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CASE REPORT

Leptospirosis Presenting as Diffuse Alveolar Hemorrhage

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Abstract

Diffuse alveolar hemorrhage (DAH) syndrome has a mortality rate of 30 to 60%. A 15-year-old male patient presented with a seven-day abdominal pain, vomiting, non-dysenteric diarrhea, conjunctival injection, and fever. Chest radiography revealed bilateral interstitial infiltrates predominating in the lower left lobe. The patient's condition worsened within hours, with the development of massive hemoptysis, acute respiratory distress syndrome (ARDS), arterial hypotension, and hematocrit decline requiring mechanical ventilation. A chest computed tomography (CT) showed ground-glass opacities with consolidation areas in lower lobes, diffuse tree-in-bud opacities, and centrilobular nodules. A bronchoscopy was conducted without endoluminal lesions and bronchoalveolar lavage (BAL) consistent with alveolar hemorrhage. DAH was diagnosed, and the patient received therapy with intravenous methylprednisolone. The outcome of treatment was successful after eight days of mechanical ventilation. Leptospirosis was diagnosed by serology after discharge. The laboratory findings were normal, and a chest CT scan showed the resolution of the infiltrates. Early recognition of severe hemorrhagic pulmonary syndrome, which has a high mortality rate, is crucial. Therefore, leptospirosis should be suspected as a differential diagnosis in every patient with alveolar hemorrhage, ARDS manifestations, and epidemiological factors.

Introduction

Diffuse alveolar hemorrhage syndrome (DAH) is characterized by hemoptysis, falling hemoglobin, and diffuse lung infiltrates on chest radiography.[1] There are numerous causes of DAH, including the severe pulmonary form of leptospirosis. The mortality rate of this clinical presentation is 30 to 60%.[2]

Case Presentation

A 15-year-old male patient presented with a seven-day abdominal pain, vomiting, non-dysenteric diarrhea, conjunctival injection, and fever. He had been exposed to a course of water resulting from a flood days before. Physical examination revealed arterial hypotension, which initially responded to volume expansion with crystalloids; epigastric pain; and adequate breathing.

Laboratory tests revealed leukocytosis, anemia, metabolic acidosis, hypochloremia, hyperlactatemia, renal failure, coagulopathy, hypertransaminasemia, and high C-reactive protein. In addition, abdominal ultrasound showed much biliary sludge in the gallbladder, while chest radiography revealed bilateral interstitial infiltrates predominantly in the lower left lobe (**Figure 1**). Severe abdominal sepsis was diagnosed, and treatment with ceftriaxone and metronidazole was initiated.

The patient's condition worsened within hours, with the development of massive hemoptysis, arterial hypotension, and hematocrit decline requiring mechanical ventilation, to severe sepsis from a possible abdominal or pulmonary source. Vancomycin and clarithromycin were added to treatment. The patient's condition progressed to severe (ARDS), requiring salvage therapies such as prone positioning and recruitment maneuvers.

A chest computed tomography (CT) showed ground-glass opacities with consolidation areas in lower lobes, diffuse tree-in-bud opacities, and centrilobular nodules (**Figure 2**). In addition, a bronchoscopy was conducted without endoluminal lesions and sequential lavages consistent with alveolar hemorrhage.

DAH was diagnosed, and the patient received therapy with intravenous pulse methylprednisolone. The laboratory results revealed normal renal function and neg-

