

# Weil's Disease with Multi-Organ Dysfunction: A Diagnostic Challenge

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Leptospirosis is a zoonotic disease caused by spirochetes from the species *Leptospira*. Weil's disease, the more severe manifestation of leptospirosis, is characterized by a combination of jaundice, renal injury, and hemorrhages. Diagnosing severe leptospirosis in patients with acute life-threatening multi-organ dysfunction at presentation can be challenging because of the non-specific clinical manifestations. This report describes a case of severe leptospirosis with jaundice, acute renal dysfunction, severe thrombocytopenia, pulmonary hemorrhage, and unusual manifestations, including rhabdomyolysis, acalculous cholecystitis, and pancreatitis, which required a comprehensive diagnostic evaluation of possible causes to confirm the diagnosis. The case highlights the importance of clinicians considering leptospirosis in the differential diagnosis of a patient with cryptogenic sepsis who develops multiple organ dysfunction.

**Keywords:** Leptospirosis; Spirochaetales Infections; Weil Disease

Leptospirosis is a zoonotic infection caused by the pathogenic spirochete belonging to the genus *Leptospira*, family Leptospiraceae, and order Spirochaetales.<sup>1</sup> It is widely prevalent in the tropics, where 73% of all cases occur. It commonly affects young male adults in rural farming populations and impoverished urban and semi-urban populations.<sup>2</sup> Male gender preference is a well-documented phenomenon in leptospirosis, attributed to occupational risk activities that are specific to gender.<sup>3</sup> Nearly all mammals can serve as carriers of leptospirosis, but the rat is the most important reservoir for human infection.<sup>2</sup> The most typical means of transmission to humans is abrasions on the skin and mucous membranes in contact with water contaminated with infected rat urine. Once the spirochete enters the human body, it multiplies in the bloodstream,

leading to its homogeneous dissemination through the body. The pathogen affects multiple organ systems, because the spirochete can cross tissue barriers.<sup>4</sup> The virulence of *Leptospira* is explained by the expression of surface-exposed proteins that may promote interactions with host tissues, leading to adhesion and penetration into various cell types, as well as binding to exposed elements of the extracellular matrix.<sup>5</sup>

Leptospirosis can present with a wide range of symptoms and severity, from a subclinical or asymptomatic, mild febrile illness to a fulminant life-threatening condition. About 90% of cases are acute and self-limited, with non-specific signs and symptoms.<sup>6</sup> However, around 10% of cases can be severe, leading to high mortality. The severe form of the disease,

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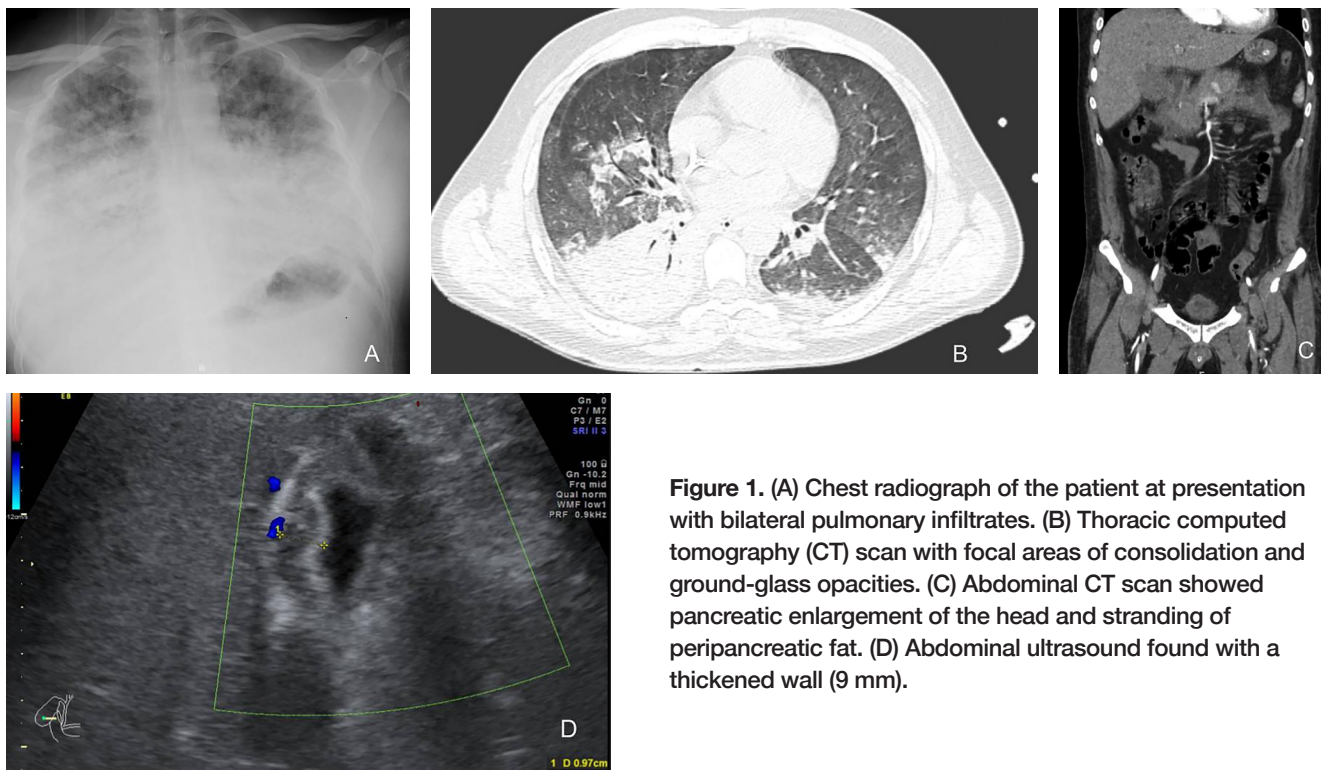
known as Weil's disease, is characterized by jaundice, renal failure, and hemorrhagic manifestations, and it can involve a broad array of organ systems.<sup>2</sup> Here, we present a case of a patient with the characteristic triad and multi-organ dysfunction, which posed a diagnostic challenge.

