

# Lemierre's Syndrome Caused by *Klebsiella pneumoniae* in a Diabetic Patient: A Case Report and Review of the Literature

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## Abstract

Lemierre's syndrome is characterized by an oropharyngeal infection with internal jugular vein thrombosis followed by metastatic infections in other organs. This infection is usually caused by *Fusobacterium* spp. In this report, we present a rare case of *Klebsiella pneumoniae*-associated Lemierre's syndrome in a patient with poorly-controlled diabetes mellitus. The infection was complicated by septic emboli in many organs, which led to the patient's death, despite combined antibiotics, anticoagulant therapy, and surgical intervention. Therein, a literature review was performed for reported cases of Lemierre's syndrome caused by *Klebsiella pneumoniae* and the results are summarized here.

## Keywords

*Klebsiella pneumoniae*, Lemierre's syndrome, diabetes mellitus, review, complications

## Introduction

Lemierre's syndrome is a rare and almost forgotten, yet potentially life-threatening, disease. The disease is commonly characterized by an oropharyngeal infection resulting in internal jugular vein thrombophlebitis and subsequent metastatic infections.<sup>1</sup> This infection is commonly caused by *Fusobacterium necrophorum* and *F. nucleatum*. However, with the increase in variety of comorbidities, use of immunosuppressive agents and prevalence of drug resistance bacteria, Lemierre's syndrome has been reported with atypical pathogens and presentations.<sup>2</sup> We report a rare case of Lemierre's syndrome caused by *Klebsiella pneumoniae* in a diabetic patient.

## Case Report

A 51-year-old woman with hypertension, recently-diagnosed type 2 diabetes mellitus (DM) was admitted to a community hospital after 2 weeks of fever and localized pain and swelling at her right neck area. As the symptoms progressed, she had difficulty moving her neck. She denied history of trauma to the neck, night sweats, weight loss, history of intravenous drug use, history of alcoholic drinking, or recent dental procedures. Physical examination revealed: temperature 38°C, blood pressure 124/62 mmHg, heart rate 104/min, respiratory rate 20/min, pulse oxygen saturation 95% on room air, and marked erythema and swelling at the right upper neck area. Laboratory data showed a white blood cell count of 18,400 cells/mm<sup>3</sup> (79.4% neutrophils, 10.7% lymphocytes, and 9.0% monocytes), hemoglobin level of 9.4 g/dl, platelet count of 407,000 cells/mm<sup>3</sup>. Computed tomography (CT) of the neck was performed and revealed a large rim-enhancing multilocular cystic mass 6x3x8 cm in size occupying the right parapharyngeal space and likely to be right parapharyngeal abscess. The patient underwent incision and drainage of the right neck abscess

along with intravenous ceftazidime at the dose of 2 grams every 8 hours as empirical therapy. *Klebsiella pneumoniae* was detected from the pus culture. The organism was susceptible to penicillins with beta-lactamase inhibitors, cephalosporins, carbapenams, fluoroquinolones, and aminoglycosides and was resistant to ampicillin only. Intravenous ceftazidime was then deescalated to ampicillin-sulbactam. Despite the treatment, she developed worsening shortness of breath on day 5. Her chest radiograph showed new patchy infiltration at right middle lung and pleural effusion at the left lower lung field. Sputum culture grew *Klebsiella pneumoniae* with the same resistance pattern as that from the pus culture. No organism was recovered from any blood culture specimens. On day 8 of the antibiotic treatment the patient was transferred to our hospital due to the suspicion of inadequate drainage of the right neck abscess. Neck and chest CT at our hospital revealed an irregular-shaped hypodense lesion with rim enhancement along right carotid space likely to be a residual abscess (Figure 1A) with thrombosis of right internal jugular vein up to the right sigmoid sinus (Figure 1B and 1C) associated with multiple various size nodules and cavitary consolidations in both lungs likely to be septic emboli (Figure 2A, 2B and 2C). All of the findings were consistent with Lemierre's syndrome. On the third day after the transfer, the patient underwent extensive incision and drainage of the abscess. Anticoagulant therapy with enoxaparin was started and antibiotic therapy was changed to meropenem at the dose of 1 gram intravenously every 8 hours to cover for other nosocomial infections and emerging drug-resistant *K. pneumoniae*. Despite all of the treatments, the patient had persistent fever and required mechanical ventilator support. Repeated CT chest revealed multiple air-fluid containing cavities various in size and scattering in both lungs, left loculated pleural effusion, consolidation with areas of necrosis and bronchiectasis in both lower lobes suggesting necrotizing pneumonia. Pleural fluid was aspirated and showed culture-negative exudative profile with polymorphonuclear predominance. Her condition did not improve despite no evidence of carbapenem-resistant bacterial infection. On the 23rd day after admission to our hospital, her hospital course was complicated by multidrug-resistance *Acinetobacter baumannii*-associated pneumonia and septic shock. Colistin 300 mg intravenous loading followed by 150 mg intravenously every 12 hours was added to her antibiotic regimen. However, due to multiple organ failure from septic shock, the patient died on the 26th day after admission to our hospital.

