Adult *Klebsiella pneumoniae* Meningitis in Taiwan: An Overview

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Abstract-

Klebsiella (K.) pneumoniae infections, including adult bacterial meningitis (ABM), are a distinct syndrome in Taiwan, which may consist of diabetes mellitus and multiple septic metastatic lesions such as liver abscess, endophthalmitis, and focal suppuration of other internal organs. In this review article, the authors will discuss the protean clinical manifestations and the complexity of the clinical course of this specific central nervous system infectious disease in Taiwan. The clinical and laboratory data of 49 *K. pneumoniae* ABM cases diagnosed at Chang Gung Memorial Hospital-Kaohsiung, collected over a period of 11 years (2000-2010), were included for analysis. This review may help clinical physicians, especially first-line, primary-care physicians, to have a better understanding of this critical CNS infection.

Key words: adult bacterial meningitis; diabetes mellitus; *Klebsiella pneumoniae*; multiple metastatic septic abscesses; prognostic factors

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INTRODUCTION

Klebsiella (K.) pneumoniae is one of the important pathogenic members of *Enterobactericeae* and exists ubiquitously in our environment [(1)]. Pulmonary infection caused by *K. pneumoniae* has been recognized for more than 100 years. A distinct syndrome consisting of community-acquired liver abscess, diabetes mellitus (DM) and multiple septic metastatic lesions has been disclosed in certain areas of the world, including Taiwan [(1-3)]. In Taiwan, several epidemiologic studies of adult bacterial meningitis (ABM) have also revealed that *K. pneumoniae* is the most commonly implicated pathogen of community-acquired infection [(2,4-8)]. Although the high prevalence of K1 serotype has been found in *K. pneumoniae*-related liver abscess infection, the studies with focus on the serotype of *K. pneumoniae* meningitis are rare. In a report of Fang et al., 56% (100/177) of the implicated strains of pyogenic *K. pneumoniae* liver abscess was K1 serotype and 81% (9/11) of the strains of the central nervous system complications from *K. pneumoniae* liver abscess were K1 serotype [(9)]. Although its increase in incidence as an implicated pathogen of ABM has been noted in other Asia countries [(10)], this unique epidemiologic trend of ABM has not been found in other Chinese communities such as Hong Kong and Singapore [(11,12)] and has become an important public health concern for Taiwan.

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A series of imaging features of an Example Case of *K. pneumoniae* central nervous system (CNS) infection, cited from a reported case with permission [13], are shown in Figure 1. This clinical example of *K. pneumonae* CNS infection revealed the protean clinical presentations, the complexity of the clinical course and the grave morbidity of this specific infectious disease in Taiwan. To obtain a better delineation of this specific CNS infectious disease, the clinical data of 49 *K. pneumoniae* ABM cases, diagnosed at Chang Gung Memorial Hospital-Kaohsiung, collected over a period of 11 years (2000 - 2010), were included for analysis. The 49 cases included 35 men and 14 women, aged 20 to 78 years (median = 56). Their clinical and laboratory data are shown in Table 1.

Underlying, preceding events

Community-acquired, spontaneous infection is the most common model of *K. pneumoniae* contraction in Taiwan [2-6,14-17], accounting for 90% (44/49) and 73% (36/49), respectively for the 49 enrolled cases of *K. pneumoniae* ABM. These infectious types of *K. pneumoniae* ABM are rarely noted in large-scale studies of ABM in western countries [18-21], in which *K. pneumoniae* infection is noted occasionally in nosocomial infection and most of the involved cases have a preceding neurosurgical condition. Presence of DM and liver disease, especially cirrhosis, are the most common underlying medical conditions of this specific group of CNS infection [2,3,5,6,14-16,22-25]. As shown in Table 1, more than 59% (29/49) of the cases had DM as the underlying medical

