Primary Liver Abscess Due to *Klebsiella pneumoniae* in Taiwan

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Pyogenic liver abscess is an uncommon complication of intra-abdominal or biliary tract infection and is usually a polymicrobial infection associated with high mortality and high rates of relapse. However, over the past 15 years, we have observed a new clinical syndrome in Taiwan: liver abscesses caused by a single microorganism, *Klebsiella pneumoniae*. We reviewed 182 cases of pyogenic liver abscess during the period September 1990 to June 1996; 160 of these cases were caused by *K. pneumoniae* alone, and 22 were polymicrobial. When patients with *K. pneumoniae* liver abscess were compared with those who had polymicrobial liver abscess, we found higher incidences of diabetes or glucose intolerance (75% vs. 4.5%) and metastatic infections (11.9% vs. 0) and lower rates of intra-abdominal abnormalities (0.6% vs. 95.5%), mortality (11.3% vs. 41%), and relapse (4.4% vs. 41%) in the former group. Liver abscess caused by *K. pneumoniae* is a new clinical syndrome that has emerged as an important infectious complication in diabetic patients in Taiwan.

Pyogenic liver abscess is an uncommon complication of intra-abdominal or biliary tract infection, despite the high incidence of cholecystitis, appendicitis, diverticulitis, and peritonitis worldwide [1–3]. The infection may be due to direct extension from contiguous structures or to hematogenous spread from a remote infectious focus such as appendicitis or diverticulitis [3]. Pyogenic liver abscess is usually polymicrobial because of the ascending route of infection from the gastrointestinal tract [1, 4–6]. Over the past 15 years in Taiwan, we have seen many cases of pyogenic liver abscess that have been contrary to the rule. In Taiwan, liver abscesses caused by a single pathogen, *Klebsiella pneumoniae*, occur in diabetic patients without intra-abdominal or biliary tract infection.

*K. pneumoniae* liver abscess is a well-known disease in Taiwan that presents as an infectious complication in diabetic patients [7]. It has been an endemic disease for at least 15 years. Infectious diseases specialists in Taiwan have reached a consensus on the diagnosis and management of *K. pneumoniae* liver abscess; this consensus has also been applied to polymicrobial liver abscess. Diagnostic examinations include three sets of blood cultures and CT- or ultrasonographically-guided aspiration of the abscess, with or without pigtail catheter drainage, to obtain a specimen for gram staining and aerobic/anaerobic cultures.

Routine tests performed on admission in our hospital include CT scanning of the whole abdomen to rule out the possibility of a tumor or biliary tract stones, HIV serology, and blood chemistry and fasting blood sugar determinations; a hemogram is also obtained. Pigtail catheter drainage is the major treatment strategy unless multiple microabscesses are present, in which case, fine-needle aspiration is satisfactory for both diagnosis and treatment. Patients’ clinical courses are usually uneventful if successful pigtail catheter drainage is combined with a 3-week course of parenteral antimicrobial treatment. Pigtail catheter drainage is usually continued for 1–2 weeks, and the drain is removed when the following criteria are met: cultures of the liver abscess become sterile, the daily drainage output is <5 mL for several days, and defervescence occurs even after the drainage tube is clamped. We usually maintain oral antimicrobial treatment for 1–2 months after discharge from the hospital to consolidate the effect of treatment.

We reviewed 182 cases of pyogenic liver abscesses treated at the Veterans General Hospital-Kaohsiung (Taiwan) from September 1990 to June 1996 and compared the epidemiological features, clinical presentations, treatment strategies, and outcomes of *K. pneumoniae* liver abscess with those of polymicrobial liver abscess.

Materials and Methods

Veterans General Hospital-Kaohsiung, a 1,000-bed facility, is one of the 11 medical centers in Taiwan and has been a reference center for four southern counties and one metropolitan area since September 1990. In our hospital the diagnostic and therapeutic strategies for pyogenic liver abscess are based on the aforementioned consensus. We retrospectively reviewed the medical and microbiological records at Veterans General Hospital-Kaohsiung to identify patients with the diagnosis of *K. pneumoniae* abscess and polymicrobial liver abscess during the period September 1990 to June 1996.

Cases were considered to be *K. pneumoniae* liver abscess if a bacterial culture of blood or of pus from a CT-confirmed liver abscess was positive for *K. pneumoniae* and a gram stain of the pus showed only gram-negative bacilli. Cases were con-
sidered to be polymicrobial liver abscess if a gram stain of the pus obtained from a CT-confirmed liver abscess showed mixed bacterial flora. In the cases were morphologically and microbiologically confirmed as *K. pneumoniae* abscess or polymicrobial liver abscess, demographic data, clinical presentations, risk factors, and treatment outcomes were gathered from the medical records and reviewed.

