

Case report

Hypervirulent *Klebsiella pneumoniae* infection in a woman with a CDH1 gene mutation



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ABSTRACT

The CDH1 gene, which encodes E-cadherin, may be associated with cancer when mutated, but the significance of mutations in the context of infection is unknown. In this report, we describe a case of disseminated hypervirulent *Klebsiella pneumoniae* infection in a 49 year old Caucasian woman with a documented CDH1 mutation.

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Introduction

E-cadherin, encoded by CDH1, is located in the cell membrane of epithelial cells at body cavities and surfaces, and serves an important function in cell-to-cell adhesion [1]. Mutations in CDH1 have been associated with a 67 % and 83 % cumulative risk of hereditary diffuse gastric cancer for men and women, respectively, by the age of 80 [2]. Additionally, women with a mutation in the CDH1 gene have a 39 % cumulative risk of lobular breast carcinoma by the age of 80 [2]. Abnormal CDH1 is also associated with colorectal, pancreatic, hepatocellular, prostate, and ovarian carcinomas [1,3]. The impact of infection with the hypervirulent strain of *Klebsiella pneumoniae*, and more generally of any infection, in someone with a CDH1 gene mutation is unknown; however a host-pathogen interaction may be suggested [10–13].

The hypervirulent (also known as hypermucoviscous) strain of *Klebsiella pneumoniae* is most commonly associated with infection in Asia, although the number of cases in North America may be increasing [4]. This hypervirulent strain has been noted to present differently from the “classic” strain of *K. pneumoniae*. The “classic” strain is more commonly associated with nosocomial infections, in

elderly or immunocompromised populations, and with a single site of infection [5]. In contrast, the hypervirulent strain is more commonly acquired in the community, in Asian, Pacific Islander, or Hispanic persons, and often with multiple sites of infection [5]. Here, we report a woman with a CDH1 gene mutation who presented with hypervirulent *K. pneumoniae* infection.

Case report

A 49-year-old Caucasian woman with a past medical history pertinent for CDH1 gene mutation and prophylactic total gastrectomy, bilateral oophorectomy, and bilateral mastectomy presented with a three-day history of right eye pain and one-day history of right eye vision loss. Her review of symptoms was significant for fatigue, generalized weakness, a dry cough, right upper quadrant abdominal pain, and a sharp, aching musculoskeletal pain in her shoulders and upper back. Her family history was pertinent for CDH1 gene mutation. Her social history was notable for drinking one bottle of wine a day for several months, but she had not been drinking regularly for two months. Her only home medication was supplemental vitamin B12, which she took intermittently. She had no known allergies.

The patient was seen by her primary care provider for her eye pain and was prescribed azithromycin. However, as the pain worsened, she presented to her local community hospital emergency department. She was ultimately referred to a tertiary health center for evaluation. Vision on presentation was hand

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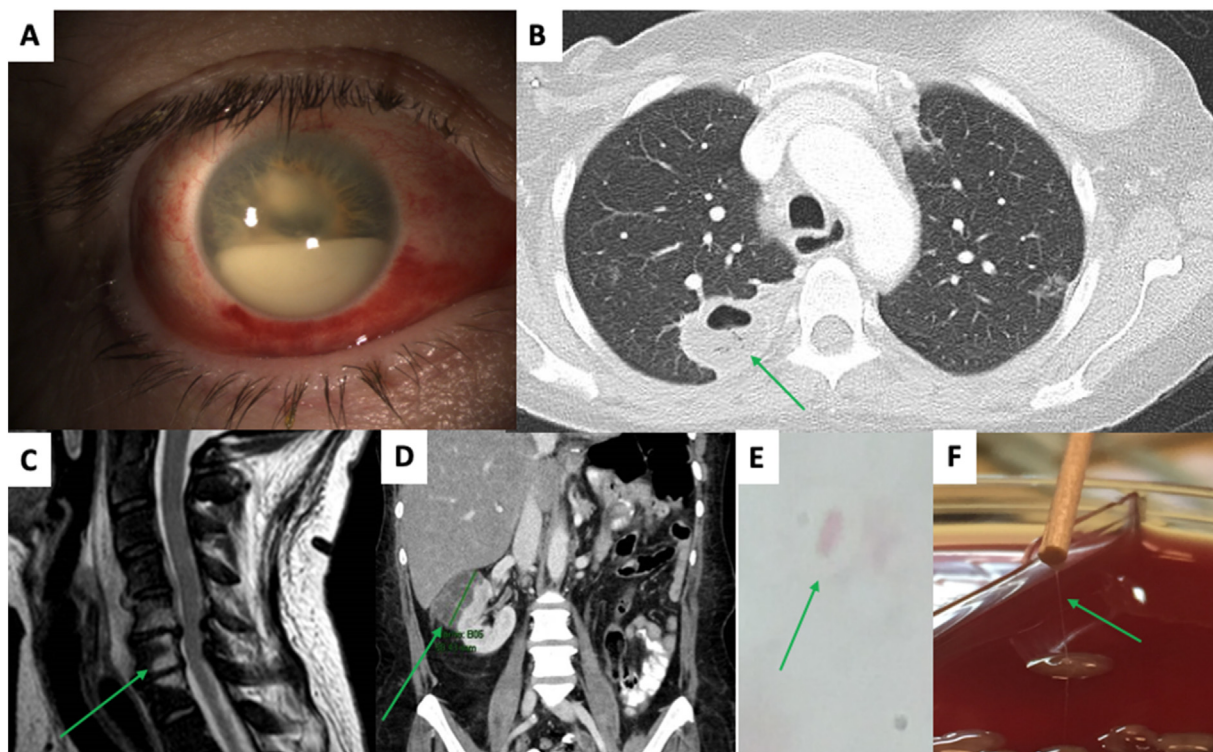