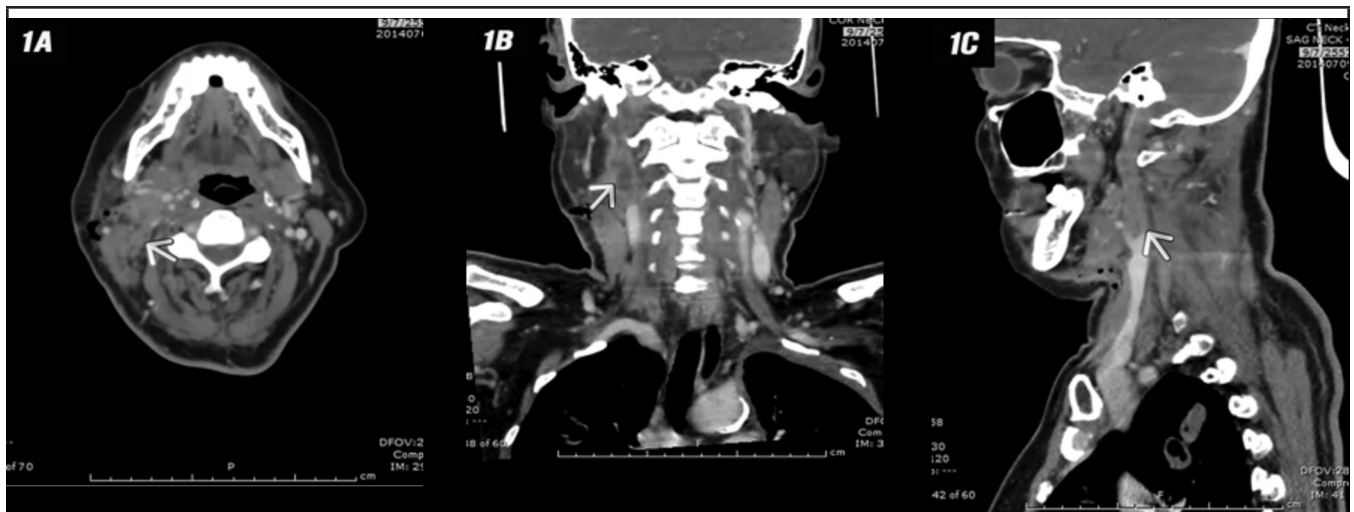


Figure 1

- 1A. Axial view neck computed tomography showing an irregular-shaped hypodense lesion with rim enhancement along the right carotid space (arrow)
- 1B. Coronal view neck computed tomography showing thrombosis of the right internal jugular vein up to the right sigmoid sinus (arrow)
- 1C. Sagittal view neck computed tomography showing thrombosis of the right internal jugular vein up to the right sigmoid sinus (arrow)



Figure 2

- 2A. Chest radiograph showing alveolar infiltration at the right middle lung area and pleural effusion at the left lower lung area (arrows)
- 2B. Axial view chest computed topography showing multiple nodules in various sizes with cavitation (white arrows) in both lungs likely to be septic emboli, and pleural effusion (arrowheads).
- 2C. Coronal view chest computed topography showing multiple nodules in various sizes with cavitation (white arrows) on both lungs likely to be septic emboli, and pleural effusion (arrowheads).