### Case Description

A previously healthy male construction worker, aged 37 years, presented to the emergency department with a 5-day history of malaise, myalgias, fevers, jaundice, and non-productive cough. He had developed dyspnea in the last 2 days. On presentation, his vital signs were: body temperature of 37.6°C (99.7°F), blood pressure of 124/76 mmHg, pulse of 132 beats per minute, and respiratory rate of 24 breaths per minute. Pulse oximetry showed hypoxia (sO<sub>2</sub> 86%) in room air. Physical examination revealed a sick young man with jaundice, bilateral rales on lung auscultation, and tenderness of the abdominal right upper region. No other abnormalities were observed. Initial laboratory tests showed leukocytosis (16,400/mm<sup>3</sup>) with over 85% of neutrophils, marked thrombocytopenia (8,000/mm<sup>3</sup>), elevated creatinine (5.37 mg/dL), hyperbilirubinemia (6.7 mg/dL) with conjugated bilirubin of 5 mg/dL, mildly elevated aspartate aminotransferase (74 U/L), alkaline phosphatase of 280 U/L, gamma-glutamyltransferase of 180 U/L, elevated fibrinogen (800 mg/dL), pro-calcitonin of 19.8 ng/mL, hyperlactatemia (7.1 mmol/L), elevated creatine phosphokinase (998 U/L), and urinalysis examination with erythrocytes positive (2+),

leucocytes positive (1+) proteinuria (100 mg/dL), and glucosuria (100 mg/dL). Tests for SARS-CoV-2 and influenza virus A and B were negative. Chest radiograph revealed bilateral pulmonary infiltrates (Figure 1A). The patient was initially diagnosed with pneumonia and received meropenem as empirical antibiotic therapy. However, a few hours after admission, the patient experienced increased respiratory difficulty and required mechanical ventilatory support. Additionally, norepinephrine and vasopressin were used to maintain the patient's mean blood pressure above 65 mmHg. The patient was then transferred to the intensive care unit for further care.

