Hemorrhagic pulmonary leptospirosis: three cases from the Yucatan peninsula, Mexico

Leptospirose hemorrágica pulmonar: três casos na península de Yucatán, México

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ABSTRACT

Three leptospirosis cases with lung involvement are reported from the Yucatan Peninsula, Mexico. All three patients were admitted to the intensive care unit due to acute respiratory failure. Treatment with antibiotics resulted in favorable evolution despite the negative prognosis. Leptospirosis should be included in the differential diagnosis of patients with fever and lung involvement.


CASE REPORT

Case 1. This was a 25-year-old male patient who was admitted to hospital with five days of symptomatic evolution, including asthenia, adynamia, general malaise, fever (39°C), conjunctival suffusion, arthralgia, myalgia and suborbital headache. Over the preceding 15 days, the patient had visited forested regions of Yucatan, including caverns and sinkholes.

Thrombocytopenia was detected on admission and required platelet concentrate transfusion. After 48 hours, the patient presented progressive dyspnea and decreased vesicular murmur in the infrascapular regions. Chest x-ray showed bilateral presence of diffuse interstitial micronodular infiltration, predominantly on the lower right side. The patient was examined and admitted to the intensive care unit (ICU) due to severe hypoxemia, requiring mechanical ventilation. There were repeated manifestations of pulmonary hemorrhage (hemoptysis) and hematuria. Multiple platelet concentrate transfusions were required due to continuing thrombocytopenia. Laboratory analyses showed normochromic normocytic anemia, leukocytosis with lymphopenia, elevated transaminases and lactic dehydrogenase, hyperglycemia, hypernatremia and hypokalemia (Table 1). The patient did not present jaundice, azotemia or visceromegaly.

The treatment began with amphotericin B, fluconazole and ceftriaxone. The response was slow and, even after treatment,
anemia, monocytosis, slightly increased transaminases, alkaline phosphatase and C-reactive protein, and increased globular sedimentation (Table 1).

He was admitted to the ICU and was administered an antimicrobial/antifungal regimen with steroids and platelet transfusions. He required an oxygen mask. Febrile peaks continued during the first days and petechiae appeared on his left arm and chest. He presented coughing with hemoptysis and lower left hyperventilation, and respiratory alkalosis and metabolic acidosis with relative hypoxemia. X-rays showed evolution to overflow and bilateral basal consolidation, with the development of leukocytosis with atypical lymphocytes, vacuolated neutrophils and toxic granulation. Bronchoscopy with bronchoalveolar lavage produced data compatible with bilateral alveolar hemorrhage and showed the presence of gram-negative bacilli. Histoplasmosis, dengue, HIV and PTB were ruled out.

Clinical and x-ray image improvements began on day five. He was transferred out of the ICU on day six and was discharged from in-patient care after eleven days, with complete resolution. The diagnosis was established using MAT, which showed antibody titers against *Leptospira interrogans* serotype grippotyphosa (serogroup Grippotyphosa) at 1:100 in paired samples after three days and at 1:1600 eleven days after entering hospital.

### Case 3

This was a 17-year-old female patient from the state of Quintana Roo, Mexico. She had a background of having a dog in her house and swimming in a lagoon before the symptoms appeared. She was admitted after five days of symptomatic evolution characterized by fever, asthenia, adynamia, headache, myalgia, arthralgia, cough, hemoptysis, hyporexia, abdominal pain, nausea, vomiting and a generally acute condition.

Examination showed toxic facies, assisted gait, paleness, signs of clinical dehydration, hypotension and right lower hyperventilation with wheezing at this level. She presented signs of hemorrhagic diathesis (petechiae on face, subconjunctival hemorrhage and transvaginal and intra-abdominal bleeding). Laboratory results indicated anemia, prolonged coagulation time, respiratory alkalosis with hypoxemia, prerenal acute renal failure, albuminuria, hematuria, bacteriuria and leukocyturia. Ultrasound showed sparse free liquid in the abdominal cavity and slight splenomegaly. Chest x-ray (Figure 1) showed reticulonodular interstitial infiltration with a tendency towards left lower consolidation.

