Klebsiella pneumoniae liver abscess: An old bug in a new bottle?

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Klebsiella pneumoniae (*K. pneumoniae*) has a long history. It is less well known that the Danish scientist Hans Christian Gram (1853–1938) when working in Carl Friedlander's (a German bacteriologist) laboratory, developed the technique now known as Gram staining in 1883 (published in 1884) not to distinguish between one group of bacteria from another but to enable bacteria to be seen more readily in stained sections of mammalian tissues. In his study on tissue sections of lungs of twenty fatal cases of lobar pneumonia, he found that in 19 cases, the bacteria retained the gentian violet stain (Gram positive) but in the twentieth case the bacteria were decolorised (Gram negative).[1] Although at that time neither Gram nor Friedlander paid any importance to this finding, subsequent observations established that the more frequently seen Gram positive bacteria were *Streptococcus pneumoniae* (*S. pneumoniae*) and less commonly seen Gram negative bacilli were 'Friedlander's bacillus', now known as *K. pneumoniae*. Interestingly *Klebsiella* was named in the honour of the German bacteriologist Edwin Klebs (1834–1913) who in 1875 observed bacteria in the bronchial contents of patients dying of pneumonia.[1] Since then *Klebsiella* has been confirmed as a well known human pathogen capable of causing infections in all organ systems.

Klebsiella pneumoniae liver abscess

The relationship between *K. pneumoniae* and liver abscess is a relatively new one – first described in a case series from Taiwan in the early 1980s. Since then, this association has become well established and is now the leading cause for liver abscesses in Taiwan, South Korea, Singapore and Hong Kong. Descriptions of a new invasive syndrome with extrahepatic manifestations, moreover, has resurrected interest in this well known pathogen. Invasive *K. pneumoniae* liver abscess syndrome (IKPLAS) is yet to have an accepted definition. Broadly, IKPLAS can be considered as a liver abscess with contemporaneous metastatic *K. pneumoniae* infections in extrahepatic sites. Siu *et al*[1] have proposed a further definition based on clinical and microbiological findings (see Panel 1).

Risk Factors

Predisposition to IKPLAS appears to be related to either host or virulence factors. Diabetes mellitus is the most significant risk factor, present in 68% of patients diagnosed with IKPLAS in Taiwan. Amongst the South Korean cohort, there is a reported 38% prevalence. The underlying mechanisms for this association is unclear, however, it has been suggested that poor glycaemic control impairs neutrophil phagocytosis of K1 and K2 capsular serotypes.[2] Other factors include the presence of underlying hepatobiliary disease and fatty liver disease. As yet, there have been no specific identified genes that predispose to IKPLAS.

Bacterial virulence factors play an important role in the development of the invasive syndrome. The strains of *K. pneumoniae* are characteristically of the hypermucoviscous phenotype associated with serotypes K1 and K2, and the regulator of mucoid phenotype A gene (*rmp A*). The increased virulence of these strains appears to be associated with a phagocytic-resistant nature of the capsule against neutophils and macrophages. Conversely, a loss of the capsule reduces the virulence of the strains. It should be remembered that while most patients with liver abscess and extra hepatic infection are infected exclusively with the K1 and K2 serotypes, not all infections with K1 and K2 serotypes result in liver abscess. Epidemiological studies in China and other southeast Asian studies have shown that these strains are widely prevalent (over 75%) in gastrointestinal flora of healthy adults and in nearly all patients with the syndrome.[3]

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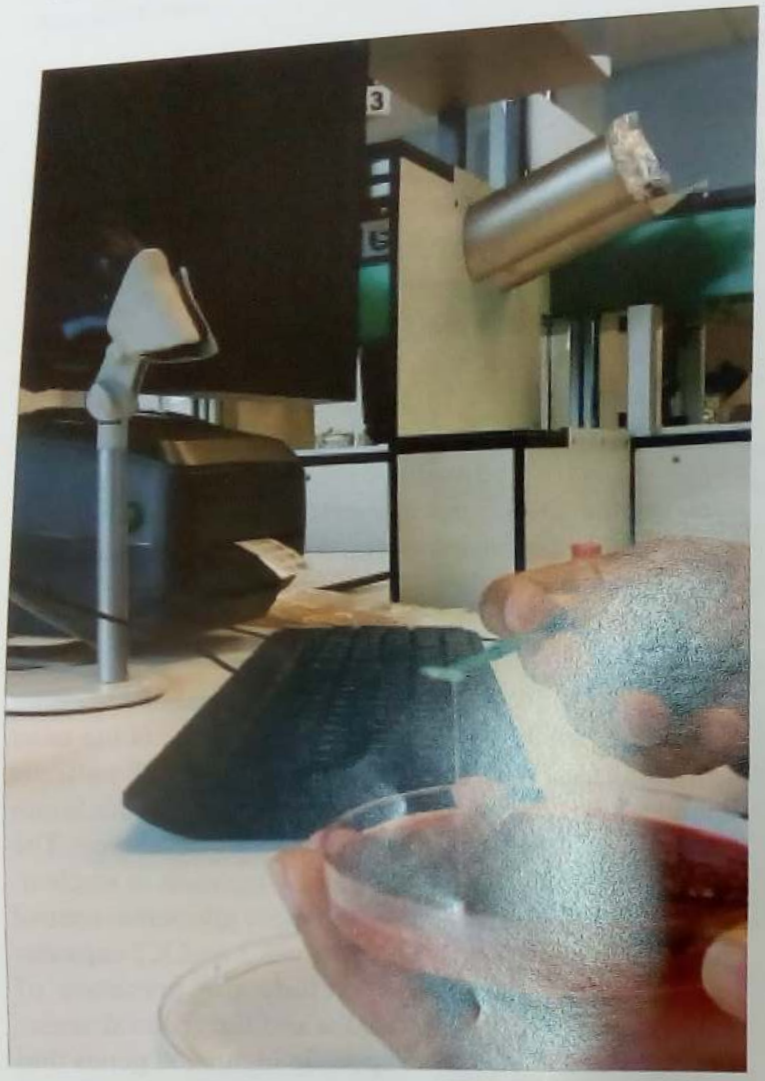

