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Case Report

A Challenging Case of Leptospirosis

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Abstract: Leptospirosis is a significant zoonosis caused by the pathogenic bacterium *Leptospira*, which is transmitted directly or indirectly from animals to humans. It is a potentially severe but treatable disease. Its symptoms may mimic those of other infections, such as rickettsiosis, influenza, meningitis, or hepatitis. The disease spectrum ranges from subclinical infection to severe multi-organ failure with high mortality. Diagnosis is usually made through serology. However, a key limitation of serological testing is that antibodies are absent during the acute phase. In the early days of illness, the only sensitive and specific test is polymerase chain reaction (PCR). In Portugal, leptospirosis has gained increasing importance and is a notifiable disease. The authors present the case of a farmer with fever, headache, and rash who progressed to pancytopenia and hepatic cholestasis. A positive real-time PCR in a blood sample, specific for *Leptospira*, confirmed the diagnosis in the acute phase of the disease before antibody titers became detectable. Leptospira serologies remained negative. After antibiotic therapy and supportive care, the patient showed favorable clinical progression. Early diagnosis prevented complications. The authors report a challenging case of leptospirosis and aim to raise awareness about the importance of early diagnosis and appropriate treatment. Occupational exposure is a significant risk factor. Public health alert systems are essential to reduce risk. The need for rapid diagnosis at admission has driven the development of various PCR assays, which carry economic implications. Their advantage lies in confirming the diagnosis during the acute phase of disease, before antibody detection, and they may support improved public health control measures. However, molecular tests are still unavailable in some areas.

Keywords: Leptospirosis; Fever; Rash; Pancytopenia; Cholestasis.

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1. Introduction

Leptospirosis has been gaining increasing importance in Portugal and is considered a notifiable disease. It is a zoonosis caused by the aerobic bacterium *Leptospira*. The excretion of this bacterium in the urine of animals contaminates the environment and contact with such environments can result in human infection. Humans are accidental hosts, and rodents are the main reservoir, although some domestic animals may be chronic carriers. Occupational exposure represents a risk factor, as do certain recreational activities [1].

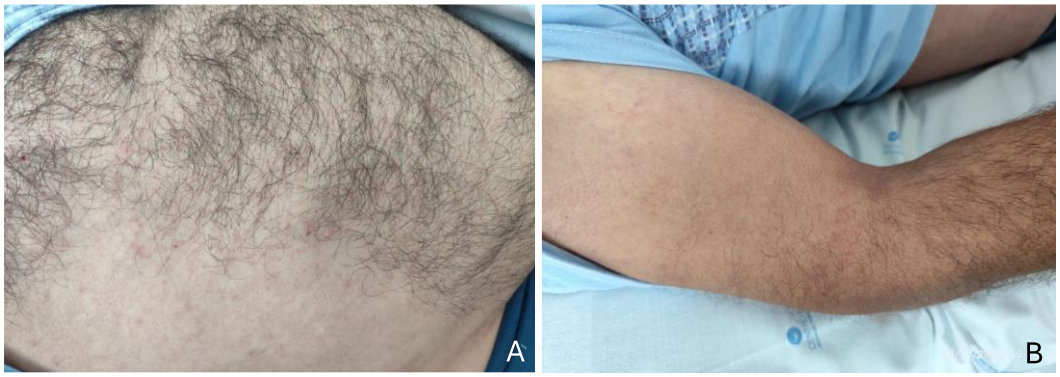
The clinical presentation is variable, ranging from asymptomatic forms to very severe cases. The incubation period varies from 2 to 26 days. In symptomatic patients, the disease typically follows a biphasic course. The leptospiremic phase lasts approximately one week and corresponds to the hematogenous dissemination of the bacterium. It is usually non-specific, with symptoms such as fever, myalgia, asthenia, abdominal pain, diarrhea, nausea, vomiting, hemoptysis, skin rash, and the absence of jaundice. In a minority of cases, the more severe icteric form occurs, which can be fatal due to respiratory, hepatic, and

renal failure. Following this phase, the immune or leptospiruric phase begins, characterized by bacterial tropism for organs such as the liver, lungs, kidneys, heart, and brain, accompanied by antibody production and urinary excretion of *Leptospira* [2].

2. Case Report

A 56-year-old male farmer, residing in a rural area, with frequent contact with farm animals and consumption of untreated well water, was admitted to the hospital with a two-day history of generalized erythematous pruritic maculopapular rash, sparing the palms of the hands and soles of the feet (Figures 1A and 1B). He also reported holocranial headache, anorexia, asthenia, nausea, myalgia, and fever (axillary temperature of 39 °C) refractory to paracetamol and ibuprofen, as well as left iliac fossa abdominal pain.

Figure 1. Presence of cutaneous rash on the abdomen (A) and right arm (B).