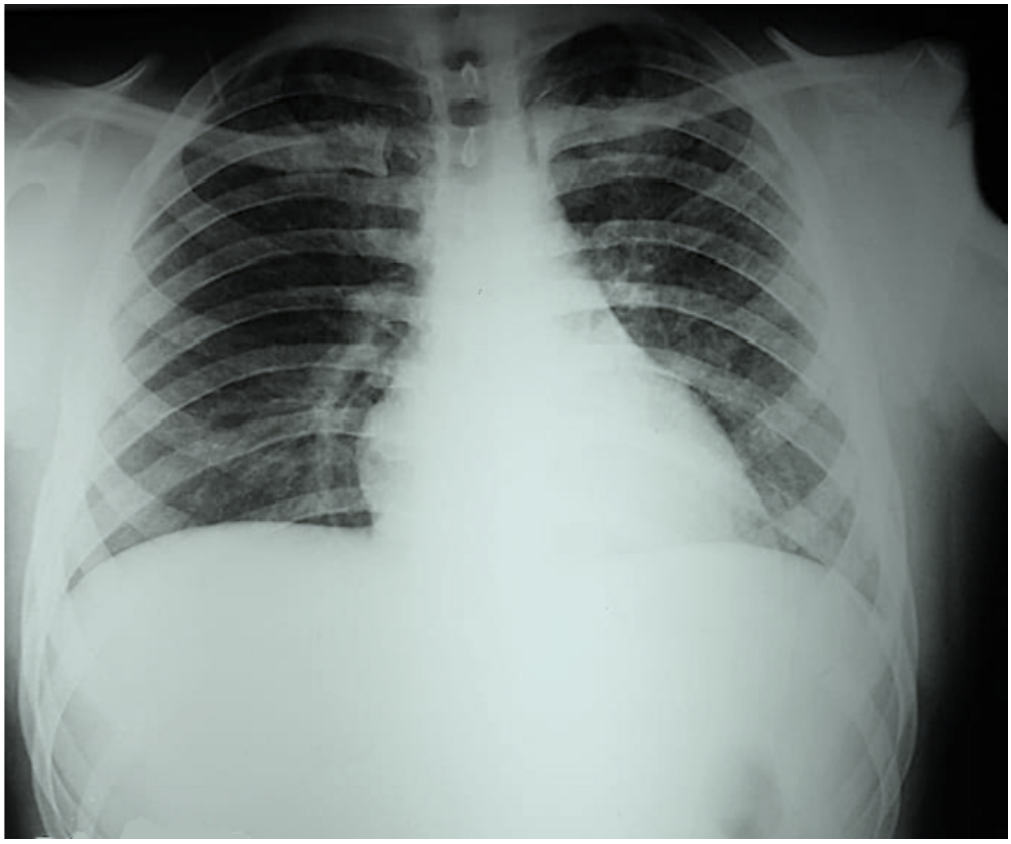

Figure 1. Chest X-ray on admission: bilateral alveolar opacities predominate in the lower left lung field.

ative autoantibody profiles (ANA, antiDNA, ENA, and ANCA).

Blood and urine cultures, pneumococcal urinary antigen, bronchoalveolar lavage (BAL)—bacteria cultures, respiratory virus polymerase chain reaction (PCR), *Chlamydia pneumoniae*, *Chlamydia psittaci*, *Mycoplasma pneumoniae*, mycobacteria, and fungi—and serological tests for leptospirosis (microscopic agglutination test [MAT]), hantavirus, human immunodeficiency virus (HIV), and hepatitis B and C were all negative.

The patient received treatment with ceftriaxone. The outcome was successful after eight days of mechanical ventilation. After discharge, a second MAT for leptospirosis was positive (1:200). The laboratory findings were normal, and a chest CT scan showed the resolution of the infiltrates (**Figure 3**).

Discussion

Leptospirosis is a worldwide zoonosis present in urban and rural areas. Floods and hurricanes are the main risks factor for leptospirosis infection. In human beings, the infection occurs by direct contact with the urine of infected animals; it enters through eroded skin or mucous membranes.[3]

Concerning its pathogenesis, in the bacteremic phase, it spreads to tissues and organs. In the immune phase, between five and seven days after infection, antibodies appear in the blood, and leptospira are expelled in urine. After infection, a systemic vasculitis occurs with damage of endothelial cell membranes of the capillaries that can cause pulmonary hemorrhage, tubular and interstitial nephritis, intrahepatic cholestasis, meningeal inflammation, and bleeding secondary to vasculitis and thrombocytopenia.

The clinical course of leptospirosis is variable, from nonspecific fever episodes to severe forms of renal failure or pulmonary hemorrhage with a mortality of up to 50%.

