Severe Pulmonary Involvement in Leptospirosis
Alternate antibiotics and systemic steroids

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Abstract:
Leptospirosis usually presents as a non-specific anicteric myalgic febrile illness, a benign aseptic meningitis syndrome, or an icteric form with severe manifestations. Pulmonary complications are common (20–70%). When a patient from a non-endemic area presents with pulmonary involvement without the classical symptoms, leptospirosis is not often suspected. We present a patient with severe lung involvement who responded to antibiotics other than penicillin or doxycycline, parenteral methyl prednisone and ventilatory support but needed oral prednisolone for 3 months to achieve a complete recovery.

Keywords: Leptospirosis; Human ARDS; Steroids; Case report; Oman.

Case Report
A 13-year-old female presented to her regional hospital in Oman with a two-day history of fever, dry cough, and shortness of breath. She had been unwell for a week and had visited private clinics. On examination, the patient was febrile (39°C), tachypnoeic, and tachycardic. Blood pressure was normal. The chest was clear on auscultation. Liver and spleen were not enlarged but a few small cervical lymph nodes were palpable. A complete blood count, erythrocyte sedimentation rate and renal function were normal. Liver enzymes were slightly raised. A chest radiograph showed bilateral symmetrical patchy opacities uniformly distributed in the middle and lower zones with a peripheral distribution. Blood, urine, and sputum cultures did not grow any organisms. An autoimmune work-up and screening for H1N1 were both negative. Bone marrow and lymph node biopsies were inconclusive. A skin biopsy showed features of urticarial vasculitis. Since she did not respond to antibiotics, a diagnosis of miliary tuberculosis (TB) was entertained. As her liver functions were deranged she was started...
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on a modified anti-TB regimen with moxifloxacin, streptomycin, and ethambutol.

The patient started to desaturate so was intubated and ventilated. A computed tomography (CT) scan of the chest revealed bilateral symmetrical interstitial infiltrates distributed predominantly in the middle and lower zones. A bronchoscopy did not reveal any abnormalities and the bronchoalveolar lavage (BAL) grew *Klebsiella pneumoniae*, for which meropenem was added. Sputum and BAL were negative for acid fast bacilli. Her haemoglobin and platelets came down, liver enzymes showed a significant rise, and the renal function started to decline.

The patient was then transferred 1,000 Km from the regional hospital to Sultan Qaboos University Hospital, Muscat, a tertiary centre. Basic investigations showed a haemoglobin level of 8.5 g/dl, white blood count of 9.2 x 10^9/L, and a platelet count of 68 x 10^9/L. Liver function was deranged with a serum alanine aminotransferase of 650 IU/L, a serum aspartate aminotransferase of 241 IU/L, and an alkaline phosphatase of 275 IU/L; bilirubin was 22 umol/L. The renal functions and c-reactive protein were normal. Repeated antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, and anti-glomerular basement membrane antibodies were all negative. Complements C3 (0.49) and C4 (0.08) were low. An echocardiogram was reported as normal. A chest radiograph showed bilateral diffuse infiltrates [Figure 1A]. The CT of the chest revealed bilateral symmetrical patchy opacities with micronodularity and intralobular and centrilobular septal thickening [Figure 1B].

Seronegative lupus with pulmonary involvement, unexplained vasculitis, acute interstitial pneumonia, eosinophilic pneumonia, drug-induced lung disease, *Pneumocystis carinii* infection, and viral pneumonia were the immediate differential diagnoses. She was pulsed with 250 mg of

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**Figure 1 A–D:** (A) Chest radiograph on admission to our centre showing bilateral uniform opacities with a peripheral distribution; (B) Computed tomography (CT) image showing bilateral symmetrical opacities with interlobular and centrilobular septal thickening and micronodularities; (C) CT scan during follow-up one month after discharge showing persistent interstitial shadows; (D) CT scan showing total resolution of the opacities but with minimal localised interstitial shadows on the right side.
methylprednisolone once daily for 3 days followed by oral prednisolone. Anti-TB medications were stopped but meropenam and moxifloxacin were continued. An open lung biopsy was planned, but because of a further drop in platelets this was deferred. The patient was extubated on the second day of pulsed steroids and was then supported with non-invasive ventilation (NIV). Slowly the oxygen requirement came down and she was weaned from NIV.

This improvement was not sustained. Her chest radiograph showed an increase in the opacities, she became more dyspnoeic, and her platelets and haemoglobin dropped to 4 x 10^9/L and 7 g/dl, respectively. The NIV was resumed and the prednisolone treatment was changed back to methylprednisolone (100 mg daily). The girl's mother then told of a family picnic to the mountains a few days prior to the onset of her symptoms, stating that other members of the family had developed a rash and a transient febrile illness. This prompted us to do a work-up for a cryptic infection. In addition to the samples sent for Legionella, Mycoplasma pneumoniae, Pneumocystis carinii and human immunodeficiency virus (HIV) earlier, further samples were collected for Leptospira, cytomegalovirus, malarial parasite, Rickettsia, and haemorrhagic fevers.

