Case Report

Relapsing *Klebsiella pneumoniae* meningitis in a patient with COVID-19

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Summary

*Klebsiella pneumoniae* is a common cause of potentially life-threatening infection. This report describes a relapsing healthcare-associated *Klebsiella pneumoniae* meningitis in a 60-year-old patient who had SARS-CoV-2 infection. During their initial admission for COVID-19 pneumonitis and treatment with corticosteroids, the patient developed signs and symptoms suggestive of bacterial meningitis. Blood and cerebrospinal fluid cultures confirmed *Klebsiella pneumoniae* as the causative organism. The patient was treated with a prolonged course of high-dose meropenem and made an apparent recovery. Four days after hospital discharge, the patient re-presented critically unwell. *Klebsiella pneumoniae* was once again isolated from cerebrospinal fluid. During their second admission, the patient deteriorated despite antimicrobial treatment, and life-sustaining therapies were withdrawn. This case highlights that all COVID-19 patients receiving immunosuppressive therapy should be monitored for potential opportunistic infection. Prompt recognition and early antimicrobial therapy are key to improving patient outcomes.

Introduction

*Klebsiella pneumoniae*, an encapsulated Gram-negative bacterium, is an increasing source of morbidity and mortality worldwide. It is an opportunistic pathogen found throughout nature, colonising human mucosal sites and acting as a healthcare contaminant[1].

In recent years, *K. pneumoniae* has garnered attention due to its acquisition of multiple antibiotic resistances, most notably through the production of extended-spectrum β-lactamases and carbapenemases [2]. Many antibiotic resistance genes now routinely found in multidrug-resistant bacteria were first described in *Klebsiella* species. The wide range of potentially life-threatening community-acquired and nosocomial infections caused by *K. pneumoniae* include those of the respiratory and urinary tracts, bloodstream, liver, surgical sites and central nervous system [2,3]. Between April 2020 and March 2021, 11,123 cases of *Klebsiella* spp. bacteraemia were reported across all NHS trusts in England, with the majority of these likely being *K. pneumoniae*[4].

Cases of recurrent *K. pneumoniae* meningitis in otherwise immunocompetent hosts are infrequently described in the literature. The aim of this report is to highlight the potential immune dysfunction resulting from SARS-CoV-2 infection and its therapies that could increase susceptibility to opportunistic infection.
During the COVID-19 pandemic, a 60-year-old female presented to hospital with respiratory failure and pyrexia. A positive SARS-CoV-2 test had been obtained six days previously in the community. The patient’s medical history included irritable bowel syndrome, partial thyroidectomy and a body mass index of 31 kg.m\(^{-2}\). She was independent in activities of daily living, had a 15 pack-year smoking history and consumed alcohol occasionally. Following admission to hospital with a diagnosis of COVID-19 pneumonitis she was treated with supplemental oxygen, dexamethasone, remdesivir and intravenous amoxicillin (changed to co-amoxiclav five days later) and clarithromycin. On the seventh day of their hospitalisation, the patient was admitted to the intensive care unit for respiratory support using continuous positive airway pressure and high-flow nasal oxygen. A computed tomography (CT) pulmonary angiogram was negative for pulmonary embolism but demonstrated bilateral multifocal ground-glass changes, in addition to moderate consolidation and right lower lobe atelectasis (Fig. 1a). The patient deteriorated further and tracheal intubation, invasive mechanical ventilation and proning were undertaken on the ninth day of hospitalisation. After a further three days weaning from ventilatory support, the patient’s trachea was successfully extubated. Medical therapy thus far had included an eight-day course of dexamethasone and 10 days of antibiotic therapy.