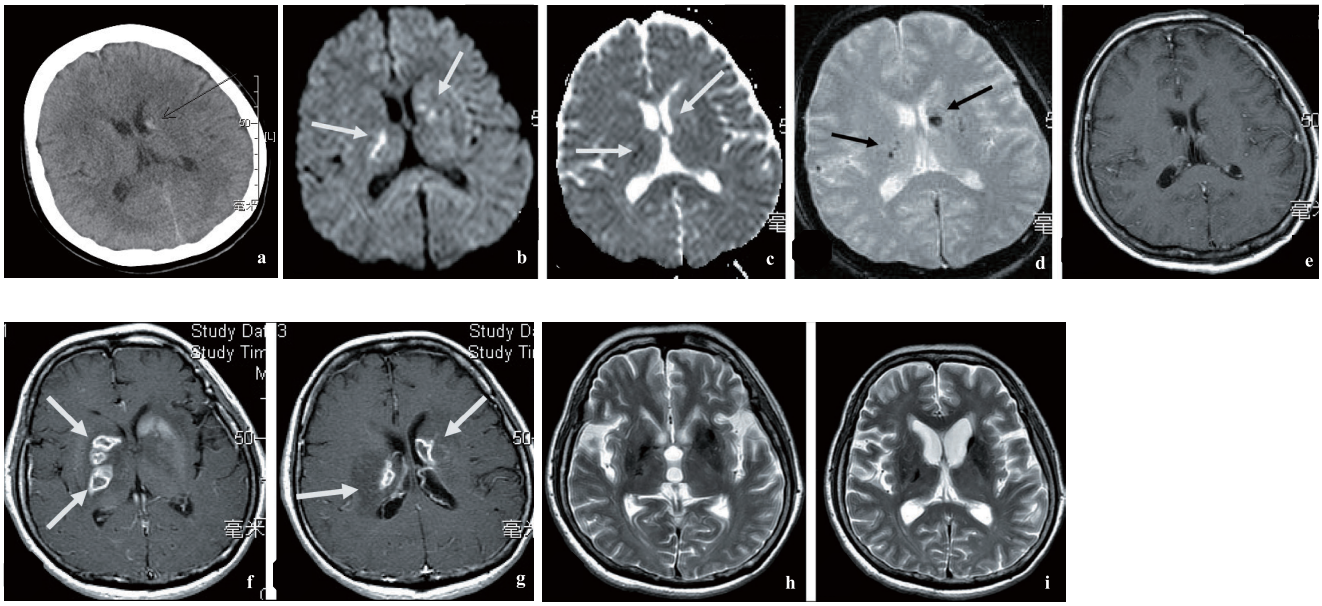

Figure 1. A series of neuroimages of a 57-year-old woman with culture proven *Klebsiella pneumoniae* meningitis [12]. The patient presented to the emergency department on June 3, 2008 with the chief complaint of fever, progressive left limb weakness and altered consciousness for 2 days. Initial cranial computed tomography (CT) (Figure 1a) revealed a small hemorrhage located at the left caudate nucleus (arrow). Brain magnetic resonance (MR) imaging study of the same day revealed infarction with hemorrhagic change over the left caudate nucleus and right basal ganglia area (Figure 1b: Diffusion-weighted image shows hyperintensities at the right internal capsule (arrow) and left caudate nucleus (arrow). Figure 1c: Apparent diffusion coefficient map shows hypointensities at the right internal capsule (arrow) and left caudate nucleus (arrow), Figure 1d: Gradient echo sequence reveals decreased signals at left caudate nucleus and right internal capsule (arrow), Figure 1e: Negative finding in gadolinium contrast-enhanced T1-weighted image). Subsequent brain MR imaging follow-up study (June 23, 2008) revealed multiple brain lesions including abscess formation (Figures 1f and 1g: Gadolinium contrast-enhanced T1-weighted images shows multiple lesions with rimmed-enhancement at the areas of bilateral basal ganglia (arrow)). MR imaging (T2-weighted images) follow-up studies on July 23, 2008 (Figure 1h) and on February 12th, 2009 (Figure 1i) revealed nearly complete remission of brain abscess. In the therapeutic course, liver and pulmonary abscess formations were noted concomitantly by subsequent CT and sonographic studies. Concurrent urinary tract infection and herpes zoster were also noted during the clinical course.

condition. The high association of DM and *K. pneumoniae* ABM has been noted in our previous study [22], in which 68.1% (32/47) of the community-acquired ABM patients with DM had *K. pneumoniae* as the causative pathogen. The other less common underlying conditions may include liver cirrhosis, alcoholism, cancer, end-stage renal disease, and some may have a preceding neurosurgical state. The presence of underlying immunocompromised states may bring further medical complications, especially other infectious problems occurred during hospitalization. The occurrence of other infections during the therapeutic course of the Example Case [13] is a good demonstration of this problem and such medical complications usually result in additional medical burden.