Fortunately, in the next 5 days the patient showed definite signs of improvement and was transferred to the general medical ward on 3 L of oxygen. Almost 6 weeks after the onset of symptoms, the serology for leptospirosis was reported positive by enzyme immunoassay for genus-specific IgM human antibodies against Leptospira (SERION ELISA classic Leptospira, Institut Virion Serion GmbH, Würzburg, Germany) from the public health laboratory. Since a microscopic agglutination test was not available, detection of IgM antibodies was taken as evidence of recent infection with Leptospira in this clinical context. Following the report, she was started on doxycycline. When discharged after 3 weeks, she was weak and had residual pulmonary infiltrates, but was saturating well on room air and could move with support. Because of the persistent pulmonary infiltrates, prednisolone was continued.

When seen in the outpatient clinic one month later, the patient’s chest was clear on auscultation, her SaO2 on room air was 99%, her laboratory investigations were back to normal, and her chest radiograph showed total resolution. Still, the CT scan showed residual linear opacities [Figure 1C] so the prednisolone was continued. A CT chest done after 3 months was normal with total resolution of the opacities [Figure 1D]. At that point, the prednisolone was discontinued.

Discussion

The first publication of lung involvement in leptospirosis is attributed to Moeschlin in 1943.1 The spectrum of pulmonary manifestations is wide, ranging from mild respiratory symptoms to the presence of acute respiratory distress syndrome (ARDS). Cough, haemoptysis, and different grades of dyspnoea are the most common pulmonary symptoms. Chest radiographs usually show bilateral lower lobe involvement with a peripheral distribution. Nodular or reticulo-nodular infiltrations, consolidations, and a ground glass appearance are the most common patterns seen.4 High-resolution CT will show bilateral ground glass opacities involving all lobes, areas of consolidations, peripheral airspace nodules, and, rarely, pleural effusions.5,6 Leptospirosis is not common in Oman and this is the first report of an Omani national contracting the disease without travelling abroad to endemic areas. Due to this, the diagnosis was not suspected in our patient on presentation.

Alveolar haemorrhage and ARDS are two of the most fatal conditions associated with leptospirosis.1,6,8 Pulmonary oedema secondary to myocarditis, renal failure, or over-rehydration during resuscitation have also been reported.1 In the most severe pulmonary form of leptospirosis, where mortality rates can be as high as 30–60%, respiratory symptoms usually appear between the 4th and 6th day of disease and may lead to death in less than 72 hours.8,9 Although the pathogenesis of pulmonary manifestations is poorly understood, vasculitis mediated by toxins and an exaggerated immune response in the host are believed to be responsible.1,6,9 Capillary endothelial damage leads to different grades of interstitial and alveolar haemorrhage. Since the BAL findings were not consistent with alveolar haemorrhage, we presume that our patient developed acute lung injury (ALI) and then ARDS, possibly with an underlying haemorrhagic pneumonitis.
For leptospirosis, the antibiotics treatment has to be started early, and supportive care with correction of dehydration, hypovolaemia, hypotension, and electrolyte abnormalities is essential. Prompt management of renal and hepatic dysfunction and acute respiratory failure may decrease the mortality rate. Human leptospirosis is generally treated with penicillin or doxycycline, but these antibiotics are not used initially if the diagnosis is not suspected. Interestingly, a recent review showed that the benefit of antibiotic therapy in the treatment of leptospirosis, particularly for severe disease, remains unclear and the choice of penicillin, doxycycline, or cephalosporin did not affect mortality rates nor the duration of fever. As often happens with severe pulmonary involvement due to any disease, broader-spectrum antibiotics were started along with assisted ventilation and supportive care while tests were being run. Our patient received meropenem and moxifloxacin which helped tide her over the crisis, thus proving that these antibiotics are active against the species. As for the laboratory proof, Hospenthal and Murray, while studying the susceptibilities of 11 serovars of *Leptospira* to 14 antibiotics, found that with the exception of chloramphenicol, all tested agents, including moxifloxacin, were found to be at least as potent as penicillin and doxycycline.

Although benefits of corticosteroids in ALI is known, evidence for use of corticosteroids in pulmonary leptospirosis is confined to occasional case reports or small studies. High doses or a pulse of dexamethasone or methylprednisolone have been used in patients with severe lung involvement in leptospirosis. In a series of 30 patients, Shenoy et al. demonstrated that corticosteroids reduce mortality and change outcomes significantly. Trivedi et al. found that mortality was higher in patients with pulmonary involvement who did not receive steroids and concluded that high dose glucocorticoids should be given as early as possible after the onset of dyspnoea to all the patients with pulmonary involvement. Our patient received methylprednisolone, which would have influenced the recovery. Not only that, since the radiological lesions persisted, oral steroids were continued leading to a total resolution. This highlights the need to use steroids for a longer time to prevent post-ARDS lung fibrosis.

**Conclusion**

In this case, the administration of broad-spectrum antibiotics, mechanical ventilation, early supportive care, and the administration of corticosteroids led to clinical improvement and complete recovery. The clinical response suggests the utility of meropenem and moxifloxacin against *Leptospira* and underlines the need for the use of corticosteroids in cases of pulmonary involvement.

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