After consensus as to the diagnosis was reached, CT of the whole abdomen was routinely performed on admission for any suspected cases to confirm the morphological diagnosis and to rule out the possibility of intrahepatic and intra-abdominal abnormalities. All patients with morphologically proven liver abscess underwent immediate pigtail catheter drainage or fine-needle aspiration of the abscess for etiologic diagnosis and treatment. Every patient with a microbiologically proven case received parenteral antimicrobial treatment according to susceptibility test results for at least 3 weeks.

In studying the risk factors for *K. pneumoniae* and polymicrobial liver abscesses, we analyzed HIV serostatus; history of steroid use; and the presence of intrahepatic abnormalities, malignancies, or diabetes mellitus. We defined diabetes mellitus as a random plasma glucose level of >200 mg/dL, a fasting plasma glucose level of >140 mg/dL, or a fasting venous whole blood glucose level of >120 mg/dL on more than one occasion, or abnormal results of an oral glucose tolerance test performed under standardized conditions, with the glucose levels at 2 hours and in at least one other sample exceeding 200 mg/dL. The term impaired glucose tolerance was reserved for patients with glucose tolerance results that fell between normal and frank diabetes. Glucose tolerance tests were performed for all patients with pyogenic liver abscess who did not have frank diabetes mellitus during the convalescent stage.

All statistical analyses were performed with the binomial test for two independent samples, and *P* values were calculated to express the difference between two groups.

**Results**

One hundred eighty-two patients with *K. pneumoniae* and polymicrobial liver abscesses were enrolled in this study, which was conducted from September 1990 to June 1996. Of these patients, 160 (87.9%) had liver abscesses caused by a single microorganism, *K. pneumoniae*, and 22 (12.1%) had liver abscesses caused by mixed flora. The male-to-female ratio was 2.40 (113:47) in the group with abscesses due to *K. pneumoniae* and 2.67 (16:6) in the group with polymicrobial abscesses. The mean age was 58.0 years in the former group and 62.6 years in the latter group (table 1). There was no specific geographic distribution for either group in the referral area covered by Veterans General Hospital-Kaohsiung.

Clinical presentations of *K. pneumoniae* and polymicrobial liver abscesses are summarized in table 1. Fever (oral temperature, >38°C), noted in 148 cases of *K. pneumoniae* liver abscess (92.5%) and 18 cases of polymicrobial liver abscess (81.8%), was the most common presenting symptom for both types of liver abscesses. Tenderness to percussion over the right upper quadrant of the abdomen was also common, occurring in 71.2% and 68.2% of patients with *K. pneumoniae* liver abscesses and polymicrobial liver abscesses, respectively. Other abdominal complaints such as nausea, vomiting, diarrhea, and abdominal pain were less common, occurring in only 38.1% and 31.8% cases of *K. pneumoniae* liver abscess and polymicrobial liver abscess, respectively. Chest complaints were rare and were found in only 11.3% of cases of *K. pneumoniae* liver abscess and 4.5% of cases of polymicrobial liver abscess. Clinically, there were no significant differences between these two types of liver abscesses.

Laboratory findings for patients with *K. pneumoniae* and polymicrobial liver abscesses are shown in table 1. Leukocytosis (70% of patients with *K. pneumoniae* abscess vs. 72.7% of patients with polymicrobial liver abscess), elevated aspartate aminotransferase levels (67.5% vs. 68.2%), and elevated alanine aminotransferase levels (59.4% vs. 45.5%) were seen in both groups; the difference was not significant. Higher incidences of elevated total bilirubin levels and alkaline phosphatase levels were observed for patients with polymicrobial liver abscesses (54.5% vs. 25.6% and 100% vs. 78.1%, respectively).

Metastatic infection was a characteristic feature of *K. pneumoniae* liver abscess. Of the 160 patients with *K. pneumoniae* liver abscesses, 143 (92.5%) and 18 cases of polymicrobial liver abscesses caused by mixed flora. The male-to-female ratio was polymicrobial liver abscesses were enrolled in this study, which was conducted from September 1990 to June 1996. Of these patients, 160 (87.9%) had liver abscesses caused by a single microorganism, *K. pneumoniae*, and 22 (12.1%) had liver abscesses caused by mixed flora. The male-to-female ratio was 2.40 (113:47) in the group with abscesses due to *K. pneumoniae* and 2.67 (16:6) in the group with polymicrobial abscesses. The mean age was 58.0 years in the former group and 62.6 years in the latter group (table 1). There was no specific geographic distribution for either group in the referral area covered by Veterans General Hospital-Kaohsiung.