Clinical manifestations

As shown in Table 1, fever, altered consciousness

Table 1. Comparison of the spontaneous and post-neurosurgical infection in patients with *Klebsiella pneumoniae* meningitis

Factors	Spontaneous (n = 36)	Post-neurosurgical (n = 13)	P
Age (years); median (range)	57.5 (31 - 77)	52 (20 - 78)	0.587
Gender			
Male	26	9	1.000
Female	10	4	
Underlying condition			
Diabetes mellitus	25	4	0.022*
Liver cirrhosis	7	0	0.167
Alcoholism	6	1	0.658
End stage renal diseases	2	0	1.000
Malignancy	1	2	0.168
Clinical presentation			
Fever	33	12	1.000
Altered consciousness	28	9	0.708
Seizure	15	1	0.037*
Shock	7	1	0.663
Hydrocephalus	6	7	0.024*
Brain abscess	8	0	0.090
Liver abscess	9	0	0.089
Positive blood culture	15	3	0.322
Leukocytosis	21	11	0.297
Cerebrospinal fluid study			
White cell count (109/L)	1.42 (0.01 - 720.0)	0.59 (0.003 - 11.52)	0.293
Glucose (mmol/L)	1.57 (0 - 20.00)	1.71 (0.16 - 4.52)	0.631
Protein (g/L)	5.38 (0.35 - 16.15)	2.43 (0.31 - 16.05)	0.084
Lactate (mmol/L)	17.90 (3.96 - 32.12)	15.23 (2.97 - 35.75)	0.212
Non-cephalosporin-susceptible	0	2	0.066
Prognosis			
Survived	17	9	0.209
Expired	19	4	

*Fisher's exact test ($p < 0.05$); **Mann-Whitney U test ($p < 0.05$)

Logistic regression analysis showed independent factor of "diabetes mellitus" ($p= 0.045$)

and seizure were the most common clinical manifestations of the 49 *K. pneumoniae* ABM cases. Their CSF study results showed a purulent profile with leukocytosis, decreased glucose level and/or ratio, and elevated lactate and total protein levels. All these clinical and laboratory characteristics were not unique and can also be found in ABM caused by other bacterial pathogens [1,2,26,27]. Therefore, a positive laboratory *K. pneumoniae* identification in CSF culture and/or blood culture, especially in patients with DM and/or cirrhosis, is the only mainstay of diagnostic confirmation for this specific group of ABM [14-16].

As shown in the Example Case, concomitant septic metastatic infection is also common in *K. pneumoniae* infection [2,3,14-16,28]. In *K. pneumoniae* ABM, the common sites of septic metastatic infection include liver, eyes, lung and kidney [2,3,14-16,28]. Usually this severe complication of *K. pneumoniae* infection can occur in the early stage of hospital admission [3], therefore, for the detection of multiple septic metastatic lesions, thorough imaging studies are usually required. For these septic metastatic lesions, an aspiration and/or drainage procedure is also needed for a diagnostic confirmation as well as a more effective therapeutic result. Lee et al. [3] found that presence of rmpA gene, APACHE II score ≥2, and the presence of septic shock were important predictors of septic metastatic lesions in *K. pneumoniae* infection. In the study of Lee et al. [29], the hypermucoviscosity phenotype of *K. pneumoniae* bacteremic isolates was associated with the development of this invasive syndrome. The presence of septic metastatic infection is also one of the important prognostic factors of *K. pneumoniae*-related infection [3].

Brain abscess, which may occur alone or in combination with ABM, is the most common form of intracranial focal suppuration of *K. pneumoniae* infection and may provide an additional focal sign in this specific infectious syndrome. *K. pneumoniae* is one of the important pathogens of adult brain abscess in Taiwan [30-33]. Brain abscess caused by *K. pneumoniae* infection can be monoloculated or multiloculated [30-32] and some (around 13%) may result in characteristic, although non-specific, intracranial gas-forming [30,34-37]. *K. pneumoniae* brain abscess can locate either superficially or deeply in the brain parenchyma [30,31,34]. These different features of *K. pneumoniae*-related brain abscess deserve attention because the choice of methods of neurosurgical intervention or the incidence of brain abscess complications such as rupture into ventricle with subsequent ventriculitis can be varied in different situations [32,33].

