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.

Key-words: Leptospirosis. Hemorrhagic pulmonary. Yucatan.

RESUMO

Analisamos três casos de leptospirose com envolvimento pulmonar na Península Yucatán, México. Os três pacientes com seqüelas pulmonares entraram na unidade de cuidados intensivos devido à insuficiência respiratória grave. Todos os casos evoluíram favoravelmente ao tratamento com antibióticos, apesar do prognóstico negativo. Leptospirose deve ser incluída no diagnóstico diferencial de pacientes com febre e comprometimento pulmonar.

Palabras-chaves: Leptospirose. Hemorragia pulmonar. Yucatán.

Leptospirosis is a zoonosis caused by *Leptospira interrogans* spirochetes and is most frequent in tropical and subtropical regions. Human beings contract the disease through direct or indirect contact with the urine of infected animals, which are usually rodents, small marsupials, cattle, pigs and dogs[6 15]. Leptospirosis is endemic to the Yucatan peninsula, Mexico. The human seroprevalence in the region is 14% and is linked to contact with rodents and natural water deposits. The most frequent clinical manifestation is the anicteric form with fever, headache, myalgia, abdominal pain and nausea as the main symptoms[13 14 16 17]. This study is a report on three recent hemorrhagic pulmonary leptospirosis cases diagnosed in the Yucatan peninsula region, Mexico, in 2005 and 2006.

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 (39ºC), 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,

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Recebido para publicação em 17/9/2007
Aceito em 25/07/2008

Table 1 - Comparison of clinical characteristics in the three leptospirosis cases studied.

Characteristics upon	Case 1	Case 2	Case 3
Hospitalization			
fever	Pres	Pres	Pres
headache	Pres	Pres	Pres
myalgia	Pres	Pres	Pres
arthralgia	Pres	Pres	Pres
exanthema	Abs	Abs	Abs
conjunctival suffusion	Pres	Abs	Pres
dyspnea	Abs	Pres	Pres
external hemorrhages	Abs	Pres	Pres
abdominal pain	Abs	Abs	Pres
nausea	Abs	Abs	Pres
vomiting	Abs	Abs	Pres
diarrhea	Abs	Abs	Abs
cough	Pres	Pres	Pres
hemoptysis	Pres	Pres	Pres
jaundice	Abs	Abs	Pres
edema	Abs	Abs	Abs
Clinical profile			
thrombocytopenia	Pres	Pres	Abs
pulmonary hemorrhage	Pres	Pres	Pres
changes on x-ray images	Pres	Pres	Pres
respiratory failure	Pres	Pres	Pres
interstitial nephritis	Abs	Abs	Abs
renal failure	Abs	Abs	Pres
rhabdomyolysis	Abs	Abs	Abs
Interventions			
mechanical ventilation	Pres	Pres	Pres
transfusions	Pres	Pres	Pres

Pres: present, Abs: absent

the pulmonary hemorrhage continued. Autoimmune (lupus), immunodepressive (AIDS, pulmonary tuberculosis) and other infectious diseases (dengue, influenza, histoplasmosis) were ruled out.

A microscopic agglutination test (MAT) was done with 10 *Leptospira interrogans* serotypes that are prevalent in that region. Antibody titers against serotype grippotyphosa (serogroup Grippotyphosa) were detected at 1:1,600 eleven days after admission and 1:12,800 twenty days after admission. Despite the severity of the case, the patient recovered satisfactorily twenty days after admission to hospital.

Case 2. This was a 21-year-old male patient who was admitted to hospital with five days of symptomatic evolution, including fever, headache, arthralgia, myalgia, dyspnea, epistaxis, gum hemorrhage and anxiety crisis. He had a background of having swum repeatedly in sinkholes during the previous month.

He was uncooperative during the initial examination, presenting pale tegument, dyspnea, diaphoresis, fever (39ºC), tachypnea of 38/min, tachycardia of 110/min, no evident external bleeding and no data on pulmonary condensation. Chest x-ray showed bilateral basal micro and macronodular infiltrations with a tendency towards consolidation in the lower left side. Laboratory results showed thrombocytopenia, normochromic microcytic 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* and *Rickettsia*, Torch profile, febrile reactions and autoimmune disease were rules 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