Subsequently, a computed tomography (CT) scan was performed, demonstrating focal areas of consolidation and ground-glass opacities, suggestive of alveolar hemorrhage (Figure 1B), and pancreatic enlargement of the head part with small focal fluid collection and stranding of peripancreatic fat, indicative of acute pancreatitis Balthazar D (Figure 1C). Abdominal ultrasound showed gallbladder with thickened wall (9 mm), consistent with acalculous cholecystitis (Figure 1D). Microbial cultures in blood, sputum, and urine were negative. Following meropenem administration, sequential regimens of ceftriaxone, azithromycin, and vancomycin were administered. Platelet count improved with antibiotic initiation, but renal function worsened, necessitating the initiation of hemodialysis. Creatine kinase continued to increase for several days and peaked at 3,554 U/L. In a



**Figure 1.** (A) Chest radiograph of the patient at presentation with bilateral pulmonary infiltrates. (B) Thoracic computed tomography (CT) scan with focal areas of consolidation and ground-glass opacities. (C) Abdominal CT scan showed pancreatic enlargement of the head and stranding of peripancreatic fat. (D) Abdominal ultrasound found with a thickened wall (9 mm).

second sputum culture, *Acinetobacter baumannii* was isolated, and antibiotic therapy with tigecycline and colistin was used. Intravenous doses of 1 g methylprednisolone daily for 3 days and cyclophosphamide 500 mg were initiated to treat the possibility of autoimmune-associated pulmonary hemorrhage, pending results. Further investigation with serology tests for viral infections and immunologic tests for vasculitis, systemic lupus erythematosus, and Goodpasture syndrome were negative (Table 1). The patient gradually improved and was weaned off assisted ventilation after 13 days. He was transferred to the ward, where IgM antibodies against *Leptospira* were positive. The diagnosis of leptospirosis was established using the modified Faine's criteria, which considers clinical data (Part A), epidemiological factors (Part B), and laboratory findings (Part C). A score of 9 on Part A, 4 on Part B, and 15 on Part C resulted in a total score of 28. A presumptive diagnosis of leptospirosis is indicated by a score of 26 or higher on Part A, Parts A and B, or 25 or more on Parts A, B, and C.<sup>7</sup> A final course of antibiotics with piperacillin-tazobactam was administered, and the patient's condition gradually improved. He was discharged with partial recovery of renal function.

## Discussion

The clinical course of leptospirosis is traditionally categorized into an "acute or leptospiremic phase," characterized by flu-like symptoms resulting from the spread of the spirochete in the bloodstream, and an "immune or leptospiruric phase," during which the immune response and leptospiral toxins can lead to a wide range of complications, depending on the extent of organ involvement.<sup>2,6</sup> However, the distinction between these phases is arbitrary, and they often overlap. Additionally, leptospirosis is known to present with varied clinical features, making it difficult to diagnose. An analysis of 353 laboratory-confirmed leptospirosis cases showed nonspecific symptoms are the most common.<sup>8</sup> In the majority of patients, leptospirosis is self-limiting and not fatal. However, a small number of infected patients experience persistent fever, jaundice, renal failure, and other organ dysfunctions.<sup>9</sup> Our patient's course was atypical, because he developed acute life-threatening multiple organ dysfunction, including severe thrombocytopenia, pulmonary hemorrhage, renal failure, and unusual manifestations, including rhabdomyolysis, acalculous cholecystitis, and pancreatitis. The initial clinical presentation strongly suggested sepsis due to bacterial pneumonia, although, due to a lack of response to antibiotic treatment, autoimmune diseases, such as granulomatosis with polyangiitis, systemic lupus erythematosus, and microscopic polyangiitis, were considered. However, these conditions were excluded. Lastly, the diagnosis of leptospirosis was considered based on the potential occupational risk of the patient, clinical manifestations, and a positive result for IgM antibodies against *Leptospira*.

The pathogenesis of severe leptospirosis is not fully elucidated; however, it is thought to be due to a form of vasculitis. Direct damage to tissues by *Leptospira* and immune-mediated