Treatment

Use of antimicrobial agent is still the mainstay of *K. pneumoniae* ABM management. In the finding of our study of in vitro antimicrobial susceptibilities of community-acquired *K. pneumoniae* strains isolated from the clinical CSF of ABM patients, all tested strains were susceptible to most of the 3rd- and 4th-generation cephalosporins [36]. According to the guidelines [38,39], in the treatment of susceptible strains-related, non-brain abscess, meningitis, ceftriaxone or cefotaxime are usually suggested for a therapeutic course of 3-4 weeks and the duration of antibiotic treatment needs to be individualized on the basis of the patient's clinical response But in a nationwide surveillance of antimicrobial resistance in Taiwan, an increasing trend of incidence in antibiotic resistance to *K. pneumoniae* strains, especially in those isolated from nosocomial infection, has been noted in recent years [37,40-44]. A resistance to the 3rd- and 4th-generation cephalosporins has been noted in the *K. pneumoniae* strains of the 49 enrolled ABM cases. The two resistant *K. pneumoniae* strains were all isolated from the cases with a postneurosurgical state as the preceding event and one of the strain was extended spectrum β-lactamase producing (Table 1). This finding is consistent with that of Tsay et al. [41] which showed that antibiotic resistance was more common in patients with nosocomial as compared with community-acquired *K. pneumoniae* bacteremia. This increase in antibiotic resistance has also been noted in other studies [43-45]. Because early use of appropriate antiobitics is one of the most important steps for the successful treatment of ABM [26], the trend of antibiotic resistance in the *K. pneumoniae* strains isolated from clincal CSF specimens should be monitored frequently in order to delineate the therapeutic strategy of empirical antibiotic choice.

Table 2. Prognostic factors analysis of the patients with *Klebsiella pneumoniae* meningitis

	Survived (n = 26)	Expired (n = 23)	P
Age (years); median (range)	57 (23 - 77)	56 (20 - 78)	0.873
Gender			
Male	17	18	0.360
Female	9	5	
Underlying condition			
Diabetes mellitus	15	14	1.000
Liver cirrhosis	1	6	0.041*
Alcoholism	3	4	0.692
End stage renal disease	0	2	0.215
Malignancy	1	2	0.594
Spontaneous	17	19	0.209
Community-acquired	22	20	1.000
Clinical presentation			
Fever	25	20	0.330
Altered consciousness	17	20	0.104
Seizure	7	9	0.542
Shock	1	7	0.019*
Hydrocephalus	7	6	1.000
Brain abscess	4	4	1.000
Liver abscess	5	4	1.000
Positive blood culture	9	9	0.775
Leukocytosis	19	16	1.000
Cerebrospinal fluid study			
White cell count (109/L)	0.75 (0.01 - 36.0)	1.99 (0.003 - 720.0)	0.166
Glucose (mmol/L)	3.14 (0 - 20.00)	0.52 (0 - 12.23)	0.178
Protein (g/L)	3.35 (0.35 - 11.84)	5.98 (0.31 - 16.15)	0.045**
Lactate (mmol/L)	15.4 (3.96 - 32.12)	20.0 (2.97 - 35.75)	0.059
Non-cephalosporin-susceptible	0	2	0.215

* Fisher's exact test ($p < 0.05$); ** Mann-Whitney U test ($p < 0.05$)
Logistic regression analysis showed independent factor of "liver cirrhosis" ($p = 0.036$) and "shock" ($p = 0.023$)

Besides CSF leukocytosis, the early rise of inflammatory factors such as interleukin-1 and tumor necrosis factor-α can be noted in ABM [46-48]. Table 3 shows this finding in five *K. pneumoniae* cases. The differential expression of certain cytokines and chemokines in the CNS may be useful in the approach to diagnosis and prognostication of patients with acute meningitis syndrome [46,48]. However, thus far, assay for these compounds is often tedious, time-comsuming, and expensive, and the positive and negative predictive values of

Table 3. Results of initial cerebrospinal fluid IL1-β and TNF-α study of *Klebsiella pneumoniae* meningitis in six adult patients

Case	Sex/age (yr)	IL1-β (pg/ml)	TNF-α (pg/ml)
1	F/44	22.57352	3.5695
2	F/56	1.9747	4.1804
3	M/76	286.07	1145.316
4	M/45	323.17	148.37
5	M/73	163.88	124.02
6	M/74	27.097	12.439

