abscess (figure 1A), diabetic ketoacidosis, and elevated liver enzyme levels. After obtaining blood cultures, treatment with insulin and broad-spectrum antibiotics (piperacillin-tazobactam and vancomycin) was started, and the patient underwent incision and drainage of his neck abscess. However, his condition deteriorated, and he developed hypotension, respiratory failure, and...
thrombocytopenia. He was treated in the intensive care unit with vasopressors, mechanical ventilation, and drotrecogin alfa (activated). The antibiotic regimen was changed to intravenous imipenem-cilastatin and levofloxacin. CT revealed multiple liver abscesses (figure 1B) and lung abscesses. CT of the patient’s head showed no evidence of any orbital or intracranial abnormalities. He underwent percutaneous drainage of 2 of the liver abscesses with pigtail catheter placement. Cultures of blood, neck abscess, liver abscess, sputum, and urine specimens all yielded K. pneumoniae. Genetic testing of the K. pneumoniae isolates later revealed the presence of magA and rmpA. Moreover, the patient’s bacterial isolate had a positive string test result, indicating hypermucoviscosity phenotype (see the Laboratory methods section below).

Our patient had a prolonged hospital course, with complications including development of a foot abscess and dysphagia. Although a complete ophthalmic examination (including retinal examination) was not performed during his hospitalization, he was clinically monitored, and he did not develop any symptoms of endophthalmitis. He completed a total of 6 weeks of intravenous antibiotic therapy, and he slowly recovered.

**Laboratory methods.** The K. pneumoniae strain was isolated from the patients’ sample and identified according to standard clinical microbiologic methods. After inoculation on 5% sheep blood agar plates and incubation at 37°C overnight, the string test was performed by touching a colony with a loop and pulling up [8]. A test result is considered to be positive when a string of ≥5 mm is observed.

We used the sample from the liver abscess of our patient and a randomly selected K. pneumoniae strain isolated from another patient with noninvasive infection as a control. DNA was extracted from liquid cultures using the Nuclisens EasyMAG Automatic Acid Extractor (bioMérieux). 16S rRNA, magA, and rmpA genes were amplified using the following primers: 5'-GCCGTAATACGGAGGTGC and 5'-CACATCCGACGTGACAGACC for 16S rRNA gene, 5'-GGTGCTCTTTA-CATCATTG and 5'-GCAAATGCGCATTTGCGTTAG for magA, 5'-ACTGGGCTACCTCTGCTTCA and 5'-CTTGCATGAGCCATCTTTCA for rmpA [9, 14]. Amplification was performed using an initial denaturation at 95°C for 10 min, followed by 35 cycles of denaturation at 94°C for 30 s, annealing at 55°C for 60 s, and extension at 72°C for 60 s, and final extension at 72°C for 5 min. Five microliters of DNA were used in a 50-µL PCR reaction. We subjected 10 µL of the PCR-amplified products to electrophoresis on a 2% agarose gel containing ethidium bromide (0.5 µg/mL). The gels were photographed under UV light.

**Results.** K. pneumoniae isolated from our patient’s sample demonstrated hypermucoviscosity, as determined by the formation of a string of ≥5 mm in length (figure 2A). This was not observed with the noninvasive strain. PCR of K. pneumoniae isolates revealed the presence of magA and rmpA in our patient’s sample, whereas both genes were absent in the noninvasive strain (figure 2B).

**Discussion.** During the past 2 decades, >900 cases of K. pneumoniae liver abscesses have been reported from East and Southeast Asia [16]. In Taiwan, K. pneumoniae is the most commonly isolated single organism associated with liver abscesses [17]. Additional cases have been reported from other countries worldwide [18, 19], although in much smaller numbers. The number of reported cases from the United States is small (~20 cases), but recent studies suggest that the incidence of K. pneumoniae liver abscesses is probably increasing [20–24]. In fact, K. pneumoniae may already be the most frequently isolated single organism recovered from liver abscesses in the United States as well [20, 25].

In addition to microbiologic risk factors, such as the hypermucoviscosity phenotype and the presence of rmpA and...
**Figure 2.** Laboratory test results for *Klebsiella pneumoniae*. A, Results of the string test. Stretching of the *K. pneumoniae* colonies isolated from our patient’s sample resulted in the formation of a string ≥5 mm in length, demonstrating the hypermucoviscosity phenotype. B, DNA extracted from our patient’s invasive *K. pneumoniae* strain and from the noninvasive strain (noninv), both of which had 16S rRNA genes. *magA* and *rmpA* genes were present only in the invasive strain but absent in the noninv strain. Ctrl, no template controls.

*magA* genes, host risk factors include diabetes mellitus and, possibly, an Asian ancestry. Diabetes is strongly associated with *K. pneumoniae* liver abscesses and with the development of metastatic complications [26]. In some studies, the frequency of diabetes among patients with *K. pneumoniae* liver abscess has been as high as 78% [27].

The majority of the reported infections were found in Southeast Asia and in Asian patients living in other countries. In an analysis of *K. pneumoniae* liver abscesses from 2 hospitals in New York by Rahimian et al. [25], 78.3% of patients were of Asian origin. This raises the possibility that genetic susceptibility or the geographical distribution pattern of virulent *K. pneumoniae* subtypes may play important roles.

The source of invasive *K. pneumoniae* infection in individual patients usually remains unknown. Most patients do not have hepatobiliary disease that would predispose to endogenous infection or a history of contact with infected persons. The possibility of fecal-oral transmission has been raised on the basis of molecular typing of isolates from siblings, family members, and the environment [28]. Genetic similarity of some of the invasive *K. pneumoniae* strains in Taiwan has been demonstrated [29]; however, according to other studies, these infections do not appear to be caused by a clonal spread strain [30, 31].

Hypermucoviscous *K. pneumoniae* strains have been found to be susceptible to most antibiotics, including third- and fourth-generation cephalosporins, monobactam, carbapenems, and ciprofloxacin, whereas they are uniformly resistant to ampicillin [31]. When selecting an antibiotic regimen, it is important to consider adequate penetration into the tissues, including, if clinically indicated, the aqueous humor of the eye and the CSF. Surgical drainage of the abscesses is often necessary.

In summary, we present, to our knowledge, the first report of *rmpA* testing for a patient with invasive *K. pneumoniae* liver abscess syndrome in North America. Increased awareness about this disease by physicians and public health officials worldwide could allow for earlier detection and treatment of patients. More research needs to be done to determine the reasons for the seemingly increasing incidence of this disease and to develop guidelines for diagnosis, treatment, and prevention. We propose that the string test and genetic testing for *rmpA* and *magA* could be used to help confirm the diagnosis in patients with a clinical presentation suggestive of invasive *K. pneumoniae* syndrome.

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**References**