## Discussion

Lemierre's syndrome is a rare disease with a prevalence of 0.6-2.3 per 1,000,000 population and a mortality rate between 4%-18% in the world.<sup>1</sup> In 1936, Dr. Andre Lemierre published a case series of 20 patients and described the term "Lemierre's syndrome" as the syndrome with development of septic thrombophlebitis of the tonsillar and peritonsillar veins secondary to pharyngotonsillitis or peritonsillar abscess formation. The rapidly progressive thrombophlebitis would then spread to involve the internal jugular and facial veins with the subsequent development of metastatic emboli to the respiratory tract and ultimately the remaining end points of circulation.<sup>2,3</sup> Most cases were caused by *Fusobacterium necrophorum* which accounted for 81% while other *Fusobacterium* species, such as *F. nucleatum* accounted for 11% of the cases. In addition, several organisms have been identified as causes of Lemierre's syndrome in many case reports and case series, such as *Streptococcus* spp., *Bacteroides* spp., *Eikenella corrodens*, *Enterococcus* spp., *Peptostreptococci*, *Proteus mirabilis* and many more.<sup>4</sup>

We performed a Pubmed literature search for English-language articles published from the inception to January 2015 using the search term "*Klebsiella pneumoniae*" and "Lemierre's syndrome". There have been 9 case reports of *K. pneumoniae* associated Lemierre's syndrome (KLS) including our case, in the English literature (Table 1). *Klebsiella pneumoniae* associated Lemierre's syndrome occurred in middle-aged adults (age ranging from 44 to 68 years) with no sex predominance. Eight of the nine patients (89%) with KLS had poorly-controlled DM with hemoglobin A1C ranging from 9.9% to 14.2% and random serum glucose ranging from 197 to 843 mg/dl upon presentation. Among the eight DM patients, 3 (38%) were newly diagnosed of DM within one month. These findings implicate the strong correlation between DM and *K. pneumoniae* associated infections and are consistent with those reported in an observational study from Singapore which found that *K. pneumoniae* was responsible for a higher proportion of deep neck infections among people with DM compared to the general population (50% vs 26%).<sup>5</sup> Impaired phagocytosis of neutrophils due to hyperglycemia has been described as an important factor associated with increased risk of infections caused by *K. pneumoniae*, especially the capsular serotype K1 and K2 strains.<sup>6</sup> In addition, patients with KLS were older than those with classic Lemierre's syndrome (44-68 vs. 10-35 years old).<sup>4</sup> This may be explained by the higher prevalence of DM among the older population.<sup>6,7</sup> All nine KLS patients presented with fever, eight patients (89%) had neck swelling and pain, while three (33%) had symptoms in the oropharynx, such as sore throat and dysphagia. Metastatic infections were found in six patients (67%). The common distantly affected organs included lungs (56%) and brain (11%). Lungs were the most common infected metastatic sites in KLS similar to those in the classic Lemierre's syndrome.<sup>8</sup> Hemagglutinin of the causative bacteria has been identified as an important factor that promotes platelet aggregation, thrombophlebitis, and subsequent septic emboli metastasis in classical Lemierre's syndrome.<sup>9</sup> In KLS, the hema-

glutinin is found in type 3 pilli, a virulent factor responsible for adhering to endothelial cells of *K. pneumoniae*.<sup>10</sup> In addition, septic emboli formation and septic metastasis in KLS may be facilitated by MagA gene-associated hypermucoviscosity property of *K. pneumoniae*. This enables the bacteria to form an exopolysaccharide web to cover itself and be able to avoid serum complement activation and phagocytic ingestion.<sup>11</sup> In our review, two of the nine KLS patients (22%) were infected by extended-spectrum beta-lactamase (ESBL)—producing *K. pneumoniae*. Given that no risk factors associated with infections due to ESBL-producing *K. pneumoniae* were identified in both cases, the occurrence of these drug-resistant infections was most-likely due to the high prevalence of ESBL-producing strain of *K. pneumoniae* in the areas of these two reported cases.<sup>12,13,14</sup> Other drug resistant strains of *K. pneumoniae*, such as carbapenam-resistant Enterobacteriaceae *K. pneumoniae* (CRE-KP) and K1/K2 serotypes were not detected in any of the case reports. However, the infections caused by this drug-resistant strain were associated with prolonged hospital stay and increased cost (Table 1).