On day 15 of admission, despite a declining C-reactive protein (114 mg.l\(^{-1}\) from a peak of 239 mg.l\(^{-1}\)), normal white cell count and improving chest radiography, the patient developed a new pyrexia. At this time, no localising signs of infection were observed, and the Glasgow Coma Scale (GCS) score was 15. The patient became mildly disorientated and irritable 24 h later, with associated headache and neck stiffness. The C-reactive protein level was found to have increased to 188 mg.l\(^{-1}\) and the white cell count was \(4 \times 10^9.l^{-1}\) (Table 1). The clinical suspicion of meningitis, along with the provisional blood culture results of Gram-negative rods led to the commencement of meropenem \(2 g\), three times daily. This empiric therapy was advised by the microbiology team in view of the high frequency of cephalosporin resistance among Gram-negative rods. Computed

![Figure 1](a) CT pulmonary angiogram demonstrating moderate-to-severe multifocal ground-glass changes within the lung fields. (b) Contrast CT of the head showing bilateral extensive low-density changes in the cerebral hemispheres involving temporal, frontal and parietal lobes. (c) Contrast CT of the head showing fluid levels in the lateral ventricles and multifocal bilateral peripheral low-attenuating parenchymal changes representing ventriculitis and septic emboli, respectively.
tomography imaging of the head showed no acute intracranial abnormality. The following day, a lumbar puncture and cerebrospinal fluid (CSF) analysis was performed which was strongly suggestive of bacterial meningitis with a white cell count of 4485 x 10^6 (21% polymorphs and 30% lymphocytes) and protein of 6.55 g.l^-1. A diagnosis of *K. pneumoniae* meningitis was later confirmed by culture from CSF and blood. A 14-day course of meropenem was completed. Computed tomography of the thorax, abdomen and pelvis showed no cryptic sources of infection. On day 31, the patient was discharged well, with normalised inflammatory markers.

Four days later, the patient re-presented with a depressed level of consciousness, pyrexia and right-sided hemiparesis. The patient had reportedly been experiencing migraines and diarrhoea since discharge. Following tracheal intubation for airway protection, the patient was recommenced on meropenem and aciclovir. A non-contrast CT scan of the head showed no acute intracranial pathology. Lumbar puncture and CSF analysis was performed 24 h later (day 36 since original hospitalisation) which again indicated bacterial meningitis and subsequently cultured *K. pneumoniae*. The patient was reviewed by otolaryngeal and spinal surgeons to assess for cryptic sources of infection.

| **Table 1** Summary of microbiological investigations during both admissions |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| **SARS-CoV-2 PCR**              | **Cerebrospinal fluid culture** | **Cerebrospinal fluid PCR**     | **Sputum culture**              |
| Day –6 (community)             | *K. pneumoniae*                  | Day 17                          | *K. pneumoniae*                 |
| Day 0                           | Positive                         | Negative                        | Sensitivities not reported      |
| Day 18                          | Negative                         | Enterovirus, herpes simplex virus types 1 and 2, parechovirus and varicella-zoster virus not detected |
| Day 19                          | Negative                         | Day 36                          | *K. pneumoniae*                 |
| Day 20                          | Negative                         | Negative                        | Sensitivities not reported      |
| Day 35 (representation)         | Negative                         | Enterovirus, herpes simplex virus types 1 and 2, parechovirus and varicella-zoster virus not detected |
| Day 42                          | Positive                         |                                 |                                 |

**Cerebrospinal fluid culture**

| Day 17 | *K. pneumoniae* | Sensitive to gentamicin, ciprofloxacin, co-amoxiclav, piperacillin/tazobactam and meropenem |
| Day 36 | *K. pneumoniae* | Sensitive to gentamicin, ciprofloxacin, piperacillin with tazobactam and meropenem |

**Cerebrospinal fluid PCR**

| Day 17 | Negative | Enterovirus, herpes simplex virus types 1 and 2, parechovirus and varicella-zoster virus not detected |
| Day 36 | Negative | Enterovirus, herpes simplex virus types 1 and 2, parechovirus and varicella-zoster virus not detected |

**Sputum culture**

| Day 7  | *K. pneumoniae* | Sensitivities not reported |
| Day 13 | *K. pneumoniae* | Sensitivities not reported |
|        | *Candida albicans* | Sensitivities not reported |