He denied recent contact with individuals presenting similar symptoms. He reported habitual contact with various animals—sheep, cows, donkeys, pigs, dogs, chickens, and rabbits—and no other relevant epidemiological factors (such as consumption of unpasteurized products, use of drugs, herbal infusions, mushrooms, or medications). On physical examination, he was hypotensive (blood pressure 99/66 mmHg), with sinus tachycardia (heart rate 103 bpm), febrile (auricular temperature of 38.9 °C), and had normal cardiac and pulmonary auscultation. There was deep tenderness in the lower abdominal quadrants without signs of peritoneal irritation. A maculopapular rash was observed on the trunk and limbs, along with petechiae on the lower limbs.

Laboratory findings showed thrombocytopenia (platelet count: 116,000/mm^3) and elevated C-reactive protein (16 mg/dL), with no other significant abnormalities. Tests for Influenza, Respiratory Syncytial Virus, and SARS-CoV-2 were negative. A computed tomography (CT) scan of the chest, abdomen, and pelvis revealed no infectious focus. Cerebral angiotomography and venotomography were unremarkable. Lumbar puncture showed normal cerebrospinal fluid. Serologies and cultures for cytomegalovirus, Epstein-Barr virus, herpesvirus, varicella, enterovirus, and bacteria were negative. Due to the hypotensive state, intravenous fluid therapy was initiated. Considering the epidemiological context and suspected zoonosis, empirical antibiotic therapy with doxycycline 100 mg every 12 hours was started. The patient was admitted for diagnostic investigation and clinical monitoring.

On the 3rd day of hospitalization, due to persistent fever and worsening laboratory findings (pancytopenia and cholestasis), antibiotic therapy was changed to ceftriaxone 2 g/day. Blood PCR for *Leptospira* was positive and became available on the 4th day of hospitalization. The disease was reported as required by public health regulations. Serologies were negative both at admission and on day 3. Blood cultures, urine culture, and serologies for other infections were also negative (Table 1). Autoimmune screening was negative.

Table 1. Serological tests.

Test	Result	Interpretation
HIV	Negative	No active infection
Hepatitis A Virus	IgM/IgG negative	No active infection
Hepatitis B Virus	HBsAg, Anti-HBs, Anti-HBc negative	No active infection
Hepatitis C Virus	IgM/IgG negative	No active infection
Hepatitis E Virus	IgM/IgG negative	No active infection
Widal	Negative	No active infection
Wright	Negative	No active infection
Rickettsia	IgM/IgG negative	No active infection
Cytomegalovirus	IgM negative / IgG positive	Past infection
Epstein-Barr Virus	IgM negative / IgG positive	Past infection
Toxoplasma gondii	IgM negative / IgG positive	Past infection
Parvovírus	IgM negative / IgG positive	Past infection
Treponema pallidum	IgM/IgG negative	No active infection
Leptospira	IgM/IgG negative,PCR blood positive	Active infection

The patient developed pancytopenia and cholestasis. Laboratory results showed minimum values of hemoglobin at 11.8 g/dL, platelets at 54,000/mm³, and leukocytes at 2,660/mm³. The maximum levels of liver enzymes included aminotransferases 2 to 4 times above the upper limit of normal, gamma-glutamyl transferase (GGT) 7 times the limit, alkaline phosphatase 4 times the limit, and peak total bilirubin at 3 mg/dL, predominantly direct (Table 2). Abdominal magnetic resonance imaging (MRI) revealed mild hepatosplenomegaly and ruled out biliary obstruction. A transthoracic echocardiogram was also performed and excluded endocarditis.

The patient received thrombosis prophylaxis with compression stockings until the platelet count exceeded 70,000/mm³. After seven days of antibiotic therapy and intravenous hydration, clinical and laboratory improvement was observed (Table 2). He was discharged on the 10th day of hospitalization. At follow-up visits on day 40 and at 5 months, he remained asymptomatic with normal laboratory tests, and repeat serologies for *Leptospira* remained negative (Table 2).

Table 2. Serological tests.

Test	D1	D4	D6	D7	D8	D9	D10	D40	5 months	Reference Range	Units
Hemoglobin	15.4	11.8	11.9	12.2	12.7	12.9	14	12.8	14.9	13.6–18	g/dL
Platelets	116	54	110	171	236	275	310	146	156	140–440	10^9/L
Leukocytes	4.37	2.66	3.54	4.25	5.97	5.96	7.28	5.42	4.96	4–10	10^9/L
C-reactive protein	16	21	11	12	16	2	1.2	0.4	4	<0.5	mg/dL
AST	34	44	89	90	95	72	30	28	29	<40	U/L
ALT	40	47	123	123	136	153	85	36	26	<41	U/L
GGT	57	385	422	425	350	275	223	53	15	<60	U/L
ALP (FA)	66	159	160	160	161	146	130	72	73	40–130	U/L