Among a variety of characteristics of Lemierre's syndrome, the diagnosis is based on the hallmark features, which include (1) history of a painful illness or compatible clinical findings, (2) evidence of either metastatic lung lesions or metastatic lesions in other sites, and (3) either evidence of internal jugular vein thrombophlebitis or isolation of *F. necrophorum* or *Fusobacterium* spp. from blood cultures or a normally sterile site.<sup>4</sup> The evidence of internal jugular vein thrombophlebitis is one of the criteria required for the diagnosis. Retrograde venography is the gold standard for diagnosis of venous thrombosis but this procedure is invasive.<sup>15,16,17</sup> Thus, many non-invasive investigation tools such as CT venography, magnetic resonance venography (MRV), ultrasonography have been used to detect the venous thrombosis. CT with venous enhancement can reveal low attenuation intraluminal filling defects and adjacent soft tissue anatomy, benefiting in the approach for surgical interventions. Magnetic resonance imaging (MRI) combined with MRV has the highest sensitivity (97%) to detect thrombosis.<sup>18</sup> With better depiction on brain parenchyma, MRI is recommended to perform in the case with suspicion of intracerebral venous thrombosis.<sup>19</sup> However, due to MRI's high cost and limited availability, CT is generally recommended as the primary investigation tool for evidence of the thrombosis.<sup>20</sup> Ultrasonography shows benefit of the least expensive cost and no radiation and contrast exposure. However, because of its difficulty seeing the fresh thrombus with low echogenicity and the anatomy of the area beneath the clavicle, it is rather used in the follow-up examinations, which the early diagnosis and anatomical structure have been successfully investigated.<sup>21</sup>

Based on the standard practice, the microbiological studies should consist of pus Gram's staining for morphology study, pus cultures and blood cultures in both aerobic and anaerobic conditions, and, if available, gas-liquid chromatography to detect butyric acid produced by *Fusobacterium* spp.<sup>4</sup> Due to difficulty culturing the causative organisms, the real time

