



Septic shock due to co-infection with *Legionella pneumophila* and *Saprochaete clavata*



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ABSTRACT

Septic shock is the most dreaded presentation of an infection, carrying a reserved prognosis. Appropriate antimicrobial therapy is therefore the mainstay of treatment, alongside organ support as needed. Legionnaires' disease is mainly due to *Legionella pneumophila* serogroup 1 but it can be caused by other serogroups and species not detected by the urinary antigen test. Anti-tumour necrosis factor α therapy may increase the risk of invasive fungal infection, which carry a poor prognosis. We present a challenging case of a septic shock due to *Legionella pneumophila* and *Saprochaete clavata* infections, with a review of the two infections presented.

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Introduction

Septic shock is the most dreaded presentation of infection, carrying a high risk of mortality. Initiation of appropriate antimicrobial therapy is therefore one of the most important mainstays of management, alongside organ support as needed. We present a challenging case of a septic shock due to *Legionella pneumophila* and *Saprochaete clavata* infections, with a review of the two infections presented.

Clinical case

A 43-year-old woman with Chron's disease, on treatment with infliximab and azathioprine, presented in another hospital with complaints of fever and thoracic pain in the middle of July 2020. Physical examination and blood analysis were unremarkable besides elevated inflammatory parameters and nasopharyngeal swab for SARS-CoV-2 was negative. She was diagnosed with bilateral

community-acquired pneumonia (CAP) after performing a chest radiograph (Fig. 1) and discharged medicated with cefuroxime.

Three days later she returned with the same symptoms. Again, she did not present any organ dysfunction. *Streptococcus pneumoniae* and *Legionella pneumophila* (Lp) urinary antigen tests (UAT), as well as a nasopharyngeal swab for SARS-CoV-2, were negative. Blood and sputum samples were collected for bacteriology and she was admitted to the hospital for piperacillin-tazobactam treatment.

On the third day of hospitalization, she developed acute rapidly progressive respiratory failure and was admitted to the intensive care unit (ICU), requiring invasive mechanical ventilation. Her cardiac function was normal, there were no signs of pulmonary embolism but there was significant consolidation of both lungs on thoracic computed tomography (Fig. 2). The suspicion of organizing pneumonia was raised, either of infectious origin or associated with Crohn's disease or infliximab, so vancomycin and methylprednisolone were initiated.

She continued to deteriorate, developing mixed acidaemia and refractory hypoxemia, despite all ventilatory adjustments and prone positioning. She was rescued using extracorporeal membrane oxygenation (ECMO) and transferred to our Infectious Diseases ICU two days after intensive care admission. All blood and sputum collected for bacteriology were negative in the former hospital.

We proceeded with the etiological investigation, collecting blood, bronchial (BL) and bronchoalveolar lavage (BAL) and urine for

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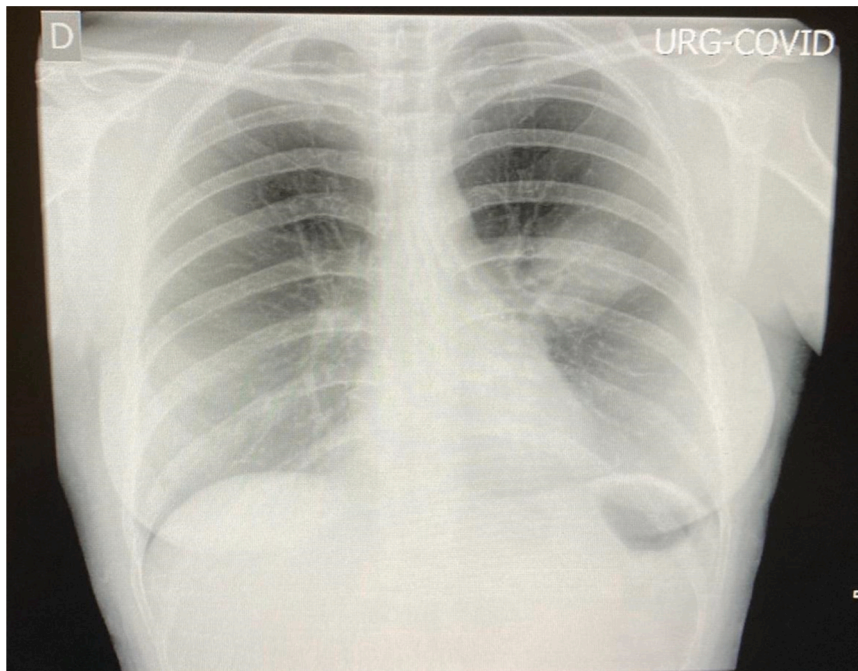


Fig. 1. Chest radiography on the day of presentation to the emergency room (day 0).

bacterial, mycobacterial, fungal, and viral studies (either by cultural or molecular biology techniques, such as nucleic acid amplification test in BAL and BL for *Streptococcus pneumoniae*, *Legionella pneumophila*, *Nocardia* spp. and *Chlamydomphila pneumoniae*) and immunochemistry (Table 1).