She was admitted to the ICU due to acute respiratory failure and prerenal symptoms of renal failure, mixed shock and sepsis. The treatment began with broad-spectrum antimicrobials, steroids, diuretics, crystalloids and vasopressors. She required transfusion with fresh frozen plasma and a globular package. Mechanical ventilation was implemented, initially with oxygen mask and CPAP, and later with orotracheal intubation. Multiple diagnostic investigations were made: dengue, *Plasmodium*, *Legionella*, *Rickettsia*, Torch profile, febrile reactions and autoimmune disease were ruled out.

Her serological tests using MAT were progressively positive for *Leptospira interrogans* serotype canicola (serogroup Canicola) in three serial samples with titers of 1:400 (two days...
**DISCUSSION**

The three cases above had similar clinical manifestations and largely coincide with the characteristics of predominantly pulmonary leptospirosis cases that have been reported in other countries. The true incidence of lung involvement in leptospirosis is unclear, but it may range from 20% to 70%. As in the present cases, the other reported cases had a background of contact with potentially polluted water and were characterized by hemorrhagic pneumopathy and respiratory failure. The initial symptoms were the same as in other forms of leptospirosis and were very similar to those presented in many tropical febrile diseases: sudden onset of fever, general malaise, myalgia and conjunctival suffusion. Dyspnea, chest pain and coughing with hemoptysis are consistently present in patients with lung involvement. In cases of acute pulmonary leptospirosis these symptoms quickly progress to respiratory failure and can lead to death by asphyxia secondary to intra-alveolar hemorrhage. The above generally occurs before development of the jaundice and renal failure that are characteristic of acute classic leptospirosis.

Possible abnormal laboratory results in leptospirosis cases can include proteinuria; pyuria; microscopic hematuria; increased VSG; decreased, normal or elevated leukocytes; thrombocytopenia; slight to moderate increases in transaminases, hyperbilirubinemia, alkaline phosphatase and LDH; and increases in serum creatinine and amylase. In the specific case of pulmonary leptospirosis, changes to x-ray and gasometric images are the most characteristic sign. Chest x-rays show three patterns characteristic of pneumopathy from leptospirosis: nodular infiltrations; consolidation; and densities with a ground-glass appearance. Resolution of these changes is more rapid than with bacterial pneumonias. Gasometry is compatible with acute pulmonary lesions with respiratory alkalosis, hypoxemia and metabolic acidosis.

Specific diagnosis of the causal agent can be done through direct microscopic observation or culturing, or with serological tests. The former are more useful in the first week of the condition and the latter are more sensitive and specific from the sixth to the tenth day. The microscopic agglutination test (MAT) is the reference method for serologically diagnosing leptospirosis: it is the method most utilized and allows identification of the infecting serotype. To demonstrate acute disease requires a fourfold increase in antibody titer in paired tests. These diagnostic tests are not always available and they require specific time windows to produce results. For this reason, clinical suspicion plays a vital role in early diagnosis and treatment for this disease.

The suggested treatments include steroids, antibiotics, respiratory assistance and platelet transfusions. According to the recommendations, general and support measures should be started during the first two to three days and proper antibiotic therapy (e.g. penicillins, cephalosporins, tetracyclines or macrolides) should be implemented over the days following a confirmed diagnosis.

Once established, the respiratory condition has a rapid and severe course, with mortality rates as high as 50% to 60%. Death usually occurs within 10 to 15 days, although it can occur as quickly as five days in severe cases. The factors contributing towards a negative prognosis include advanced age, malnourishment, concomitant diseases, hemodynamic deterioration, presence of low serum creatinine, volume overload, oliguria, dyspnea,
death rattle, alveolar infiltration, hemoptysis, metabolic acidosis, thrombocytopenia and leukocytosis > 12,900/mm\(^3\)\(^{15}\).