| Table 1. Summary of Cases of <i>Klebsiella pneumoniae</i> -associated Lemierre's Syndrome Reported in the Literature. |                                           |                                                                                                 |                                                                                          |                                                                           |
|-----------------------------------------------------------------------------------------------------------------------|-------------------------------------------|-------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Article                                                                                                               | Bhagat, et al <sup>39</sup>               | Tsai, et al <sup>40</sup>                                                                       | Phua, et al <sup>41</sup>                                                                | Our case                                                                  |
| Age (year)/Sex                                                                                                        | 44/F                                      | 45/F                                                                                            | 50/M                                                                                     | 51/F                                                                      |
| Comorbidities                                                                                                         | DM                                        | DM                                                                                              | DM*                                                                                      | HT,DM*                                                                    |
| History of alcoholic drinking                                                                                         | NR                                        | NR                                                                                              | NR                                                                                       | No                                                                        |
| Location                                                                                                              | New York, US                              | Taipei, Taiwan                                                                                  | Singapore                                                                                | Pathumthani, Thailand                                                     |
| Area prevalence of DRS <sup>Ref</sup> (ESBL/CRE-KP/K1/K2) (%)                                                         | 7.6 <sup>42</sup> /8 <sup>43</sup> /NR/NR | 28.4 <sup>44</sup> /1.2 <sup>45</sup> /27.5 <sup>46</sup> /15.7 <sup>46</sup>                   | 38 <sup>47</sup> / <sup>&lt;1</sup> <sup>45</sup> /7.7 <sup>46</sup> /19.2 <sup>46</sup> | 56.9 <sup>48</sup> /5.1 <sup>49</sup> /0 <sup>46</sup> /8.6 <sup>46</sup> |
| Clinical Presentation                                                                                                 | Fever, sore throat, vomiting              | Fever with chill, sore throat, productive cough, dysphagia, odynophagia, neck pain and swelling | Fever with chill, neck swelling, syncope                                                 | Fever, neck swelling, neck pain                                           |
| Duration from onset to presentation (days)                                                                            | 7                                         | 3                                                                                               | 8                                                                                        | 5                                                                         |
| Primary infectious source                                                                                             | Acute pharyngotonsillitis                 | Neck cellulitis                                                                                 | Retroclavicular abscesses                                                                | Parapharyngeal abscess                                                    |
| Thrombosis                                                                                                            | IJV                                       | IJV, Sigmoid sinus                                                                              | IJV, Sigmoid sinus, Transverse sinus                                                     | IJV                                                                       |
| Complications                                                                                                         | Lung metastasis                           | Lung metastasis                                                                                 | None                                                                                     | Lung metastasis, HAP                                                      |
| Culture-positive specimen                                                                                             | Blood                                     | Blood and pus                                                                                   | Blood and pus                                                                            | Pus and sputum                                                            |
| Multidrug-resistant strain                                                                                            | No                                        | No                                                                                              | No                                                                                       | No                                                                        |
| Glycemic control                                                                                                      |                                           |                                                                                                 |                                                                                          |                                                                           |
| BS upon admission(mg/dl)                                                                                              | 843                                       | 206                                                                                             | 220                                                                                      | NR                                                                        |
| HbA1C (%)                                                                                                             | 14.2                                      | 11.6                                                                                            | 12.1                                                                                     | 9.4                                                                       |
| Surgical treatment                                                                                                    |                                           |                                                                                                 |                                                                                          |                                                                           |
| I&D (times)                                                                                                           | No                                        | Yes (1)                                                                                         | Yes (1)                                                                                  | Yes (2)                                                                   |
| IJV ligation                                                                                                          | None                                      | None                                                                                            | None                                                                                     | None                                                                      |
| Further operations                                                                                                    | None                                      | None                                                                                            | None                                                                                     | Debridement                                                               |
| Anticoagulants                                                                                                        |                                           |                                                                                                 |                                                                                          |                                                                           |
| Type                                                                                                                  | UFH                                       | LMWH                                                                                            | LMWH                                                                                     | Warfarin                                                                  |
| Duration (days)                                                                                                       | NR                                        | 42                                                                                              | 90                                                                                       | 20                                                                        |
| Antibiotics                                                                                                           |                                           |                                                                                                 |                                                                                          |                                                                           |
| ATB prior admission                                                                                                   | Oral penicillin                           | None                                                                                            | None                                                                                     | Ceftazidime                                                               |
| Initial ATB after diagnosis                                                                                           | Ampicillin, cefotaxime, metronidazole     | Ceftriaxone, gentamicin                                                                         | Ceftazidime, cloxacillin, clindamycin                                                    | Ampicillin-sulbactam                                                      |
| After known culture result                                                                                            | Ampicillin, cefotaxime, metronidazole     | Flomoxef                                                                                        | Cefazolin                                                                                | Meropenem                                                                 |
| Duration (days)                                                                                                       | 42                                        | 42                                                                                              | 42                                                                                       | 26                                                                        |
| Outcomes                                                                                                              |                                           |                                                                                                 |                                                                                          |                                                                           |
| Duration to clinical response (day)                                                                                   | 7                                         | 2                                                                                               | NR                                                                                       | None                                                                      |
| Hospital stay (day)                                                                                                   | NR                                        | 15                                                                                              | NR                                                                                       | 26                                                                        |
| Resolution of infection                                                                                               | Yes                                       | Yes                                                                                             | NR                                                                                       | No                                                                        |
| Resolution of thrombosis                                                                                              | Yes                                       | NR                                                                                              | NR                                                                                       | Yes                                                                       |
| Survival                                                                                                              | Survived                                  | Survived                                                                                        | Survived                                                                                 | Died                                                                      |