Treatment was changed to meropenem, vancomycin and liposomal amphotericin.

She developed cardiovascular failure with hypoperfusion, hypotension, anasarca and hyperlacticaemia, anuric acute kidney injury, liver failure and worsening pancytopenia, requiring multiple blood transfusions, vasopressor therapy, continuous renal replacement therapy, sodium bicarbonate and albumin supplementation and plasmapheresis. A yeast was found to be growing in one mycological blood bottle at the end of the third day and was identified as *Saprochaete clavata* by MALDI-TOF technology the next day. The same fungus was again isolated in more blood bottles despite ongoing antifungal treatment and central venous catheter exchange.

Despite all efforts, the patient died on the morning of the fifth day in our ICU. Posthumously, the positivity of non-Lp serogroup 1 polymerase chain reaction (PCR) in bronchoalveolar lavage collected at our ICU was known.

Legionnaires' disease

Legionnaires' disease refers to pneumonia caused by the bacteria of the genus *Legionella*. It accounts for 2–9% of cases of CAP [1], with Lp serogroup 1 (Lp1) being responsible for about 85% of cases [2].

There are no pathognomonic clinical, radiological or analytical features. Its clinical manifestations resemble (though usually more severe) those of atypical pneumonia by *Chlamydomphila pneumoniae*, *Chlamydomphila psittacia* and *Mycoplasma pneumoniae*, with a mild cough only slightly productive [3]. Sometimes there is a prodromal illness with unspecific symptoms, and gastrointestinal symptoms and neurological manifestations are also common and should raise the possibility of this diagnosis [1]. Laboratory findings include hyponatremia and elevated inflammatory parameters, and it can present in chest imaging with uni to bilateral changes such as infiltrates, consolidations, cavitations or pleural effusion [1,3].

The preferred diagnostic tests are the culture of respiratory secretions on selective media (buffered charcoal yeast extract), the UAT and PCR in respiratory samples [4]. Although cultural exams have high specificity and allow the detection of all species and serogroups, it is a complex technique and it takes more than 5 days for the bacteria to grow [1,4]. UAT has high sensitivity (70–100%) and specificity (95–100%), is quick and inexpensive. However, it is only reliable only for Lp1. The antigen is detectable 3 days after the onset of clinical disease and disappears over 2 months and it is not affected by antibiotic administration [4]. PCR, like culture, allows for the identification of species and serogroups other than Lp1 and has a sensitivity and sensibility > 95%. However, assays vary by laboratory and are not available in all medical centers [4].

Because *Legionella* is an intracellular pathogen, antibiotics such as fluoroquinolones and especially macrolides, that attain high intracellular concentrations, are the most effective [3,5]. Beta-lactams are ineffective due to the production of beta-lactamase [6].

Saprochaete clavata

Saprochaete clavata, formerly known as *Geotrichum clavatum*, is a ubiquitous, filamentous, yeast-like fungi, found worldwide in soil, water, air, wood, animals and dairy products [7]. Its transmission is poorly understood. The possibility of fungal transmission through contaminated medical devices or with dairy products has been suspected but not proven [8]. It has also been considered a commensal fungus especially of Mediterranean people, with the main sources being the respiratory tract, followed by the urogenital and gastrointestinal tract [9].

It has been recognized as an emerging pathogen, mostly in patients with haematological malignancies. Several risk factors have been described and resemble those of invasive fungal infection, the most common being haematological malignancy, prolonged neutropenia, high-dose corticosteroid therapy, cytarabine-based chemotherapy, broad-spectrum antibiotic therapy, previous gastrointestinal colonization and presence of central venous catheters [7, 8, 10].