Fig. 1. Clinical, microbiological, and radiographic findings of *K. Pneumoniae* infection. A, Right eye hypopyon. B, Chest CT demonstrating one of multiple lung abscesses. C, Cervical spine MRI demonstrating osteomyelitis. D, Abdominal CT demonstrating perinephric abscess. E, Encapsulated gram negative rod. F, Positive string test.

motion in the right eye. Ocular examination revealed conjunctival injection, a 4 mm hypopyon (Fig. 1A), and vitritis on ultrasonography, concerning for endogenous endophthalmitis. Her left eye was unremarkable. A vitreous tap was performed and sent to microbiology and intravitreal injections of vancomycin and ceftazidime were administered. She was subsequently admitted to the hospital for systemic work up. At the time of admission, the patient's vital signs were within normal limits. Her physical exam was significant only for mild tenderness in her neck during active extension. She was started empirically on cefepime.

Laboratory tests were notable for a white blood cell count of 42,100 cells/ μ L with 88 % neutrophils, 4% immature granulocytes, 4% lymphocytes, 3% monocytes, 0% eosinophils, and 0% basophils, hemoglobin of 9.9 g/dL, ESR > 120 mm/hr, INR of 1.9, AST of 559 IU/L, ALT of 84 IU/L, alkaline phosphatase of 280 IU/L, total bilirubin of 3.2 mg/dL, direct bilirubin of 2.7 mg/dL, and lactate dehydrogenase of 306 U/L. Tests for HIV 1 and 2 were negative. Urinalysis revealed negative nitrite but 1+ leukocyte esterase, 68 white blood cells, mucous, and few bacteria.

Chest radiograph revealed nodular opacities bilaterally. Subsequent chest CT revealed multiple nodular consolidations throughout the lungs bilaterally, some of which demonstrated cavitation with air-fluid levels (Fig. 1B), with the largest in the right upper lung measuring 3.8 cm \times 3.9 cm. CT and MRI of the neck showed prevertebral multilobulated fluid collections extending from C4 to C7 and discitis/osteomyelitis centered at C4-C5 along with an epidural abscess (Fig. 1C). Abdominal CT revealed mild dilation of the common bile duct measuring 0.9 mm and a septate, fluid collection in the right kidney measuring 4.6 cm \times 4.2 cm \times 5.8 cm (Fig. 1D). HIDA scan did not demonstrate biliary obstruction. The patient also underwent transthoracic echocardiogram, which did not demonstrate any valvular lesions.

Blood and vitreous cultures grew *Klebsiella pneumoniae* (Fig. 1E) that passed the >5 mm "string test" (Fig. 1F) consistent with the hypervirulent strain [4]. Antimicrobial(s) sensitivity test results

revealed resistance only to ampicillin. Given her eye involvement, vitreous penetration was a consideration in starting her systemic antibiotic therapy. Based on the existing literature regarding vitreous penetration, intravenous moxifloxacin 400 mg daily and meropenem 2000 mg every 8 h were initiated [6–9].

Throughout her hospital course, the patient remained hemodynamically stable. She received multiple injections of additional intravitreal antibiotics as well as two vitrectomies and anterior chamber washouts for persistent and/or worsening inflammation. While vision in her right eye remained poor, her systemic symptoms improved on intravenous antibiotics and after drainage of the right perinephric abscess. Despite another vitrectomy, anterior chamber washout, and intravitreal injection of antibiotics after discharge from the hospital, the patient had persistent severe pain and inflammation in her eye and a decision was made to eviscerate her right eye. The remainder of the patient's symptoms resolved as an outpatient and she has continued to be asymptomatic through four months after discharge.

Discussion

E-cadherin downregulation has been noted in association with certain infections such as those caused by hepatitis C Virus, adenovirus, *Helicobacter pylori*, and *Coxiella burnetii*. It has been hypothesized that there may be a direct association between the downregulation of E-cadherin and the pathophysiology of these infections [10–13]. However, prior reports have not described infection in the setting of CDH1 gene mutation, a condition which results in abnormal E-cadherin. Interestingly, *Klebsiella pneumoniae* is known to trigger airway epithelial cells to transition to mesenchymal cells which are characterized by the suppression of E-cadherin [14]. Therefore, the patient's abnormality of the E-cadherin gene in addition to *Klebsiella's* effect on E-cadherin may have contributed to the patient's severe, widespread infection involving her right eye, right kidney, both lungs, and cervical spine.

The patient remained remarkably asymptomatic, and her hemodynamics were stable and within normal limits despite her significant infection. Why the patient did not demonstrate more prominent symptomatology other than right eye vision loss, mild dry cough, mild upper back and shoulder pain, and mild right upper abdominal discomfort during her initial presentation is not clear. It is possible that the CDH1 gene may alter the ability of neutrophils to extravasate and migrate in the setting of altered cell-to-cell adhesion, which might explain the high degree of neutrophilia and absence of more prominent systemic symptoms. Other than possibly the CDH1 mutation and prior history of heavy drinking, the patient did not have any obvious risk factors that might predispose her to hypervirulent *Klebsiella pneumoniae* infection. The patient is of Caucasian descent while Asian, Pacific Islander, and Hispanic persons are the populations at highest risk. Overall, this case describes a severe hypervirulent *Klebsiella pneumoniae* infection in the setting of CDH1 gene mutation, suggesting an abnormality in this gene may have been a risk factor for infection in this patient.

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Consent

“Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request”.

CRedit authorship contribution statement

Alexander J. Kaye: Conceptualization, Writing - original draft. **Adam T. Chin:** Supervision, Writing - review & editing. **Michelle C. Liang:** Supervision, Writing - review & editing. **Roberto Viau Colindres:** Conceptualization, Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors report no declarations of interest.

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