| Table 1. Summary of Cases of <i>Klebsiella pneumoniae</i> -associated Lemierre's Syndrome Reported in the Literature. (Continued) |                                                                                |                                                                              |                                                                              |                                                                        |                                                                                           |
|-----------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| Article                                                                                                                           | Lee, et al <sup>50</sup>                                                       | Lim, et al <sup>51</sup>                                                     | Nguyen, et al <sup>52</sup>                                                  | Garbati, et al <sup>53</sup>                                           | Singapore-walla, et al <sup>54</sup>                                                      |
| Age (year)/Sex                                                                                                                    | 56/F                                                                           | 57/M                                                                         | 63/M                                                                         | 63/M                                                                   | 68/M                                                                                      |
| Comorbidities                                                                                                                     | None                                                                           | DM*                                                                          | HT, DM,DLP                                                                   | DM, Asthma                                                             | DM                                                                                        |
| History of alcoholic drinking                                                                                                     | NR                                                                             | NR                                                                           | NR                                                                           | NR                                                                     | NR                                                                                        |
| Location                                                                                                                          | Taipei, Taiwan                                                                 | Penang, Malaysia                                                             | Kuala Lumpur, Malaysia                                                       | Riyadh, Saudi Arabia                                                   | Singapore                                                                                 |
| Area prevalence of DRS <sup>Ref</sup> (ESBL/ CRE-KP/K1/K2) (%)                                                                    | 28.4 <sup>44</sup> /1.2 <sup>45</sup> / 27.5 <sup>46</sup> /15.7 <sup>46</sup> | 38 <sup>55</sup> /4.05 <sup>56</sup> / 12.5 <sup>57</sup> /1.6 <sup>57</sup> | 38 <sup>55</sup> /4.05 <sup>56</sup> / 12.5 <sup>57</sup> /1.6 <sup>57</sup> | 55 <sup>58</sup> /1.17 <sup>59</sup> / NR/NR                           | 38 <sup>47</sup> / <sup>&lt;1</sup> <sup>45</sup> /7.7 <sup>46</sup> / 19.2 <sup>46</sup> |
| Clinical Presentation                                                                                                             | Fever, headache, neck swelling                                                 | Neck swelling                                                                | Fever with chill, neck pain and swelling                                     | Fever, neck pain and swelling, dysphagia, odynophagia, change of voice | Fever, neck pain and swelling                                                             |
| Duration from onset to presentation (days)                                                                                        | 5                                                                              | 7                                                                            | 7                                                                            | 5                                                                      | 7                                                                                         |
| Primary infectious source                                                                                                         | Neck abscess                                                                   | Parotid gland abscess                                                        | NF at neck                                                                   | Right carotid space abscess                                            | Neck cellulitis                                                                           |
| Thrombosis                                                                                                                        | IJV                                                                            | IJV                                                                          | IJV                                                                          | IJV, sigmoid sinus, transverse sinus                                   | IJV                                                                                       |
| Complication                                                                                                                      | Brain metastasis                                                               | Lung metastasis                                                              | Lung metastasis                                                              | None                                                                   | None                                                                                      |
| Culture-positive specimen                                                                                                         | Blood and pus                                                                  | Pus                                                                          | Blood and pus                                                                | Pus                                                                    | Blood and pus                                                                             |
| Multidrug-resistant strain                                                                                                        | ESBL                                                                           | No                                                                           | ESBL                                                                         | No                                                                     | No                                                                                        |
| Glycemic control                                                                                                                  |                                                                                |                                                                              |                                                                              |                                                                        |                                                                                           |
| BS upon admission (mg/dl)                                                                                                         | NR                                                                             | NR                                                                           | NR                                                                           | 230                                                                    | 398                                                                                       |
| HbA1C(%)                                                                                                                          | NR                                                                             | 12.7                                                                         | NR                                                                           | 9.9                                                                    | NR                                                                                        |
