Hypermucoviscous *Klebsiella* Syndrome Without Liver Abscess in a Patient With Immunoglobulin G2 Immune Deficiency

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Background. Hypermucoviscous *Klebsiella pneumoniae* (HMVKP) emerged as a cause of invasive infections in South-East (SE) Asia. It has become the most common cause of liver abscess in that region, and it is a significant causative organism in endogenous endophthalmitis and meningitis. During the past decade, cases of this uniquely virulent organism have been reported outside of SE Asia, with a propensity to affect individuals of SE Asian descent. Cases have been reported from North America including Canada.

Methods. We report a case of a patient of Filipino descent living in Canada who presented with recurrent HMVKP bacteremia in the absence of pyogenic liver abscess or other localized metastatic *Klebsiella* infection.

Results. Investigations identified an immunoglobulin (Ig)G2 deficiency and low IgM indicating potential common variable immunodeficiency, and administration of intravenous immunoglobulins was associated with prevention of further recurrences.

Conclusions. To our knowledge, this is the first report of HMVKP associated with predisposing antibody deficiency.

Keywords. hypermucoviscous; IgG2 deficiency; *Klebsiella pneumonia*.

Klebsiella pneumoniae is an important Gram-negative bacilli capable of causing both community- and hospital-acquired infections. There have been numerous case reports of *K pneumoniae* causing community-acquired primary liver abscesses, most of which have been reported in Taiwan and other regions in South-East (SE) Asia. Strains of the organism possessing *magA* or *rmpA* (regulator of mucoid phenotype) are capable of producing large amounts of polysaccharide capsule, making them resistant to serum killing and phagocytosis. The gene encoding *magA* is a virulence marker specific to the K1 serotype found in a significant proportion of invasive strains, and its presence has been correlated with a greater lethality in a mouse model [1, 2]. We report what we believe to be the first case report of a patient with hypermucoviscous *K pneumoniae* without liver abscess and in the setting of an immunoglobulin (Ig)G2 subclass deficiency.

CASE REPORT

A 62-year-old, nondiabetic, male, with chronic hepatitis B virus infection, who is a Canadian resident of Filipino decent and had immigrated to Canada in 1978 presented with 3 episodes of acute febrile illnesses. The symptoms in each episode were similar and included fever, sweating, chills, and generalized weakness, and *K pneumoniae* was isolated from blood in all 3 episodes. The first and second events occurred at age of 58 years followed by a third recurrence was at age 59. In all 3 episodes of bacteremia, no liver abscess was seen and a definite source of bacteremia could not be determined.

Past medical history included treated pulmonary tuberculosis at the age of 12 in the Philippines, hypertension, mild chronic renal insufficiency, chronic obstructive lung disease, and chronic hepatitis B virus with baseline viral load of 226 IU/mL that was diagnosed 1 year before his presentation. Serum transaminase levels were mildly elevated, and liver ultrasound and biopsy revealed no evidence of cirrhosis. In addition, the medical history was remarkable for a granulomatous disease of head and neck of unknown etiology consisting of right ear mucosal thickening, nasopharyngeal mucosal thickening, and a tracheal mass demonstrated on imaging. Tissue biopsies from these sites documented the presence of a granulomatous inflammation with no evidence of malignancy. Cultures from nasopharyngeal samples showed mild growth of *Stenotrophomonas maltophilia* (treated with a short course of oral trimethoprim-sulfamethoxazole) and the presence of fungal elements that could not be elucidated (despite absence of documented fungal infection, the patient received a 9-month course of oral itraconazole). All samples were stain and culture negative for mycobacteria. The patient had no history of diabetes mellitus, and he was receiving a thiazide and a bronchodilator.

Table 1. Laboratory Results on Initial Presentation With Normal Values

Test	Result	Normal Values
Total WBC	15.1 × 10*9 (H)	4.5–11.0 × 10*9 cells/L
Neutrophils	10.5 × 0*9 (H)	1.8–5.4 × 10*9 cells/L
Lymphocytes	2.3 × 10*9	1.3–3.2 × 10*9 cells/L
Monocytes	2.3 × 10*9 (H)	0.3–0.8 × 10*9 cells/L
Eosinophils	0.1 × 10*9	0.0–0.4 × 10*9 cells/L
Hemoglobin	161 × 10*9	140–180 × 10*9 cells/L
Platelets	322 × 10*9	140–440 × 10*9 cells/L
Sodium	135	135–147 mmol/L
Potassium	3.5	3.5–5.0 mmol/L
Bicarbonate	33	22–30 mmol/L
Glucose	5.5	3.6–6.0 mmol/L
Urea	4.0	2.8–7.1 mmol/L
Creatinine	83	44–106 µmol/L
Calcium	2.4	2.1–2.6 mmol/L
Total protein	85	60–80 g/L
Albumin	36	35–45 g/L
APTT	29.8	26.0–36.0 s
INR	1.0	0.9–1.1
Aspartate aminotransferase	32	10–32 U/L
Alanine aminotransferase	55 (H)	0–30 U/L
Alkaline phosphatase	112	30–120 U/L
Total Bilirubin	8	2–20 µmol/L
Gamma glutamyl transpeptidase	47 (H)	5–38 U/L
ESR	22 (H)	0–15

Abbreviations: APTT, activated partial thromboplastin time; ESR, erythrocyte sedimentation rate; H, high above normal range; INR, international normalized ratio; WBC, white blood cell count.