**Peripheral blood culture**

| Day 15 (arterial and venous) | *K. pneumoniae* | Sensitive to gentamicin, ciprofloxacin, co-amoxiclav, piperacillin/tazobactam, meropenem and co-trimoxazole |
| Day 24  | No growth | |
| Day 35  | No growth | |
| Day 39  | No growth | |

**Urine culture**

| Day 7  | No growth | Sensitive to nitrofurantoin, gentamicin, trimethoprim |
| Day 15 | *Klebsiella group* | Sensitivities not reported |
| Day 36 | *Enterococcus spp.* | |

**Non-directed bronchoalveolar lavage**

| Day 35 | *Candida albicans* | Sensitivities not reported |

**HIV 1 + 2 antibody and P24 antigen**

| Day 39 | Not detected | |

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hypothesis (Fig. 1b). A transoesophageal echocardiogram was normal. On day 39, repeat CT of the head with contrast showed ventriculitis and possible cerebral septic emboli or early cerebritis (Fig. 1c). Immunological screening which included smooth muscle, mitochondrial, liver kidney microsomal, anti-cyclic citrullinated peptide and gastric parietal cell antibodies, rheumatoid factor, antineutrophil cytoplasmic antibodies, antinuclear antibodies, complement and immunoglobulins excluded any pre-existing immunosuppression. Following a sedation hold on day 40, the patient's GCS score was Eyes 1, Voice T and Motor 2. Neurosurgical colleagues were consulted and opined that there were no surgical options available, and that outcomes were likely to be poor. On day 43, neurology colleagues agreed with this assessment. On day 45, in conjunction with the patient's family, the decision was made to withdraw life-sustaining therapies and provide end-of-life care. The patient died on day 53, six days following tracheal extubation.

**Discussion**

Bacterial meningitis is an inflammation of the membranous coverings of the brain and spinal cord caused by a bacterial organism. In this report, we describe a relapsing, healthcare-associated, *K. pneumoniae* meningitis in a SARS-CoV-2-positive patient. Given the organism, timescale of symptoms (symptomatic 15 days after admission), iatrogenic immunosuppression and repeated invasive procedures associated with care of the critically ill patient, this case is highly likely to be nosocomial in origin. These risk factors are especially relevant given that *K. pneumoniae* rarely causes meningitis outside the context of neurosurgery [2].

Relapsing meningitis has been defined as any repeat episode of infection with the same organism which occurs within three weeks of initial infection and treatment completion. Re-infections outside this timeframe would be considered recurrent meningitis. Despite being initially asymptomatic, the patient reportedly developed migraines in the community shortly after discharge. Given the persistence of the original organism and re-presentation four days after discharge, this indicates a case of relapsing meningitis. Immunosuppression from dexamethasone and disruption of the blood–brain barrier as a consequence of SARS-CoV-2 infection could, in theory, have contributed to this patient's clinical course.

*Klebsiella pneumoniae* meningitis is broadly characterised into three separate clinical syndromes. The first is post-intracranial surgery, the second is a result of metastatic spread from liver abscesses (commonly hypervirulent strains) and, finally, immunocompromised or elderly patients may develop spontaneous meningitis [3]. Although further characterisation of the pathogen was not performed, the absence of any radiological evidence of intra-abdominal pathology means it is unlikely to have been a hypervirulent strain. This case likely represents a spontaneous *K. pneumoniae* meningitis in the setting of an immunocompromised host. One possible source was from the oropharynx, with subsequent respiratory infection and dissemination. The earliest culture of *K. pneumoniae* in this case was from sputum obtained on day seven, 48 h before tracheal intubation (Table 1). Seeding via the urinary system is another explanation but this seems unlikely given the negative urine culture on day seven.