Three forms of clinical presentation are described:

Anicteric leptospirosis (90% of cases): manifests itself with fever, myalgias, headaches, and aseptic meningitis; conjunctival injection is characteristic. After five to seven days, if the disease is not self-limited, the systemic infection appears.

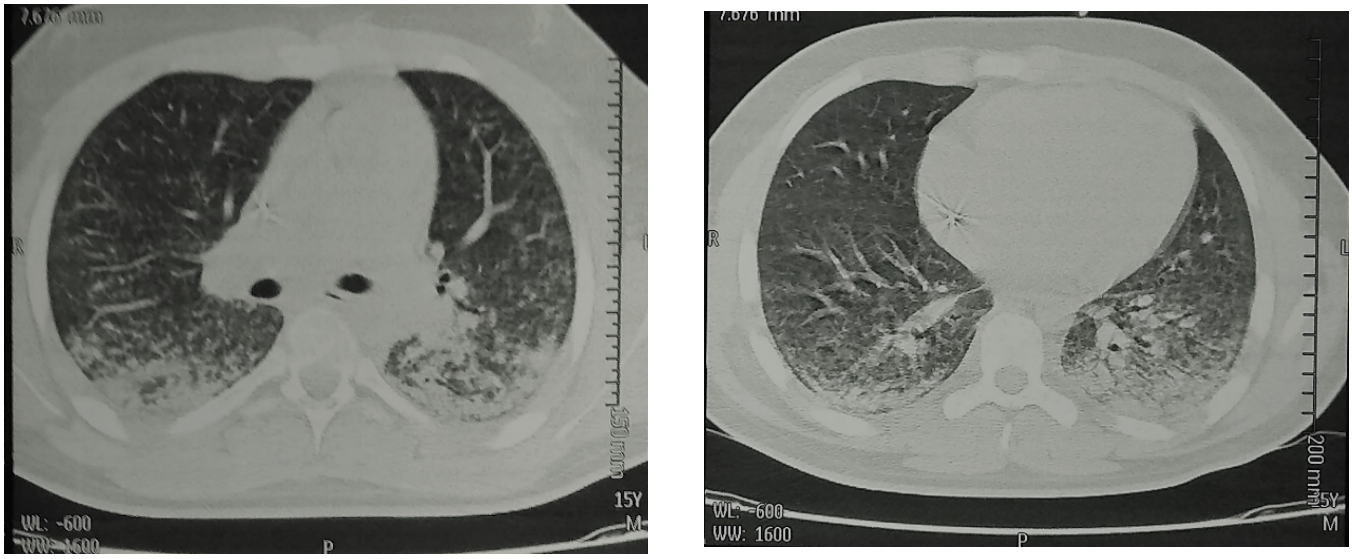

Figure 2. Chest computed tomography on admission: ground glass infiltrates with consolidation areas predominantly in lower lobes, associated with diffuse tree-in-bud infiltrate and centrilobular nodules.