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liver abscess, 19 (11.9%) had metastatic foci other than the liver (table 1), including endophthalmitis (five patients), meningitis (four), lung abscess (four), psoas muscle abscess (two), brain abscess (one), lung and brain abscess (one), splenic abscess (one), and necrotizing fasciitis of the right leg (one). None of the 22 patients with polymicrobial liver abscess had any detectable metastatic foci.

The susceptibility of *K. pneumoniae* causing liver abscess in Taiwan was also a characteristic finding. The antimicrobial susceptibility pattern was the same in all 160 cases, with resistance to ampicillin and ticarcillin/carbenicillin but susceptibility to the other antibiotics including all the cephalosporins and aminoglycosides. Susceptibility to piperacillin was variable. This pattern of susceptibility has remained unchanged since the onset of outbreak 15 years ago. Although multiresistant strains of *K. pneumoniae*, whether nosocomial or community-acquired, are not unusual in Taiwan, these strains had not been isolated previously from patients with primary *K. pneumoniae* liver abscess.

Standard treatment in our hospital for both types of liver abscesses included pigtail catheter drainage by negative-pressure suction and parenteral cephalosporins and aminoglycosides, according to susceptibility test results. For *K. pneumoniae* liver abscess, cefazolin plus gentamicin was the standard therapy. We usually discontinued treatment with gentamicin after 2 weeks to avoid nephrotoxicity but continued treatment with cefazolin for at least 3 weeks or longer, depending on the clinical response and adequacy of abscess drainage. An oral cephalosporin was administered for an additional 1–2 months to prevent relapse. Pigtail catheter drainage was usually discontinued during the second week of hospitalization if culture of the drainage fluid yielded no growth, the patient was afebrile, and the daily amount of drainage was <5 mL for several days. With this treatment strategy, the mortality (18 of 160 patients; 11.3%) and relapse (7 of 160; 4.4%) rates for *K. pneumoniae* liver abscess were low in contrast to those for polymicrobial liver abscess (9 of 22; 41.0%, and 9 of 22; 41.0%, respectively) (table 1).

Causes of mortality among patients with *K. pneumoniae* liver abscess included fulminant sepsis (9 of 18 patients; 50%), metastasis of infection to critical organs (4 of 18; 22.2%), rupture of the abscess (2 of 18; 11.1%), diabetic complications (1 of 18; 5.6%), chronic obstructive pulmonary disease (1 of 18; 5.6%), and nosocomial pneumonia (1 of 18; 5.6%). All cases of fulminant sepsis were due to inadequate (4 of 9) or delayed (5 of 9) pigtail catheter drainage. The prognosis for metastatic infection depended on the organs involved. Of the four fatal metastatic infections, two were meningitis, one, a lung and brain abscess, and one, severe necrotizing fasciitis. Rupture of the liver abscess before pigtail catheter drainage is performed can induce peritonitis and result in death. In spite of pigtail catheter drainage and antimicrobial treatment, sepsis was the only cause of death among patients with polymicrobial liver abscess.

Seven cases of *K. pneumoniae* liver abscess relapsed after treatment. Two relapses were due to early removal of drain tube. One relapse was due to discontinuation of oral consolidation treatment. There were no specific risk factors in four of the relapsed cases. Relapses of polymicrobial liver abscess were all due to the presence of inoperable intrahepatic stones or malignancies.

Of 160 patients with *K. pneumoniae* liver abscess, 108 (67.5%) had frank diabetes, 12 (7.5%) had impaired glucose tolerance, and 40 (25%) were nondiabetic (table 2). The incidence of impaired glucose metabolism was as high as 75% in this group. Of the patients with polymicrobial liver abscess, one (4.5%) was diabetic, none had impaired glucose tolerance, and 22 (95.5%) were nondiabetic (table 2). There was an obvious difference in the incidence of impaired glucose metabolism between patients with *K. pneumoniae* liver abscess and those with polymicrobial liver abscess.