The SARS-CoV-2 virus has been isolated from cerebral neurons and central microvascular endothelial cells in human and animal specimens [5]. It is thought to disrupt the blood–brain barrier via various mechanisms including cytotoxicity and dysregulation of the inflammatory response [5]. This provides a hypothetical mechanism of haematological seeding to the central nervous system, facilitated by impaired host factors. Later stages of SARS-CoV-2 infection are characterised by a dysregulated and pathological immune response. This process is mediated via various inflammatory cytokines, including interleukin (IL)-2, IL-6 and tumour necrosis factor-α [6–7]. Corticosteroids are thought to exert their immunomodulatory effects by downregulating pro-inflammatory agents and upregulating anti-inflammatory molecules such as annexin-1, nuclear factor of κ light polypeptide gene enhancer in B-cell inhibitor (IkB-α), secretory leukocyte protease inhibitor (SLPI) and IL-10 [6–7]. Potential adverse effects of corticosteroids in patients with COVID-19 include superadded infection and hyperglycaemia [6]. These are especially relevant given the immune dysregulation associated with COVID-19 [7]. Corticosteroid administration is also an independent risk factor for nosocomial infection [2].

The RECOVERY trial provided 59% of the total patient numbers to the WHO rapid evidence appraisal of corticosteroid therapy in COVID-19, but did not record adverse events as part of the planned analysis [8]. Adverse event rates were not included in previous meta-analyses due to limitations in assessment and recording [6, 8]. Additional research is therefore needed to quantify the risk of adverse reactions of corticosteroids in the setting of SARS-CoV-2 infection and indiscriminate prescribing should be avoided. However, given the patient population and severity of COVID-19 within critical care, corticosteroid use is supported by current data [8].
With an increasing number of immunosuppressive modalities being utilised in a broader patient cohort, the risk of opportunistic infection is a concern. The IL-6 inhibitors, tocilizumab and sarilumab are now recommended for some patients with COVID-19 [9]. Additionally, inhaled budesonide has demonstrated benefit in early COVID-19 [10].

This case report emphasises that a high degree of clinical suspicion needs to be maintained for common and cryptic sources of superadded infection in patients with COVID-19 receiving corticosteroids or other immunomodulatory therapies. There are currently no national routine screening protocols in place for these patients. Early detection and appropriate antimicrobial administration are vital to reduce patient morbidity and mortality.

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**References**

1. Bengoechea JA, Sa P.J. Klebsiella pneumoniae infection biology: living to counteract host defences. *FEMS Microbiology Reviews* 2019; 43: 123–44.
2. Paczosa MK, Mecsas J. Klebsiella pneumoniae: Going on the Offense with a Strong Defense. *Microbiology and Molecular Biology Reviews: MMBR* 2016; 80: 629–61.
3. Ku Y-H, Chuang Y-C, Chen C-C, et al. Klebsiella pneumoniae Isolates from Meningitis: epidemiology, *Virulence and Antibiotic Resistance. Scientific Reports* 2017; 7: 6634.
4. Public Health England. Klebsiella species (Klebsiella spp.) bacteraemia: financial year counts and rates by acute trust and CCG, up to financial year 2020 to 2021, 2021. https://www.gov.uk/government/statistics/klebsiella-species-bacteraemia-annual-data (accessed 04/10/2021).
5. Alquisiras-Burgos I, Peralta-Arrieta I, Alonso-Palomares LA, Zacapala-Gómez AE, Salmerón-Bárcenas EG, Aguilera P. Neurological complications associated with the blood-brain barrier damage induced by the inflammatory response during SARS-CoV-2 infection. *Molecular Neurobiology* 2021; 58: 520–35.
6. Cano EJ, Fonseca Fuentes X, Corsini Campioli C, et al. Impact of corticosteroids in coronavirus disease 2019 outcomes: systematic review and meta-analysis. *Chest* 2021; 159: 1019–40.
7. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nature Reviews. Immunology* 2020; 20: 363–74.
8. The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients With COVID-19: a meta-analysis. *Journal of the American Medical Association* 2020; 324: 1330–41.
9. National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing COVID-19. 2021. https://www.nice.org.uk/guidance/NG191 (accessed 04/10/2021).
10. Ramakrishnan S, Niculau DV, Langford B, et al. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial. *Lancet Respiratory Medicine* 2021; 9: 763–72.