mechanisms are responsible for tissue and organ damage, deranged tissue microcirculation, and endothelial dysfunction.<sup>2,4</sup> Between 20%–70% of infected individuals experience pulmonary complications, which can range from non-productive cough to respiratory failure caused by pulmonary hemorrhage. The pulmonary symptoms can become very severe shortly after they appear, and patients can die within 48 hours due to respiratory failure. The presence of pulmonary involvement is linked to poorer outcomes, and the most severe form, hemorrhagic pneumonitis, has a mortality rate of up to 60%.<sup>10,11</sup> Acute kidney injury associated with leptospirosis is related to several factors, such as hyperbilirubinemia, hypovolemia, rhabdomyolysis, and the direct nephrotoxic action of *Leptospira*. Studies indicate an alteration in the tubular function, which further causes changes in the proximal tubule and the glomerular filtrate rate. Mortality in renal failure with leptospirosis is around 20%.<sup>4</sup> Thrombocytopenia is frequently observed during the acute stage, probably because of both diffuse intravascular coagulation and immune-mediated mechanisms.<sup>12</sup> Nearly all patients with leptospirosis experience severe myalgias, and most show laboratory evidence of mild elevation in the creatine kinase; however, severe rhabdomyolysis is rare. Damage to muscle from spirochetal exotoxin or invasion of leptospire into muscle, causing inflammation and destruction, has been proposed as the cause of rhabdomyolysis.<sup>13,14</sup> While jaundice may be an accompanying sign, liver involvement is usually transient, as it results from liver cell dysfunction rather than hepatocyte loss or apoptosis. Clinically, plasma bilirubin levels are elevated, particularly conjugated bilirubin, with transaminase plasma concentrations remaining normal or only slightly increased.<sup>12</sup> Acalculous cholecystitis is an uncommon manifestation of leptospirosis, and the pathophysiology could be an immunogenic reaction against the infiltrating spirochete in the gallbladder. Early antibiotic treatment can be sufficient to treat acalculous cholecystitis.<sup>15</sup> Leptospirosis-associated pancreatitis has been linked to higher rates of morbidity and mortality. Diagnosing pancreatitis in severe cases of leptospirosis with kidney injury can be difficult, as hyperamylasemia may be explained by renal failure. However, when pancreatitis is suspected, diagnostic imaging techniques such as ultrasound or computed tomography scans can be used to confirm the diagnosis.<sup>16</sup>

Epidemiological history is crucial for the diagnosis of leptospirosis. Exposure to leptospire may occur through direct contact with an infected animal or indirectly via soil or water contaminated with the urine of an infected animal.<sup>1</sup> In this context, the patient's occupation as a construction worker posed a risk factor for developing the disease, as it is typically associated with poor sanitation and potential exposure to rodents.

The laboratory tests for diagnosing leptospirosis are categorized into those that provide direct evidence of infection (demonstration of leptospire or their DNA or culture) and

**Table 1. Laboratory characteristics of the patient**

Laboratory values (reference range and units)	Initial values	Peak / nadir values	At discharge
Hemoglobin (12.0-18.0 g/dL)	12.4	6.1	12.9
Platelets (150,000-450,000 x mm <sup>3</sup> )	8,000	185,000	199,000
Leukocytes (5,000-10,000 x mm <sup>3</sup> )	16,400	67,300	7,900
Neutrophils (2,000-7,500 x mm <sup>3</sup> )	14,600	57,900	4,000
Lymphocytes (1,300-4,000 x mm <sup>3</sup> )	820	2,630	2,800
Creatinine (0.55-1.3 mg/dL)	5.37	8.29	1.59
Urea (10.0-50.0 mg/dL)	139.1	340.3	74.9
BUN (0.0-21.0 mg/dL)	65	159	35
Creatinine kinase (21.0-232.0 U/L)	998	3,554	542
AST (17.0-48.0 U/L)	74	560	68
ALT (21.0-62.0 U/L)	53	772	146
Alkaline phosphatase (53.0-128.0 U/L)	280	445	215
GGT (8.0-78.0 U/L)	180	667	
LDH (313.0-618.0 U/L)	258	3,120	321
Total bilirubin (0.2-1.0 mg/dL)	6.7	29.3	2.1
Conjugated bilirubin (0.0-0.3 mg/dL)	5.0	20.7	1.6
Unconjugated bilirubin (0.0-0.8 mg/dL)	1.7	8.6	0.5
aTTP (24.0-35.0 s)	33.9	24.5	25.6
PT (11.8-15.6 s)	17.1	21.1	14.4
INR (0.73-1.26)	1.49	1.85	1.25
Pro-calcitonin (0.0-0.5 ng/mL)	19.8	>50.0	1.02
Ferritine (4.63-204.0 ng/mL)	>1650		
ANA (negative titers <1:20)	<1:20		
Anti-dsDNA antibodies (negative <20 U/mL)	0.31		
Complement C3 (83-193 mg/dL)	116.4		
Complement C4 (15-57 mg/dL)	25.6		
c-ANCA (negative <1:20)	<1:20		
p-ANCA (negative <1:20)	<1:20		
Anti-LKM antibodies (0.0-15.0 U/L)	0.5		
Anti-GBM antibodies (negative <1 AI)	0		
Anti-smooth muscle antibodies (negative)	Negative		
Anti-mitochondrial antibodies (0.0-0.99 U/mL)	0.5		
Direct Coombs (negative)	Negative		
Cryoglobulins (negative)	Negative		
Anti-HIV 1/HIV 2 antibodies (negative <1.0 S/CO)	0.1		
HBsAg (negative <1.0 S/CO)	0.31		
HCAc (negative <1.0 S/CO)	0.1		
Anti-toxoplasma gondii IgG antibodies (negative <1.0 U/mL)	61.7		
Anti-toxoplasma gondii IgM antibodies (negative <0.79 INDEX)	0.14		
Anti-rubella IgG antibodies (negative <1.0 U/mL)	136		
Anti-rubella IgM antibodies (negative <0.8 S/CO)	0.2		
Anti-herpes simplex IgG antibodies (negative (negative <0.9 U/mL)	2.1		
Anti-herpes simplex IgM antibodies (negative <1.0 S/CO)	0.1		
Anti-cytomegalovirus IgG antibodies (negative <0.5 U/mL)	453		
Anti-cytomegalovirus IgM antibodies (negative <0.69 INDEX)	0.2		
Anti-Leptospira IgG antibodies (negative <10 U/mL)*	39.5		
Anti-Leptospira IgM antibodies (negative <15 U/mL)*	51.2		