F: female ; M: male; IL1: interleukin 1; TNF: tumor necrosis factor

Table 4. Results of CSF 14-3-3 protein detection of three *Klebsiella pneumoniae* meningitis patients at the initial stage of infection and before the discharge from the hospital

		Initial		Before discharge	
Case	Sex/age (yr)	14-3-3p (DU)	14-3-3 γ (DU)	14-3-3p (DU)	14-3-3 γ (DU)
1	F/42	222.53	319.7	21.8	12.13
2	F/55	486.09	146.17	29.41	22.24
3	M/26	291.07	443.68	0	0

F= female; M= male; DU= densitometric units; p=pan; $\gamma = \gamma$ -isoform

the assay results preclude routine utilization for the seperation of patients with bacterial versus viral meningitis with a negative CSF Gram stain. Because several proinflammatory cytokines rise rapidly following bacteriolytic antimicrobial therapy, consideration of anti-inflammatory approaches must reflect the appropriate timing in reference to the first dose of antimicrobial treatment [26,46,48,49]. It is also known that host immune response is incapable of controlling infection within the CNS, particularly the CSF within the subarachnoid space and this host inflammatory response may be responsible for many adverse events during bacterial meningitis and result in secondary destructive effects [26,27]. Therefore, early treatment with dexamethasone significantly reduces mortality and morbidity from some groups of ABM patients, especially in those with community-acquired *Streptococcus pneumoniae* infection [26,27,39,49]. But because of different epidemiologic trends, it is uncertain whether overall ABM cases benefit from treatment with adjunctive dexamethasone [50-52]. In *K. pneumoniae* ABM, the early use of dexamethasone therapy should be considered with a degree of caution. This concern is primarily related to the high incidence of DM as the the underlying condition among this specific group of patients.

In a study of Lu et al. [31], *K. pneumoniae* accounted for 10.6%, 13.8% and 16.8% of the causative pathogens of overall, culture-proven and monomicrobial adult brain abscess, respectively. In these 46 enrolled cases of *K. pneumoniae* ABM, 16.3% (8/49) of them had concomitant brain abscess. The presence of this focal suppuration in brain parenchyma may cause medical and neurosurgical complexity in the choice of therapeutic strategies [31,53] including the use of anticonvulsant, medical treatment with or without surgical intervention. The choice of surgical intervention methods such as aspiration and/or excision procedure depending on the number and location of the abscess(es), physical condition of the patient and the fascilities as related to the hospital setting.

Prognosis

The therapeutic results of the enrolled 49 *K. pneumoniae* ABM cases showed a mortality rate of 53% (26/49). The reported mortality rates of overall *K. pneumoniae* ABM in Taiwan are high, ranging from 33.3% to 93.0% [14-16,36,54]. Many factors can prognosticate the therapeutic outcome of ABM [12,47,55-59]. In the enrolled 49 *K. pneumoniae* ABM cases, underlying liver cirrhosis and presence of septic shock were significant in a univariate analysis. Underlying condition of immunocompromised status, delay of diagnosis in meningitis due to coexistence with hepatic encephalopahy, and medical complication (such as bleeding and hypotension) were possible causes of poor prognostic factor of liver cirrhosis [59]. As reported by Lu, et al. [60], serial CSF 14-3-3 protein, especially the gamma isoform, check-ups can be of value in predicting the outcome of community-acquired ABM; but again, this measurement may not be of practical value in clinical management of ABM. As shown in Table 4, all three *K. pneumoniae* ABM cases initially had marked rise of 14-3-3 proteins and decrease of them before they were discharged in a survival state. However, thus far, when treating *K. pneumoniae* ABM patients, the early use of appropriate antibiotics is still the most consistent positive prognostic factor.

CONCLUSION

K. pneumoniae ABM is an unique infectious syndrome that is comprised of a multiplicity of systemic

involvement. DM and other immuocompromised conditions such as liver cirrhosis are the most common preceding events, and the presence of multiple septic metastatic lesions is characteristic and may occur in the early stage of hospital admission. Because a delay in diagnosis and treatment may result in grave therapeutic concequences for those suffering from this specific infectious syndrome in Taiwan, a more careful and thorough approach in handling *K. pneumoniae* ABM is needed. The therapeutic strategies discussed in this review article may help clinicians, especially the first-line primary-care physicians, to have a better understanding of this specific infectious syndrome in Taiwan.

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