| Surgical Treatment                                                                                                                |                                                                                |                                                                              |                                                                              |                                                                        |                                                                                           |
| I&D (times)                                                                                                                       | Yes(1)                                                                         | Yes(1)                                                                       | Yes(1)                                                                       | Yes(1)                                                                 | Yes(1)                                                                                    |
| IJV ligation                                                                                                                      | None                                                                           | None                                                                         | None                                                                         | None                                                                   | None                                                                                      |
| Further operations                                                                                                                | None                                                                           | None                                                                         | Debridement                                                                  | None                                                                   | Debridement                                                                               |
| Anticoagulants                                                                                                                    |                                                                                |                                                                              |                                                                              |                                                                        |                                                                                           |
| Type                                                                                                                              | NR                                                                             | Warfarin, LMWH                                                               | None                                                                         | Warfarin                                                               | None                                                                                      |
| Duration (Days)                                                                                                                   | NR                                                                             | 56                                                                           | None                                                                         | 42                                                                     | None                                                                                      |
| Antibiotics                                                                                                                       |                                                                                |                                                                              |                                                                              |                                                                        |                                                                                           |
| ATB prior admission                                                                                                               | Ceftazidime, metronidazole                                                     | Penicillin, cloxacillin                                                      | NR                                                                           | None                                                                   | None                                                                                      |
| Initial ATB after diagnosis                                                                                                       | Ceftazidime, amikacin                                                          | Ceftriaxone, metronidazole                                                   | Ceftriaxone, metronidazole, ciprofloxacin                                    | Clindamycin cefuroxime                                                 | Ceftriaxone, metronidazole                                                                |
| After known culture result                                                                                                        | Fosfomycin, meropenem                                                          | Amikacin                                                                     | Meropenem, amoxicillin-clavulanate                                           | Clindamycin, cefuroxime                                                | Amoxicillin-clavulanate                                                                   |
| Duration (days)                                                                                                                   | 56                                                                             | 42                                                                           | 56                                                                           | 35                                                                     | 35                                                                                        |
| Outcomes                                                                                                                          |                                                                                |                                                                              |                                                                              |                                                                        |                                                                                           |
| Duration to clinical response (day)                                                                                               | NR                                                                             | NR                                                                           | 7                                                                            | NR                                                                     | NR                                                                                        |
| Hospital stay (day)                                                                                                               | 60                                                                             | NR                                                                           | 56                                                                           | NR                                                                     | NR                                                                                        |
| Resolution of infection                                                                                                           | Yes                                                                            | Yes                                                                          | Yes                                                                          | Yes                                                                    | Yes                                                                                       |
| Resolution of thrombosis                                                                                                          | NR                                                                             | NR                                                                           | NR                                                                           | Yes                                                                    | Yes                                                                                       |
| Survival                                                                                                                          | Survived                                                                       | Survived                                                                     | Survived                                                                     | Survived                                                               | Survived                                                                                  |