Figure 1: String test on a strain of hypermucoviscous K. pneumoniae

Clinical features and diagnosis

The clinical manifestations are similar to those of pyogenic liver abscess. Features include fever (93%), right upper quadrant tenderness (71%) and nausea (40%). Metastatic manifestations of IKPLAS include endopthalmitis, meningitis and necrotising fasciitis. Biochemically, there are elevations in inflammatory markers and deranged liver function tests.[4] Blood cultures should be obtained in all suspected cases. Isolation of a hypermucoviscous phenotype in the blood culture or an aspirate is indicative of IKPLAS.[3] Hypermucoviscous phenotype is easily identified using the 'string' test (Figure 1). IKPLAS may also have distinctive imaging characteristics. Ultrasonography demonstrates a more solid appearance than other pyogenic abscesses.[5] The CT appearance of IKPLAS, is often single and multiloculated. Ideally, diagnostic aspiration must be performed to confirm a *K. pneumoniae* aetiology can be difficult given the multiloculated nature.

Management

The principles of management of IKPLAS are similar those for pyogenic liver abscess: drainage and institution of appropriate antibiotics. For abscesses <5 drainage should be with an image-guided percutaneous approach – either via needle aspiration or catheter insertion. The management of abscesses >5cm remains controversial, however, it is still recommended to drain percutaneously via a catheter prior to surgical consideration. Given the frequent association of IKPLAS with diabetes, attention should be paid to ensure good glycaemic control.

Antibiotic choice depends on the local prevalence of antibiotic resistance. Interestingly, in the reported cases from Taiwan, extended spectrum beta lactamase producing carbapenem resistant *K. pneumoniae* strains were rare. Third generation cephalosporins, quinolones, piperacillin/tazobactam, ampicillin/sulbactam with or without aminoglycosides have been used in the treatment of IKPLAS. The treatment is usually for 4 weeks (2 weeks IV antibiotics) for a solitary abscess and 6 weeks for multiple abscesses. Metastatic infections especially of the eyes and CNS are difficult to treat and require prolonged treatment with high dose of third generation cephalosporins (cefotaxime 2G, 4 hourly or ceftriaxone 2G, 12 hourly) or meropenem or imipenem if ESBL producing strain. Despite appropriate treatment, the prognosis of endophthalmitis is particularly poor with 85% of patients developing severe visual deficit. Given the variability of penetration of antibiotics into the vitreous humour, it is particularly important that antibiotics such as third generation cephalosporins or ciprofloxacin, which achieve good levels in the vitreous humour should be chosen if possible. IKPLAS is associated with 5% mortality.[3]

Unanswered questions

There are many unanswered questions regarding IKPLAS. Why is IKPLAS seen mainly in Southeast Asians and why there is such high gastrointestinal carriage in healthy population? What is the prevalence of IKPLAS and gastrointestinal carriage of hypermucoviscous phenotype and K1 and K2 serotypes in other parts of the world especially South Asia (Indian subcontinent)? Does the low level of ESBL and carbapenem resistance

Panel 1

Proposed definitions of invasive liver abscess syndrome[3]

Clinical definitions:

Definite invasive syndrome: *K. pneumoniae* liver abscess with extrahepatic complications, especially of the CNS, necrotising fasciitis or endophthalmitis

Probable invasive syndrome: *K. pneumoniae* liver abscess as the sole presenting clinical manifestation.

Microbiological definitions:

Definite invasive syndrome: *K. pneumoniae* liver abscess caused by K1 or K2 serotype.

Probable invasive syndrome: Isolation of hypermucoviscous phenotype of *K. pneumoniae* from abscess. Hypermucoviscous phenotype is defined using the 'string test' where the mucous string is greater than 0.5cm in length stretched by the inoculation loop.

reported in the Taiwanese series hold true in the subcontinent where ESBL and carbapenemase producing *Klebsiella* are much commoner? What implications does it have for management of patients? Similarly given the high prevalence of diabetes in the subcontinent, is IKPLAS likely to be more common? Although there are several publications relating to amoebic liver abscesses, there are surprisingly few recent published reports in indexed journals describing the microbiology of pyogenic liver abscess in adults in India and only reported case of primary *K. pneumoniae* liver abscess IKPLAS in an Indian man who presented in Italy.[6,7] It is not clear if this reflects true rarity of the infection, failure to recognise the condition or under-reporting.

Microbiologists and physicians in India should be aware of IKPLAS and its association with hypermucoviscous phenotype of *K. pneumoniae*. Early diagnosis and aggressive treatment are likely to improve clinical outcomes.

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