CT of the whole abdomen was performed for all patients for evaluation of intra-abdominal abnormalities including common bile duct and intrahepatic duct stones, intra-abdominal infections, and malignancies. Of the 160 patients with *K. pneumoniae* liver abscess, only one (0.6%) had intrahepatic duct stones, and none had intra-abdominal infections or malignancies (table 2). Seventeen (77.3%) of 22 patients with polymicrobial liver abscess had intrahepatic duct or common bile duct stones, four (18.2%) had intra-abdominal malignancies, and none had other intra-abdominal infections (table 2). The rate of intra-abdomi-

### Table 2. Risk factors for Klebsiella pneumoniae liver abscess vs. polymicrobial liver abscess at Veterans General Hospital-Kaohsiung, Taiwan, September 1990 to June 1996.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>K. pneumoniae liver abscess (n = 160)</th>
<th>Polymicrobial liver abscess (n = 22)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus†</td>
<td>120 (75)</td>
<td>1 (4.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Frank diabetes</td>
<td>108 (67.5)</td>
<td>1 (4.5)</td>
<td>...</td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td>12 (7.5)</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>No diabetes</td>
<td>40 (25)</td>
<td>21 (95.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Intra-abdominal abnormalities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biliary tree stone</td>
<td>1 (0.6)</td>
<td>17 (77.3)</td>
<td>...</td>
</tr>
<tr>
<td>Malignancy</td>
<td>0</td>
<td>4 (18.2)</td>
<td>...</td>
</tr>
<tr>
<td>Infection</td>
<td>0</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>Steroid use</td>
<td>0</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>Seropositive for HIV†</td>
<td>0†</td>
<td>0‖</td>
<td>...</td>
</tr>
</tbody>
</table>

* P values were estimated by using the binomial test for two independent samples.
† Diabetes mellitus was defined as a random plasma glucose level of >200 mg/dL, a fasting plasma glucose level of >140 mg/dL, a fasting venous whole blood glucose level of >120 mg/dL on more than one occasion, or an abnormal oral glucose tolerance test, performed under standardized conditions, with glucose levels at 2 hours and in at least one other sample exceeding 200 mg/dL. Impaired glucose tolerance was defined as glucose tolerance falling between normal and frank diabetes.
‡ n = 132.
‖ n = 18.
nal abnormalities in the polymicrobial group was 95.5%, in contrast to only 0.6% in the \textit{K. pneumoniae} group.

HIV serostatus was determined for 150 patients by performing a single antibody measurement; these patients included 132 with \textit{K. pneumoniae} liver abscess and 18 with polymicrobial liver abscess. Sera were measured by using the Wellcozyme Recombinant HIV 1 and 2 ELISAs (Murex Diagnostics, Dartford, UK). All serological tests were negative (table 2). Histories of steroid use were obtained by reviewing the patients’ charts; none of the patients had taken steroids within 3 months before the onset of \textit{K. pneumoniae} liver abscess or polymicrobial liver abscess.

**Discussion**

Primary \textit{K. pneumoniae} liver abscess has rarely been reported in the literature; however, this condition is a prevalent infectious complication in diabetic patients in Taiwan. In our hospital, a maximum of 50 patients with liver abscess are admitted to our infectious diseases wards annually.

In our country, infectious diseases physicians are highly alert to the possibility of \textit{K. pneumoniae} liver abscess. This disease is one of the foremost differential diagnoses considered for any diabetic patient who presents with fever or for any patient with a blood culture positive for multisusceptible \textit{K. pneumoniae}. A CT scan or gallium scan is routinely obtained for patients with multisusceptible \textit{K. pneumoniae} bacteremia to locate abscesses in the liver or other organs.

\textit{K. pneumoniae} liver abscess is a relatively benign disease that is associated with a low mortality rate, good clinical response, and low relapse rate. Standardized treatment, including pigtail catheter drainage and combination antimicrobial therapy for 2–3 weeks, is highly effective. Complications such as severe sepsis, metastatic infection, and rupture of the abscess are not uncommon and are usually associated with a poor prognosis. Some patients present with extrapleural involvement alone; the conditions include meningitis, prostatic abscess, psoas muscle abscess, spinal abscess, septic arthritis, lung abscess, and splenic abscess. Multisusceptible \textit{K. pneumoniae} is now the leading cause of primary gram-negative bacillary meningitis in our hospital; the annual incidence is 15–20 cases. Patients who recover from \textit{K. pneumoniae} liver abscess after adequate treatment usually remain free of relapse.

In contrast to primary \textit{K. pneumoniae} liver abscess, cases of polymicrobial liver abscess are usually secondary to biliary tract stones, malignancies, or intra-abdominal infections. Surgical intervention is mandatory for cure, since standard therapy for liver abscess will be ineffective in nearly one-half of cases. The rate of relapse is high despite successful treatment, since bacteriologic eradication often fails because underlying malignancies or intrahepatic stones are present.