Table 2. Immunological Laboratory Test and Lymphocytes Subset Results With Normal Values

Test	Result	Normal Values
RF	<20	0–20
ANA	Negative (1:40)	Negative
P-ANCA	Negative	Negative
C-ANCA	Negative	Negative
Anti-ds DNA antibodies	8	0.34 IU/mL
SSA (Ro) antibodies	Negative	Negative
SSB (La) antibodies	Negative	Negative
Sm antibodies	Negative	Negative
RNP/Sm antibodies	Negative	Negative
Jo-1 antibodies	Negative	Negative
Scl-70 antibodies	Negative	Negative
CAE complement (CH50)	122	65–145 g/L
C3 complement	1.49	0.88–2.01 g/L
C4 complement	0.31	0.16–0.47 g/L
CD4	306 (L)	700–1100 cell/mm^3
CD3	3026 (H)	1100–1700 cell/mm^3
CD4/CD3 ratio	0.13 (L)	1.17–2.13
CD8	2346 (H)	150–1000 cells/mm^3
CD56+	374	200–400 g/L
CD19+	<34 (L)	200–400 g/L
CD20+	<34 (L)	200–400 g/L
IgA	8.40 g/L (H)	0.7–3.8 g/L
IgM	0.22 g/L (L)	0.6–2.6 g/L
IgE	5.00 g/L	2.0–120 g/L
Total IgG	25.30 g/L (H)	6.9–16.2 g/L
IgG1	22.45 g/L (H)	3.82–9.29 g/L
IgG2	0.60 g/L (L)	2.42–7.00 g/L
IgG3	0.63 g/L	0.22–1.76 g/L
IgG4	0.079 g/L	0.039–0.864 g/L

Abbreviations: ANA, antinuclear antibody; CAE, complement activity enzyme; C-ANCA, antineutrophil cytoplasmic antibodies; ds, double-stranded; H, high above normal range; Ig, immunoglobulin; L, low below normal range; P-ANCA, perinuclear antineutrophil cytoplasmic antibodies; RF, rheumatoid factor; RNO, ribonucleoprotein.

Initial assessment in the emergency room showed a temperature of 38.1°C, blood pressure of 143/90 mmHg, respiratory rate of 16/minute, and a heart rate of 97 beats per minute. The remainder of the examination was unremarkable. He had an elevated white blood cell count ([WBC] pertinent laboratory results are reported in Table 1). Blood cultures were drawn and empirical cefazolin was administered. *Klebsiella pneumoniae* was isolated from blood cultures obtained during the initial assessment. The organism was resistant to ampicillin and piperacillin and susceptible to amoxicillin/clavulanic acid, cefazolin, cefuroxime, cefotaxime, gentamicin, ciprofloxacin, and trimethoprim-sulfamethoxazole. Clinical response with and clearance of bacteremia were followed by a change to oral cephalexin with completion of 21-day course.

Investigations

During admission, due to recurrence of *K pneumoniae* bacteremia, ultrasound of liver, computed tomography scan of head, neck, chest, and abdomen, transthoracic echocardiogram, and a WBC indium scan were performed without evidence of deep-seated infection. In addition, serology tests for human immunodeficiency virus, human T-lymphotropic virus-1 and human T-lymphotropic virus-2, hepatitis C virus, and syphilis were all negative as was urine culture. Eye exam was normal and lumbar puncture was not performed. Colonoscopy was normal, and *K pneumoniae* could not be recovered from a stool culture.

The *K pneumoniae* strain was string test positive (a sensitive but nonspecific test), and the isolate was pan-sensitive (except ampicillin). Subsequently, polymerase chain reaction of the isolate, using 2 primer sets for *magA* and *rmpA* revealed that it was negative for *magA* but positive for *rmpA*. These results were confirmed at Taiwan National Laboratory. The organism was serotyped and was found to be *K pneumoniae* serotype 1 and confirmed to be positive for the *rmpA*, whereas *magA* was

Table 3. Postvaccination Antibody Levels

Immunoglobulin	Result
Tetanus antibodies	Undetectable
Pneumococcal antibodies total immunoglobulin (Ig)G level	4.8 mg/L
Pneumococcal antibodies IgG 2 level	1.4 mg/L

absent. The presence of these is thought to be a marker for the hypermucoviscous isolates.

