Case report

An unusual presentation of *Legionella* pneumonia in a returning traveller

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Accepted 19 July 2019

To cite: Shorten RJ, Norman J, Sweeney LC. *BMJ Case Rep* 2019;**12**:e230130. doi:10.1136/bcr-2019-230130

ABSTRACT

A male patient in his mid-60s presented with a severe pneumonia following return to the UK after travel to Crete. He was diagnosed with Legionnaire's disease (caused by an uncommon serogroup of *Legionella pneumophila*). He was pancytopenic on admission, and during a long stay on critical care he was diagnosed with a disseminated *Aspergillus* infection. Bone marrow aspiration revealed an underlying hairy cell leukaemia that undoubtedly contributed to his acute presentation and subsequent invasive fungal infection.

BACKGROUND

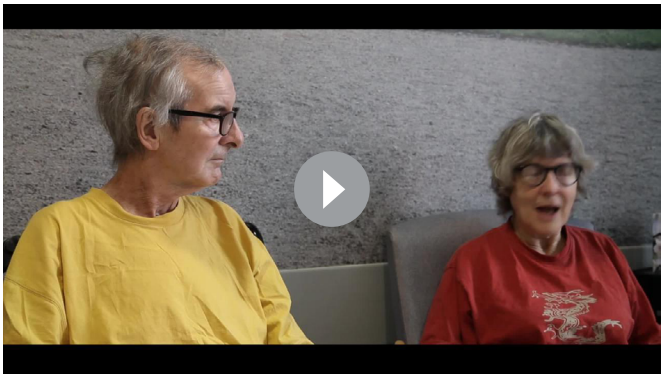
The strain of *Legionella* in the patient was not detected by the routine laboratory method—presence of urinary antigen for serogroup 1 as it was an uncommon serogroup. Treating empirically while requesting further diagnostic samples should be considered when there is strong clinical and epidemiological evidence. Failure to respond to appropriate antimicrobial agents and prolonged neutropaenia led to investigation for a fungal infection. Positive biomarker and culture results prompted the initiation of empirical antifungals. Prolonged pancytopenia, and neutropaenia in particular, should be investigated thoroughly and not attributed to sepsis alone as other underlying causes may be present.

CASE PRESENTATION

A previously fit and well man in his mid-60s returned to the UK after a week's holiday in Crete. His medical history was unremarkable but reported a 25 pack year smoking history. First symptoms were recorded by the patient 8 days after returning, initially with decreased exercise tolerance and shortness of breath. He developed fever and a non-productive cough 3 days later. The patient presented to the emergency department septic 16 days after his return to the UK. Paramedic review observed: temperature 39.8°C, heart rate 131 beats/min, blood pressure 80/50 mm Hg, respiratory rate 36 breaths/min with oxygen saturation of 82% on room air, GCS 15. Blood taken in the emergency department showed the following: C reactive protein (CRP) 431 mg/L, total protein 53 g/L, albumin 17 g/L, bilirubin 22 µmol/L, urea 10.9 mmol/L, creatinine 143 µmol/L, sodium 133 mmol/L, potassium 3.9 mmol/L, white blood cell 1.7×10^9/L, neutrophils 0.58×10^9/L, red blood cell 3.49×10^{12}/L, haemoglobin 116 g/L, platelets 123×10^9/L, lactate 2.0 mmol/L, pH 7.48. Anisocytosis, poikilocytosis and hypochromia were observed. Neutrophils showed toxic granulation. Platelet anisocytosis and some large platelets were present. His blood pressure improved to 124/81 mm Hg with intravenous fluid resuscitation but he required 60% supplemental oxygen via Venturi mask to maintain saturations of 94%. He was admitted directly to intensive care unit (ICU) due to severe sepsis with hypotension requiring intravenous fluid support and monitoring, an acute kidney injury, neutropaenia and for ventilatory support. Chest radiograph showed extensive consolidation throughout the left lung consistent with pneumonia. Appropriate diagnostic samples were taken and the patient was initiated on meropenem and clarithromycin for a severe community acquired pneumonia on the background of an unclear penicillin allergy.

Sputum viral and mycoplasma nucleic acid amplification tests (NAATs) were negative as were pneumococcal and *Legionella* urinary antigens. Sputum cultures were ongoing. Blood cultures became positive and Gram stain demonstrated Gram-positive cocci resembling streptococci. The kidney injury of the patient was resolved but he required intubation. Linezolid was added to provide additional cover for a potential penicillin-resistant pneumococcus with good lung penetration. The organism in the blood culture was subsequently identified as *Streptococcus oralis* and thought not to be significant. The patient remained septic; he had increasing norepinephrine requirements and procalcitonin (PCT) remained >100 µg/L. Ciprofloxacin was added empirically for additional anti-*Legionella* activity.

An in-house NAAT to detect *Legionella pneumophilia* was performed on sputum. This duplex assay detects the *mip* and *wzm* genes. The assay detected *mip* but not *wzm* indicating that a non-serogroup 1 *L. pneumophila* species was present. The local Public Health England (PHE) Health Protection Team was notified of a suspected case of *Legionella* pneumonia. The patient began to improve with falling CRP and PCT, and reduced norepinephrine and oxygen requirements. Peripheral blood neutrophil count of the patient remained between 0.5 and 1.8×10^9/L. Linezolid was stopped and the patient continued on meropenem, clarithromycin and ciprofloxacin for a further 3 days when meropenem was discontinued. *L. pneumophila* was subsequently isolated from bacterial culture of sputum and was referred for further analysis at the PHE Respiratory and Vaccine Preventable Bacteria Reference Unit (RVPBRU).