Abbreviations : ATB, antibiotics; BS, blood sugar; CRE-KP, carbapenem-resistant Enterobacteriaceae- *Klebsiella pneumoniae*; DLP, dyslipidemia; DM, diabetes mellitus; DRS, drug resistant strain; ESBL, extended-spectrum beta-lactamases; F, female; HAP, hospital acquired pneumonia; HT, hypertension; IJV, internal jugular vein; I&D, incision and drainage; K1, K1 capsular serotype of *Klebsiella pneumoniae*; K2, K2 capsular serotype of *Klebsiella pneumoniae*; LMWH, low molecular weight heparin; M, male; No., number of patients; NR, not recorded; UFH, unfractionated heparin.

\* newly diagnosed DM within 1 month.

polymerase chain reactions (PCR), such as PCR targeting on *rpoB* sequence in the classic Lemierre's syndrome and PCR targeting on 16s rRNA gene in cases suspected of having *K. pneumoniae* infection, have been used.<sup>22</sup>

The mainstay treatment of Lemierre's syndrome is the combination of antibiotic therapy and surgical intervention.<sup>23</sup> For classic Lemierre's syndrome, a beta-lactamase resistant beta-lactam antibiotic is recommended as empirical therapy since there have been reports of treatment failure with penicillin and beta-lactamase producing *F. necrophorum*.<sup>24,25</sup> The treatment drugs include ampicillin-sulbactam and piperacillin-tazobactam. Antibiotics should be tailored accordingly to culture and susceptibility data when available. An alternative option is clindamycin or metronidazole if the organism is found susceptible.<sup>4,19,26,27,28</sup> For patients suspected to have KLS, the empirical regimen should be antibiotics that can be used for classic Lemierre's syndrome and are also active against *K. pneumoniae* based on the local susceptibility data and the risk of acquiring the ESBL-producing strain. These antibiotics include ampicillin-sulbactam or piperacillin-tazobactam while a carbapenem should be used in cases with risks for ESBL-associated infections.<sup>29</sup> In the setting where CRE-KP is prevalent, combination therapy with tigecycline and colistin should be considered as empirical therapy.<sup>30</sup> The definitive antibiotic for KLS patients should be based on the susceptibility results. Commonly-used antibiotics that are active against *K. pneumoniae* are ampicillin-sulbactam, amoxicillin-clavulanate, piperacillin-tazobactam, cephalosporins, fluoroquinolones, and carbapenems.<sup>29</sup> The duration of therapy should be prolonged (2–6 weeks) to allow for antibiotic penetration through fibrin clots and prevention of relapse.<sup>28</sup>

Surgical management is often performed in order to gain primary source control in patients with refractory sepsis and/or multiple septic metastasis, respiratory distress due to pulmonary thrombus metastasis and in those with intracerebral or mediastinal extension of thrombus.<sup>31</sup> Surgical interventions may include incision and drainage of the infected sites and excision of the affected vein and its tributaries if incision and drainage alone cannot adequately remove the septic focus and bacteremia persists.<sup>32</sup> Anticoagulant therapy in patients with Lemierre's syndrome is controversial. The therapy may be considered in cases with thrombophilia, the thrombosis extending into the cerebral sinuses, and/or poor improvement of the symptoms within 72 hours despite adequate antibiotics and surgical interventions.<sup>9,27,33,34</sup> Previous reports suggest giving the anticoagulant for 4 weeks to 6 months depending on the patients' responses.<sup>27,34</sup> In our review of the nine KLS cases, anticoagulant drugs were given to six patients (67%) due to intra-cerebral thrombosis (3 cases) and poor responses after antibiotic therapy (3 cases). In these six cases, the median duration of anticoagulant therapy was 16.5 days (range 7–26 days).

The mortality rates of the classic Lemierre's syndrome were reported to be 4.9% in cases with septic metastasis and up to 18% in some case series.<sup>1,4,26</sup> In our review, the mortality rate of KLS patients was 11% while the mortality rate in cases

with septic metastasis was 17%. The overall mortality rate of KLS was higher than the classic Lemierre's syndrome, while both group had no difference in the rates of septic metastasis. The possible explanation may be the higher incidence of beta-lactam-resistance among *K. pneumoniae* (51%) compared to that of *Fusobacterium spp.* (41.1 %) which might have led to inappropriate initial empirical therapy.<sup>35,36</sup> The previous studies of classic Lemierre's syndrome indicated that a delay in antibiotic treatment, multiple metastatic sites, advanced age and persistent fever were associated with mortality.<sup>8,37,38</sup> In this report, our KLS patient was at high-risk for death due to the delayed antibiotic treatment (5 days after the onset of infection), having lung metastasis and persistent fever for 26 days.

In conclusion, KLS is a rare and emerging condition associated with poorly-controlled DM. Although the clinical presentations of KLS are similar to the classic Lemierre's syndrome, additional coverage with antibiotics that are active against *K. pneumoniae* is needed. In cases with risk factors for acquiring multidrug-resistant *K. pneumoniae*, such as ESBL-producing strains and CRE-KP, empirical antibiotic regimens should be adjusted accordingly. Early control of infection at the primary site with appropriate empirical antibiotics and surgical interventions remains the critical strategy to prevent metastasis, achieve clinical responses and reduce mortality among KLS patients.

## Conflict of Interest

None of the authors identify a conflict of interest.

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