Abbreviations: *ALT*, alanine aminotransferase; *ANA*, antinuclear antibodies; *Anti-dsDNA*, anti-double stranded deoxyribonucleic acid antibodies; *AST*, aspartate aminotransferase; *aTTP*, activated partial thromboplastin time; *BUN*, blood urea nitrogen; *c-ANCA*, antineutrophils cytoplasmic antibodies, cytoplasmic; *GGT*, gamma glutamyl transaminase; *HBsAg*, hepatitis B surface antigen; *HCAc*, hepatitis C antibody; *HIV*, human immunodeficiency virus; *INR*, international normalized ratio; *LDH*, lactate dehydrogenase; *LKM*, liver-kidney microsomal; *p-ANCA*, antineutrophils cytoplasmic antibodies, perynuclear; *PT*, prothrombin time

\* Detection method: enzyme linked immunoabsorbent assay (ELISA), dilution 1:100

tests that show indirect evidence of disease (demonstration of antibodies against leptospires). Serology tests are the most used methods. These include the microscopic agglutination test (MAT) and enzyme-linked immunosorbent assay (ELISA) for detecting *Leptospira* IgM antibodies, which appear 5 to 7 days after the onset of symptoms. Molecular methods, such as conventional polymerase chain reaction (PCR) and real-time PCR, are useful in the early stages of the illness (within the first 5 days), since leptospiral DNA in serum disappears once antibodies are detected. Other less commonly used diagnostic tools include direct observation of the pathogen in serum and urine via microscopy and culture.<sup>2,17</sup> However, culture plays a significant role in studying global epidemiology and outbreaks, providing clinical strains of *Leptospira* spp. for pathogenesis studies.<sup>17</sup>

In any suspicion of leptospirosis, starting empirical antibiotic therapy is advisable. The antibiotics used to treat severe cases of leptospirosis range from benzylpenicillin and third-generation cephalosporins to piperacillin-tazobactam and meropenem.<sup>9</sup> It is considered that the disease's progression to more severe forms can be prevented by early initiation of antibiotic treatment.<sup>4</sup> However, antimicrobial therapy does not appear to improve prognosis or survival after the onset of severe pulmonary symptoms.<sup>6</sup> Furthermore, in a recent Cochrane systematic review that included nine randomized clinical trials (1,019 participants), the evidence was very uncertain about the effect of antibiotics on all causes of mortality.<sup>18</sup> Nevertheless, antibiotics are recommended, particularly for severe disease. On the other hand, routine use of steroids is not recommended because there is insufficient evidence, although there are reports of potential adjunctive benefits with high-dose corticosteroids in severely ill patients.<sup>2</sup> In our patient, neither early treatment with antibiotics nor administration of high doses of steroids seemed to have altered the course of the disease. Although the patient survived, renal function did not recover fully. This emphasizes that unresponsive treatment does not necessarily eliminate the possibility of leptospirosis.

In summary, leptospirosis is a rare but important differential diagnosis to be considered in febrile patients with multi-organ involvement. Physicians should maintain a high level of suspicion to start treatment on time.

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