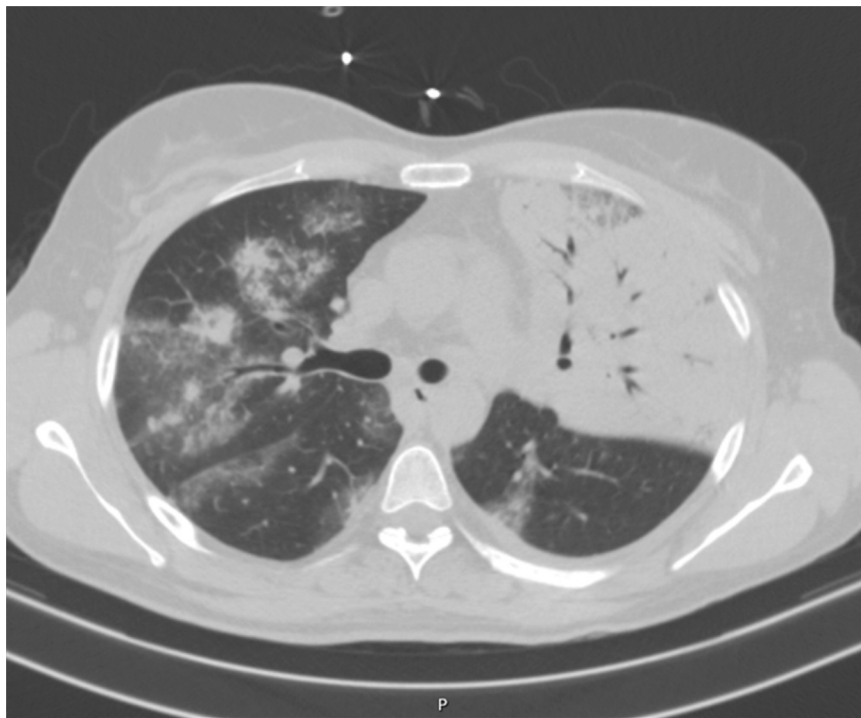


Fig. 2. Tomography scan showing consolidation of the left lung and ground glass areas on the right lung (day 5).

Table 1
Evolution of analytical parameters and organ support techniques.

	Emergency room	Hospital admission	ICU admission	ICU transfer	Infectious Diseases ICU			
Day of hospital presentation	0	3	5	7	8	9	10	11
Haemoglobin (g/dL)	13.4	12.9	11.5	12.2	10.9	8.4	6.9	8.4
Platelets (x10³(3) /µL)	256	244	224	165	48	18	<10	36
Leucocytes (/µL)	14500	7500	5900	2800	5170	1380	2060	6090
C-reactive protein (mg/L)	143	305	290	373	544	438	267	94
Lactate dehydrogenase (U/L)	226	244	334	752	1957	Not requested	Not requested	12366
Creatinine kinase (U/L)	98	Not requested	28	42	363	Not requested	Not requested	20658
Creatinine (mg/dL)	0.6	0.6	0.6	0.5	2.33	1.65	1.52	1.19
Urea (mg/dL)	28	21	30	58	110	63	18	11
Activated partial thromboplastin time (s)	28.1	28.6	25.2	38.4	48.7	50.6	77	58.4
Prothrombin time (s)	12.2	12.4	12.3	12.7	12.9	16.2	28	26
Fibrinogen (mg/dL)	720	1020	960	583	609	359	103	79
Aspartate aminotransferase (U/L)	15	20	28	55	159	1474	5216	10183
Alanine aminotransferase (U/L)	11	14	10	11	20	209	545	652
Alkaline phosphatase (U/L)	50	Not requested	42	42	34	30	35	128
Gamma glutamyl transferase (U/L)	9.6	Not requested	10	9.8	44	308	56	85
Total bilirubin (mg/dL)	0.5	Not requested	0.3	0.3	2.05	5.15	9.64	11.7
Ammonia (µg/L)	Not requested						1137	549

Abbreviations: ICU, Intensive Care Unit

After breaching host defences, the fungus can disseminate via the bloodstream and cause multiorgan disease such as pneumonia, liver, renal, spleen and brain abscesses and peritonitis, with evolution to multiorgan dysfunction and mortality rates up to 80% [9]. Disseminated infection initially presents with nonspecific symptoms such as fever, followed by signs and symptoms reflecting specific organ diseases such as diarrhoea and respiratory symptoms [9]. Its virulence mechanisms are poorly understood, but biofilm production may have a role due to the relationship between the presence of central venous catheter and disseminated disease [9].