RESULTS

Outcome and Follow-up

After the diagnosis of recurrent hypermucoviscous *K pneumoniae* bacteremia, despite the absence of a liver abscess, prolonged >6 weeks of ceftriaxone therapy was administered, and immunological investigations were performed (Table 2). In addition, serum total Ig and IgG subclass levels were measured (Table 2). Results showed a hypergammaglobulinemia with low levels of IgG2 subclass and low IgM in keeping with common variable immune deficiency. Humoral dysfunction was confirmed by lack of normal response to immunization with pneumococcal and tetanus vaccines. Table 3 shows postvaccination antibody levels measured 4 weeks after receiving Pneumovax and Tetanus vaccines. The patient received intravenous Ig (IVIG) 25 g vaccines once a month without further recurrences, over a follow-up period of >1 year.

DISCUSSION

Infections attributed to *Klebsiella pneumoniae* include septicemia, pneumonia, and urinary tract infections [3]. *Klebsiella pneumoniae* was found as the second most common cause of Gram-negative bacteremia in Korea [4]. Similar results were found in a recent 10-year, population-based study in North America, which also identified *K pneumonia* as the most common Gram-negative isolate associated with recurrent bacteremia [5]. A distinct constellation of bacteremia with metastatic pyogenic infections including liver abscess, endophthalmitis, and meningitis has emerged as an increasingly common disease presentation in SE Asia [6]. This distinct invasive syndrome of primary community-acquired *K pneumoniae* liver abscess was initially observed in SE Asia including Taiwan [7], Singapore [8], Korea [9], and Japan [10]. Since the original descriptions, a similar syndrome has been increasingly reported outside SE Asia, with a propensity to affect individuals of Asian descent living in other countries [11] and occasionally in non-Asians [12]. The exposures associated with acquisition of the organism or host factors associated with this predilection among people of SE Asian decent remain to be elucidated.

Wang et al [13] found that this syndrome is associated with higher blood glucose levels, a higher rate of metastatic infections, as well as lower rates of preexisting intra-abdominal abnormalities and carries a favorable prognosis with lower rate of associated mortality.

The reasons behind the tendency to cause metastatic infection and affect individuals without hepatobiliary pathology have been attributed to several virulence mechanisms. These *K pneumoniae* strains possess a unique protective exopolysaccharide capsule that is responsible for the hypermucoviscous phenotype of the colonies. This can be detected in the laboratory by a positive string test with formation of viscous strings >5 mm in length on agar plates [1]. The copious capsule containing polysaccharide is an important virulence factor for *K pneumoniae* that has been shown to impart protection against phagocytosis and intracellular killing [7]. Hypermucoviscous *K pneumoniae* demonstrated increased virulence in mice, increased serum insensitivity, and phagocytosis resistance [1]. Siderophores play a role in facilitating increased iron acquisition and increased growth and survival. In a recent study [14], aerobactin has been demonstrated as a pivotal siderophore, organisms with deficient aerobactin encoded by ΔiucA, had decreased virulence.

Based on the capsular antigens, *K pneumoniae* can be classified into 77 capsular serotypes [15]. *Klebsiella pneumoniae* with K1 or K2 capsular serotypes are of a special significance because they are more virulent and are often hypermucoviscous [7].

There are 4 IgG subclasses: (1) IgG1, which makes up most of the total IgG (66%), (2) IgG2 (24%), (3) IgG3 (7%), and (4) IgG4 (3%). Functions of the IgG subclasses include opsonization and complement activation [16]. Immunoglobulin G2 antibodies' major role is the recognition of polysaccharide antigens that are associated with encapsulated bacteria [16, 17]. Phenotypically, low serum levels of IgG2 can be asymptomatic or can be associated with recurrent upper respiratory tract infections, otitis media, sinusitis, and bronchopulmonary infections [18, 19] and can occur as an isolated deficiency or be associated with other IgG subclass deficiencies [20, 21].

Multiple publications demonstrated the association between IgG2 subclass deficiency and infections with encapsulated organisms as *Streptococcus pneumoniae* [22, 23] and *Haemophilus influenzae* [24]. We speculate that the IgG2 deficiency may have predisposed individuals to infection with this heavily encapsulated strain of *K pneumonia*.

Because the incidence of infection was found to be inversely related to the steady-state IgG level [25, 26], use of IVIG in symptomatic patients with IgG subclass deficiencies resulted in decreased rates of recurrent infections [25, 27, 28].

CONCLUSIONS

To the best of our knowledge, this is the first case report of a patient with hypermucoviscous *K pneumoniae* without liver

abscess and in the setting of an IgG2 subclass deficiency. The present case highlights the occurrence hypermucoviscous *K pneumoniae* infection in the absence of a liver abscess and suggests that IgG2 deficiency may be a risk factor for recurrent infection. The association between subnormal IgG2 level and hypermucoviscous *K pneumoniae* infection may reflect the fact that *K pneumoniae* polysaccharide antigens are recognized by serum IgG2. It is conceivable that IgG2 subclass deficiency led to impaired phagocytosis and recurrence of *K pneumoniae* bacteremia. The role of antibody-mediated opsonization in this increasingly common syndrome suggests a potential role for active immunization against hypermucoviscous *K pneumoniae* infection.

Acknowledgments

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