Video 1 The patient and his partner were recorded discussing their experience.

Learning points

- An uncommon serogroup of *Legionella pneumophila* was detected (ST-728, serogroup 6). All diagnostic tests have limitations and the urinary antigen tests used in the UK only detect the most commonly seen serogroup 1. Consider other assays when there is strong clinical suspicion.
- Failure to respond to appropriate antimicrobial agents in an immunocompromised patient should lead to further assessment and investigations.
- Prolonged neutropaenia in sepsis should be questioned and other causes investigated.
- Is there a role for antifungal prophylaxis in such patients?

One week later the patient remained feverish, and CT imaging showed a white out of the entire left lung with some areas demonstrating tree in bud characteristics. Serum samples showed beta-D-glucan levels of >500 pg/mL (cut-off 80) and galactomannan index of 2.319 (cut-off 0.5). Repeat samples were taken, and due to hepatic dysfunction first seen 1 week after admission (alanine transaminase 132 IU/L, alkaline phosphatase 376 U/L, bilirubin 70 µmol/L) liposomal amphotericin B, rather than an azole, was initiated alongside meropenem for broad spectrum antibacterial cover. The patient remained critically unwell on meropenem and liposomal amphotericin B. Treatment for the *Legionella* infection had been optimised to ciprofloxacin and azithromycin in line with European guidelines.[1] The patient experienced a sigmoid perforation 9 days later and underwent an emergency laparotomy and Hartman's procedure. Intraoperative peritoneal fluid cultured *Aspergillus fumigatus*. This fungus was isolated again from peritoneal fluid over 2 weeks after the procedure as well as twice from respiratory samples (sputum and bronchoalveolar lavage). Voriconazole was added after the first isolation of this pathogen as his liver function had improved and as this is considered the treatment of choice for invasive aspergillosis infections (in leukaemia and haematopoietic stem cell transplant patients).[2] Liposomal amphotericin B was discontinued once therapeutic voriconazole levels were achieved.

The patient was intermittently neutropaenic which responded to granulocyte-colony stimulating factor_(GCSF). It was also noted that he was monocytopenic and a bone marrow aspirate and trephine was performed. The trephine biopsy demonstrated classical hairy cell leukaemia (HCL) with a BRAF V600E mutation present. His marrow showed an infiltration of 60% HCL. There was no nodal disease or splenomegaly.

The recommended first line therapy for HCL is a purine analogue (cladribine or pentostatin); however, due to the myelosuppression associated with this therapy it was felt that this may reduce his chance of recovery from his invasive fungal infection. Therefore, he was given four doses weekly of rituximab monotherapy with the aim of improving his neutropaenia. He tolerated the treatment well and his blood counts responded. Due to his unusual presentation, and prolonged disease course and admission, he agreed to be recorded, along with his partner, for a Patient Experience interview (video 1).

OUTCOME AND FOLLOW-UP

We are following the patient in haematology clinic and if his blood counts fall with progressive HCL we will commence cladribine in the context of his ongoing recovery from *A. fumigatus* infection.

DISCUSSION

Our patient presented with a severe case of Legionnaire's disease caused by an uncommon serogroup (serogroup 6) of *L. pneumophila*.[3] The sequence type (ST728) is very rare and was not recorded in the UK prior to 2017. Investigations into the source of the infection in Crete were not performed but genotyping data coordinated by the European Centre for Disease Prevention and Control showed no linked cases (Chalker, personal communication 2018). Empirical treatment was initiated and then refined when the diagnosis was confirmed by a less frequently used diagnostic assay. While leucopenia is commonly seen in *Legionella* pneumonia,[4 5] sepsis[6 7] and pneumonia,[8] it was prolonged in our patient despite appropriate antimicrobial treatment. Legionnaire's disease has been described in immunocompromised patients, including patients with HCL.[9 10] Cases have been reported of uncommon *Legionella* species in patients already diagnosed with HCL.[11 12] Neutropaenia may increase the risk of severe legionellosis as demonstrated in a murine model.[13]

Prolonged leucopenia was initially attributed to ongoing sepsis or as potentially drug induced (the antimicrobials, particularly beta-lactams, having prolonged the leucopenia caused by sepsis). Initial peripheral blood films to investigate the ongoing leucopenia showed no indication of underlying haematological malignancy. Invasive fungal infection is well recognised in prolonged neutropaenia.[2] His failure to respond clinically, coupled with prolonged pancytopenia, led to appropriate investigations including imaging, biomarkers and fungal culture. Furthermore, invasive aspergillosis has been reported concomitantly or following *Legionella* infection.[14 15]

Given the prolonged neutropaenia in this patient, the use of antifungal prophylaxis may have been appropriate. There are clear guidelines in place for patients deemed to be at high risk of invasive fungal infection, more often patients with known leukaemia or haematopoietic stem cell transplant. It is not uncommon to see patients, who are neutropenic, particularly in critical care, often as a result of sepsis, the duration of which may be variable. These patients would fall outside of these guidelines, however.[2]

Acknowledgements Dr Vicky Chalker, Head of the Public Health England respiratory and vaccine preventable bacteria reference unit (RVPBRU). Colleagues in the intensive care unit (ICU) of Central Manchester Foundation Trust.

Contributors RJS, JN and LCS were involved in the diagnosis and management of the patient and have contributed to writing the manuscript. JN is currently caring for the patient.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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