Although \textit{K. pneumoniae} liver abscess is a well-known disease in Taiwan, many questions remain to be answered. The first is the association of this disease with diabetes mellitus. As our series indicates, 75% of patients with \textit{K. pneumoniae} liver abscess have diabetes or glucose intolerance. Diabetes is known to interfere with neutrophil chemotaxis and phagocytosis [8–11], but its influence on the function of macrophages, including Kupffer’s cells, is still unknown. However, if the function of Kupffer’s cells is also impaired in diabetic patients, the preponderance of \textit{K. pneumoniae} liver abscess cases in this population could be explained by the escape of enteric \textit{K. pneumoniae} from phagocytosis by Kupffer’s cells. Further studies are required for validation of this hypothesis.

In spite of the fact that diabetes is the most important predisposing factor for \textit{K. pneumoniae} liver abscess, we found that 25% of cases occurred in patients without diabetes or glucose intolerance, and we did not find any correlation between the severity of diabetes and the occurrence of \textit{K. pneumoniae} liver abscess (authors’ unpublished data). Therefore, impaired function of Kupffer’s cells may be a contributing factor, but unlikely the sole factor, in the development of \textit{K. pneumoniae} liver abscess in diabetic patients.

The microbiological characteristics of \textit{K. pneumoniae} are also subjects of interest. \textit{K. pneumoniae} liver abscess has been an endemic disease in Taiwan for >15 years. During this period, we have not detected any changes in the antibiogram of \textit{K. pneumoniae} strains isolated from patients with liver abscess, i.e., all strains have remained susceptible to all antibiotics tested except ampicillin and ticarcillin/carbenicillin. This phenomenon can be explained by the fact that \textit{K. pneumoniae} causes liver abscess is community acquired and is not naturally a multiresistant strain. On the other hand, this is not a plausible hypothesis since antibiotics are freely used in many hospitals, pharmacies, and in traditional medicine and the livestock industry in Taiwan.

Community-acquired infections caused by nosocomial strains or multiresistant strains of \textit{K. pneumoniae} are not uncommon. It is therefore surprising that strains of \textit{K. pneumoniae} causing liver abscess have persisted in our community for >15 years without any changes in susceptibility patterns. It has been observed that patients septicemia due to multiresistant \textit{K. pneumoniae}, whether nosocomial or community acquired, do not develop liver abscesses. It remains to be determined if these strains have different biological properties despite the fact that they have the same biochemical characteristics.

The development of metastatic infection, a rare infectious complication of gram-negative septicemia, is a characteristic feature of \textit{K. pneumoniae} liver abscess. In the first few cases of the outbreak in Taiwan, metastatic \textit{K. pneumoniae} endophthalmitis was the principal diagnostic clue to the presence of liver abscess [12, 13]. As the experience with \textit{K. pneumoniae} liver abscess increased, metastatic infections were detected in many organs including the spleen, lungs, brain, meninges, paravertebral space, prostate, bones, joints, and soft tissues [13]. However, \textit{K. pneumoniae} abscesses may occur alone in the absence of liver abscess, with clinical presentations very similar to those of \textit{Staphylococcus aureus} infection. According to our
unpublished data, *K. pneumoniae* has been one of the leading causes of gram-negative meningitis, brain abscesses, bone and joint infections, splenic abscesses, and endophthalmitis over the past 15 years.

Clinical detection of *K. pneumoniae* liver abscess with metastatic infection is not difficult. In patients with uncomplicated *K. pneumoniae* liver abscess, fever usually subsides after several days of adequate pigtail catheter drainage and antimicrobial treatment. If defervescence is delayed, a gallium scan should be obtained to detect the presence of metastatic infection. All isolates of *K. pneumoniae* from sites of metastatic infection are multisusceptible strains, identical to those recovered from liver abscesses.

Relapse of *K. pneumoniae* liver abscess after adequate treatment is rare. The liver has a dual blood supply: sterile arterial blood from the hepatic artery and venous blood from the gut, where transient bacteremia of the portal system is not unusual. Therefore, the most probable source of *K. pneumoniae* in cases of liver abscess is the gut. If this hypothesis is true, a high relapse rate would be expected, since conditions predisposing to the formation of liver abscess do not change after treatment. The low relapse rate in our series can only be explained by the acquisition of immunity after infection. Determination of the type of immunity involved, and its quantification, are topics for future studies.

*K. pneumoniae* liver abscess is an interesting infectious entity in Taiwan. The relation of this condition to race, environment, and the presence of diabetes mellitus, as well as its pathogenesis, remain uncertain. Whether the bacterial strains of *K. pneumoniae* found in liver abscesses are unique or are no different from other *K. pneumoniae* strains is another point requiring further clarification. The present report marks the beginning of an effort to further the understanding of the pathogenesis of *K. pneumoniae* liver abscess.

References