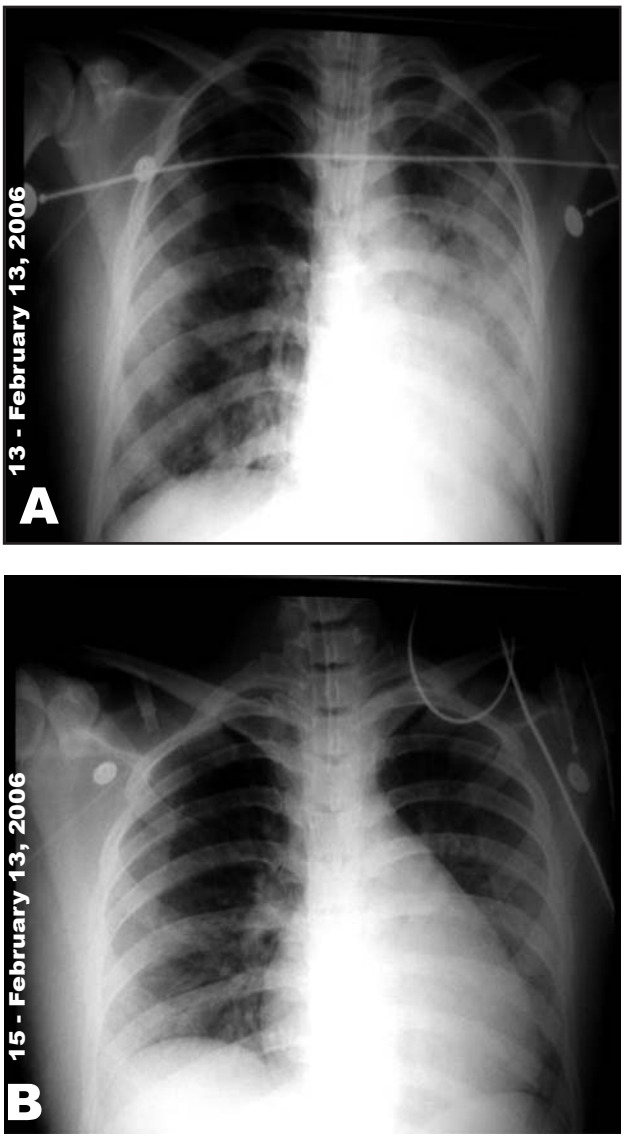

Figure 1 - X-ray images of case 3. A) Reticulonodular interstitial infiltration seen initially, with tendency towards lower left consolidation. B) Partial resolution of pulmonary lesions.

after admission), 1:1,600 (seven days) and 1:6,400 (seventeen days). Despite acute multisystemic pulmonary, renal and hepatic involvement, the patient recovered fully and was discharged seventeen days after hospitalization, including nine days in the ICU and five days with mechanical ventilation. A blood sample from a dog that was analyzed using MAT was seropositive for *Leptospira interrogans* serotype canicola (serogroup Canicola) with a 1:100 titer.

In addition, all three cases presented positive results when their samples were analyzed using an IgM ELISA test.

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[3 8 9 10 12]. The true incidence of lung involvement in leptospirosis is unclear, but it may range from 20% to 70%[2 6 15]. 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[11]. 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[2 6 15]. 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[5 11].

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[5]. 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[4]. Resolution of these changes is more rapid than with bacterial pneumonias[7]. 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[2]. 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[11]. 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[5].

Once established, the respiratory condition has a rapid and severe course, with mortality rates as high as 30% to 60%[9]. Death usually occurs within 10 to 15 days, although it can occur as quickly as five days in severe cases[5]. 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[9].

In conclusion, the polysyndromatic 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[2,6,15]. 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.

	Days after hospitalization								
	case 1			case 2			case 3		
Laboratory Values	1	5	10	1	5	10	1	5	10
Leukocytes/mm^3	7.6	21.5	22.9	6.9	14.5	18.1	8.5	10	11.9
Neutrophils (%)	75.9	85.5	91.9	65.0	82.0	82.0	92.0	85.7	63.0
Platelets/mm^3	46	37	49	12	70	208	228	226	290
Total bilirubin (mg/dl)	0.8	1.1	1.0	1.3	1.2	1.5	0.58	0.6	Nd
AST (U/l)	37.0	155.0	66.0	75.0	29.0	23.0	48.0	75.0	Nd
ALT (U/l)	79.0	160.0	125.0	114.0	53.0	31.0	Nd	54.0	Nd
GGT (U/l)	Nd	Nd	Nd	Nd	Nd	Nd	Nd	64.0	Nd
LDH (U/l)	129	582	577	Nd	Nd	Nd	Nd	385.0	Nd

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

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