The three case studies presented here all involved patients at high epidemiological risk due to their recreational activities in an endemic area. The most consistent data were: a background of exposure to potentially contaminated water; general symptoms (fever, headache, myalgia and arthralgia); presence of aggregated respiratory symptoms (dyspnea, thoracic pain and coughing with hemoptysis); thrombocytopenia (with or without external hemorrhagic manifestations); and nodular infiltrations in chest x-rays. Severe leptospirosis has traditionally been linked to the presence of jaundice and renal failure, despite reports of leptospirosis with pulmonary hemorrhage from Korea, China and Brazil in which few or no patients developed jaundice\(^{12}\). In the present cases, only one patient presented with jaundice. None of the patients presented the characteristic biphasic form of the disease (Tables 1 and 2). The clinical profile was progressive and the most serious manifestation was alveolar hemorrhage, which led to development of life-threatening respiratory failure. All three patients were admitted to the ICU quickly, in order to establish respiratory and hemodynamic support measures, perform transfusions and institute antimicrobial therapy within the first week after the appearance of symptoms. This early treatment, the patients’ youth and the absence of other concomitant diseases probably contributed to the absence of mortality in this case series, despite multiple factors indicating a negative prognosis.

In tropical and subtropical regions like the Yucatan peninsula, it is important to establish a differential diagnosis, particularly from dengue and other hemorrhagic viral fevers, malaria and atypical pneumonias (tuberculosis, histoplasmosis, etc.) that are also prevalent in southeast Mexico and may be related to recreational activities (visits to forested areas, caverns and sinkholes). In response to these factors, specific tests were done in these three cases to determine the causal agent and rule out other possible agents. A definitive diagnosis for leptospirosis was established, and in two of the patients, the agent was serotype *Grippotyphosa*, which is one of the main causes of pulmonary leptospirosis\(^{6}\).

In conclusion, the polysyndromic nature of leptospirosis often complicates its clinical diagnosis. When added to the scarcity of laboratories specializing in its serological diagnosis, this produces diagnostic underestimation of this disease\(^{14,15}\). Given this, and that leptospirosis is endemic and prevalent on the Yucatan peninsula\(^{13,14,16}\), it is likely that this disease is underrepresented in epidemiological statistics due to confusion with other, equally frequent febrile entities\(^{17}\). There are no previous reports in Mexico showing the lungs as the organ of primary attack. The cases presented here illustrate the importance of considering leptospirosis in differential diagnoses for patients with febrile manifestations associated with pneumonitis and respiratory failure, especially if hemoptysis is present as a sign of pulmonary hemorrhage. The clinical profile of cases and the endemicity of leptospirosis in the region should alert health workers, primary care physicians and ICU services to the possibility of pulmonary leptospirosis, so that it can be included in diagnostic studies and thus enable timely treatment for this potentially fatal disease.

### Table 2 - Comparison of laboratory results in three pulmonary leptospirosis cases.

<table>
<thead>
<tr>
<th>Laboratory Values</th>
<th>Days after hospitalization</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>case 1</td>
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<tr>
<td>Leucocytes/mm(^3)</td>
<td>7.6</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>75.9</td>
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<tr>
<td>Platelets/mm(^3)</td>
<td>46</td>
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<tr>
<td>Total bilirubin (mg/dl)</td>
<td>0.8</td>
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<tr>
<td>AST (U/l)</td>
<td>57.0</td>
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<tr>
<td>ALT (U/l)</td>
<td>79.0</td>
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<tr>
<td>GGT (U/l)</td>
<td>Nd</td>
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<tr>
<td>LDH (U/l)</td>
<td>129</td>
</tr>
</tbody>
</table>

AST: aspartate transaminase, ALT: alanine transaminase, GGT: gamma-glutamyl tranpeptidase, LDH: lactate dehydrogenase, Nd: not determined

### REFERENCES