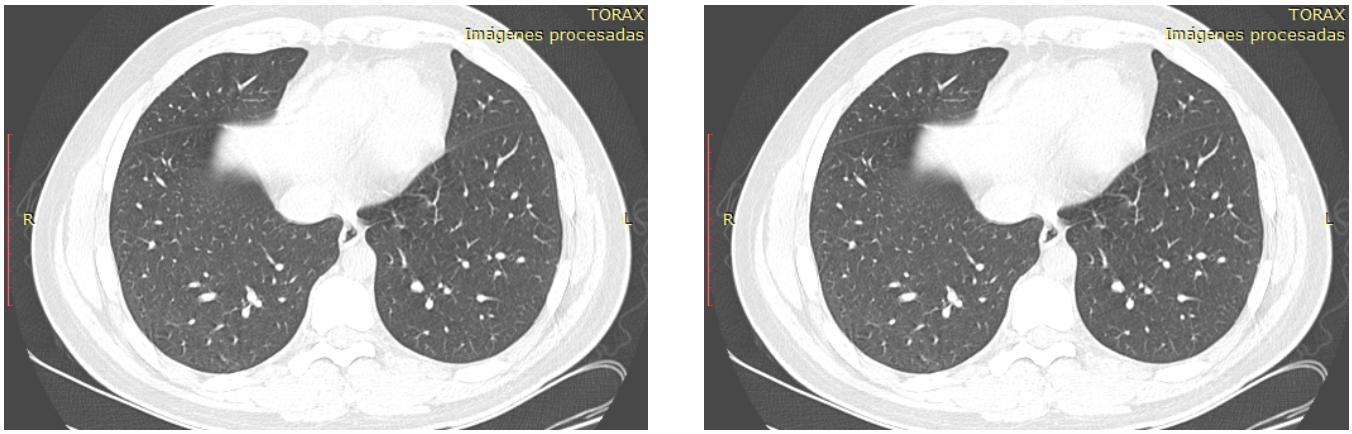

Figure 3. Control chest computed tomography: normal.

Icteric leptospirosis or Weil syndrome (5–10%): severe icteric disease; renal failure; hemorrhagic phenomena; and hemodynamic, pulmonary, and neurologic disorders. It presents with abdominal tenderness and hepatomegaly in 70% of cases. In addition, petechiae, ecchymosis, hematemesis, hemoptysis, melena, or enterorrhagia frequently occur.

Severe hemorrhagic pulmonary syndrome: presents with dyspnea and hemoptysis. Alveolar hemorrhage presents as ARDS, generally anicteric, without severe nephropathy, and with mild thrombocytopenia.

Most cases of leptospirosis are diagnosed by serology; the gold standard test is the MAT. Both serum samples of our patient were tested for leptospirosis antibodies using MAT. Although the specificity is high (higher than 95% in some series), the sensitivity changes according to the time of illness. MAT was reported to have a sensitivity of 41% during the first week, 82% during the second to fourth week, and 96% beyond the fourth week.[4] Niloofa *et al.* reported that acute MAT had a sensitivity of 55.3%, specificity of 95.7%, a positive predictive value (PPV) of 0.95, and a negative predictive value (NPV) of 0.55.[5] It is worth mentioning that, in Argentina, the definition of a confirmed case is based on a MAT titer of $\geq$200 or the presence of seroconversion (two-fold increase in antibody titer or a positive second MAT test if the first one is negative).[6]

The most frequent tomographic findings are ground-glass opacities, nodules, consolidation, crazy-paving pattern, and pleural effusion. The tomographic findings present a diffuse and symmetric distribution, with a predominance of the lower lobes in most cases.[7]

Bronchoscopy in severe pulmonary leptospirosis enables early detection of the alveolar hemorrhage.[8] In addition, early antibiotic treatment shortens fever and length of hospitalization. However, the benefits of antibiotics after the fifth day of illness are debatable.[6]

The role of corticosteroids in leptospirosis with lung involvement is controversial. Four studies with methodological limitations demonstrated its benefit in severe lung disease when administered early. A randomized controlled trial showed that corticosteroids are ineffective and may increase the risk of infection.[9] A double-blind, randomized clinical trial is underway to evaluate treatment efficacy with methylprednisolone pulse therapy compared with placebo in patients with lung involvement due to leptospira.[10]

Another treatment used in severe forms is cyclophosphamide; in Trivedi *et al.*'s study of 33 patients treated with cyclophosphamide, 22 (66.7%) survived, while in the control group of 32 patients, 3 (9.4%) survived.[11]

A systematic review in Sri Lanka evaluated the benefits of extracorporeal membrane oxygenation (ECMO) and plasmapheresis in severe pulmonary leptospirosis; one clinical trial showed significant survival with plasmapheresis, but the study's design has significant limitations. Another study described more prolonged survival with ECMO. Current evidence is insufficient to recommend routine use of plasmapheresis or ECMO.[12]

Conclusions

Early recognition of severe hemorrhagic pulmonary syndrome, which has a high mortality rate, is crucial. Leptospirosis should be suspected as a differential diagnosis in every patient with alveolar hemorrhage, ARDS manifestations, and epidemiological factors.

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