The diagnosis is based on the positivity of blood cultures. Since antigens of *S. clavata* may cross-react with the *Aspergillus* galactomannan assay and beta-1–3-D-glucan can be detected in vitro in

culture supernatants, detection of these biomarkers can be helpful but there are no diagnostic criteria [10].

There are no antifungal breakpoint cut-offs defined by the Clinical and Laboratory Standards Institute (CLSI) or The European Committee on Antimicrobial Susceptibility Testing (EUCAST). There are no guidelines either regarding the treatment of *Saprochaete* spp. infections. In fact, in the European Society of Clinical Microbiology and Infectious Diseases and the European Confederation of Medical Mycology joint clinical guidelines for the diagnosis and management of rare invasive yeast infections of 2014 [11], there is just a brief mention to these microorganisms without actually any reference to its management. In the update of 2020, these fungi are not even mentioned [12]. *S. clavata* is intrinsically resistant to echinocandins.

Voriconazole, itraconazole, posaconazole, amphotericin B and 5-fluorocytosine appear to be the most effective drugs, and the combination of liposomal amphotericin B and voriconazole was used in some cases with good outcomes [10].

Discussion

From the beginning, an infectious aetiology was the main diagnostic hypothesis and the patient was kept under broad antimicrobial treatment.

However, all the prescribed antibiotics lacked activity against *Lp*, whose diagnosis went unnoticed based on the negative UAT and the rapid pace of deterioration in need of specific care. In fact, we wrongly ruled out legionellosis after the negative UAT and we were more concerned about resistant bacteria. Clinicians should be aware of the limitations of the *Legionella* UAT (it can miss a third of patients with a positive PCR from respiratory specimens [13]) and consider using PCR on respiratory tract specimens in patients with atypical pneumonia and negative UAT. Also, in severe CAP there should always be empirical coverage for atypical bacteria with a macrolide, a quinolone or a tetracycline since a delay in appropriate treatment can worsen the prognosis.

The antifungal therapy was initiated based on the anti-TNF- α therapy history of the patient, the previous use of corticosteroids and broad-spectrum antibiotics and the severe multiorgan dysfunction. Infliximab may cause neutropenia, a known risk factor for invasive fungal infections (though this particular patient did not present it), and impairs the formation and activity of granulomas, which may explain the occurrence of some case reports of invasive fungal infections in anti-TNF- α treated patients [14]. Corticosteroids affect almost every cell type involved in the immune and inflammatory responses, therefore being a major risk factor for any kind of infection, especially with its prolonged use [15]. Increased fungal growth is a common side effect of antibiotic therapy and the intestinal barrier dysfunction and microbial translocation seen in sepsis also increase the risk of fungal infections.

When yeasts were found to be growing in blood cultures, we thought *Candida* spp. was going to be isolated since candidemia is among the most common cause of healthcare-associated bloodstream infections [16]. This was the first case of *S. clavata* infection diagnosed in our hospital. Since there were no more infections diagnosed in both hospitals, a nosocomial source seems unlikely. Possibly, the patient was already colonized by *S. clavata*, which became an opportunist pathogenic (the persistence in blood cultures makes it more likely to be an infective than a contamination) due to the critical condition of the patient.

Despite all the organ support techniques, we failed to treat properly the underlying causes, leading to the fatal outcome of the patient.

Conclusion

Septic shock is a medical emergency and a delay in the administration of appropriate antimicrobials is associated with a significant increase in mortality. Empirical treatment must be promptly started and broad enough to cover all most probable pathogens. Therefore, treatment of severe CAP should always consider atypical agents, and in immunocompromised patients with an uncontrolled infection of unknown cause fungal aetiology should also be considered. Clinicians must be aware of the limitations of the diagnostic methods and do not let themselves be misguided by them.

CRedit authorship contribution statement

João Paulo Caldas: Writing – original draft, Writing – review & editing, Conceptualization, Project administration. **André Silva-**

Pinto: Writing – review & editing, Conceptualization, Project administration. **Ana Sofia Faustino:** investigation. **Paulo Figueiredo:** Investigation. **António Sarmento:** Investigation. **Lurdes Santos:** Writing – review & editing, Supervision.

Author Agreement Statement

All authors declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We understand that the Corresponding Author is the sole contact for the Editorial process. He is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

Conflicts of Interest

none.

Patient Consent Statement

consent was given by the patient's family. The design of the work was approved by the local ethics committee of Centro Hospitalar Universitário de São João, Oporto, Portugal.

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