Total bilirubin (TB)	0.9	3	1.3	0.9	0.8	0.8	0.8	0.5	0.85	<1.1	mg/dL
Direct bilirubin (DB)	0.4	2.4	1.0	0.5	0.5	0.5	0.48	0.26	0.3	<0.3	mg/dL
Total protein	7.3	–	–	–	–	6.05	–	–	–	6.6–8.7	g/dL
Albumin	4.3	–	–	–	–	3.25	–	–	–	3.5–5.2	g/dL
aPTT	26.7	26	26.8	–	26	28.7	–	–	–	23.6–34.8	s
PT	14.9	14	13.6	–	14	14	–	–	–	12–15.5	s
LDH	265	265	–	–	–	–	–	–	247	135–225	U/L
Urea	31	23	20	26	–	30	30	42	37.8	10–50	mg/dL
Creatinine	0.95	0.7	0.5	0.6	–	0.6	0.7	0.6	0.6	0.7–1.2	mg/dL
Sodium	134	137	135	139	–	136	137	139	136	135–145	mmol/L
Potassium	4.0	4.0	4.0	3.7	–	4.0	4.8	4.4	4.0	3.5–5.0	mmol/L

Legend: AST – aspartate aminotransferase; ALT – alanine aminotransferase; GGT – gamma-glutamyl transferase; ALP (FA) – alkaline phosphatase; TB – total bilirubin; DB – direct bilirubin; PT – prothrombin time; LDH – lactate dehydrogenase.

3. Discussion and Conclusion

Portugal is one of the European countries with the highest number of leptospirosis cases [3]. The increasing incidence of leptospirosis may be explained by imports from endemic regions, climate variations, or increased travel [1]. Occupational exposure is a known risk factor, as are certain recreational activities [1,2].

Leptospirosis should be considered both as a potential cause and a differential diagnosis in the presence of fever, skin rash, pancytopenia, and hepatic cholestasis [2,9,10,12,22]. Diagnosis is challenging due to the nonspecific nature of clinical signs and symptoms, especially in anicteric forms, and the difficulty of identifying the pathogen in the acute phase, which is often only detectable through PCR testing of a blood sample [4,6,7]. Depending on the epidemiological context, a high degree of clinical suspicion is crucial and may justify early initiation of antibiotic therapy before laboratory confirmation of infection [2,5,9,11,20].

In the present case, the patient was a previously healthy farmer. The epidemiological context—contact with various animals and consumption of untreated well water—combined with fever, skin rash, pancytopenia, and hepatic cholestasis, led to a high clinical suspicion of leptospirosis, which was considered the most likely diagnosis even before the blood PCR result confirmed it in real time.

The authors reflect on the broad spectrum of differential diagnoses associated with leptospirosis. Given the epidemiological setting and clinical overlap with other infectious diseases, the possibility of cross-reactivity or coinfection was considered. Alternative infectious etiologies were investigated, although leptospirosis remained the main working diagnosis. Clinical and laboratory worsening, along with the absence of immediate diagnostic confirmation, prompted extensive complementary testing to rule out other causes. The differential diagnosis included diseases that were considered unlikely in this case based on negative laboratory results: rickettsioses, hepatitis, brucellosis, salmonellosis, cytomegalovirus, Epstein-Barr virus, *Toxoplasma gondii*, parvovirus, syphilis, influenza, SARS-CoV, endocarditis, meningitis, cholecystitis, pyelonephritis, appendicitis, HIV-related immunodeficiency, autoimmune diseases, or malignancies. Other fungal infections were also deemed unlikely due to a negative HIV test and absence of immunosuppression history. The broad diagnostic panel excluded alternative causes, and the positive real-time PCR for *Leptospira* in blood reinforced leptospirosis as the sole causative agent [8,22].

Given the high morbidity and mortality associated with leptospirosis involving hepatic and hematologic dysfunction, early diagnosis and treatment are essential. In underdiagnosed cases, delays in recognition and intervention may be fatal. Thrombocytopenia and older age are markers of poor prognosis and mortality risk in leptospirosis. Early initiation of antibiotic therapy has been shown to reduce mortality [9,10,20]. In cases of high clinical suspicion, empirical antibiotic treatment with doxycycline is recommended [8].

In this case, due to the initial clinical suspicion of leptospirosis, oral doxycycline 100 mg every 12 hours was started, as this antibiotic is effective against both leptospirosis and rickettsiosis, which was also part of the differential diagnosis. Due to clinical worsening (fever and headache) and laboratory progression (leukocytosis, increased C-reactive protein, pancytopenia, and hepatic cholestasis), antibiotic therapy escalated from oral doxycycline to intravenous ceftriaxone [11,20]. Hematologic involvement is a known feature of leptospirosis [9]. Given the possibility of other causes of pancytopenia, the patient was evaluated by Hematology, and a bone marrow aspiration or biopsy was considered, but not performed, due to the strong clinical and epidemiological suspicion of an infectious etiology and the patient's clinical improvement, all suggestive of leptospirosis.

After confirmation of *Leptospira* by real-time PCR in the blood, the fever, rash, and laboratory abnormalities were attributed to the natural course of the disease, and leptospirosis was confirmed as the main diagnosis. The patient showed favorable progression, with clinical and laboratory improvement (resolution of pancytopenia and cholestasis). After hospital discharge, he remained under outpatient follow-up and was re-evaluated at 40 days and 5 months for clinical and laboratory monitoring. He remained asymptomatic, with no late clinical complications and no abnormal test results.

This case demonstrates that the diagnosis of leptospirosis requires a high degree of clinical suspicion, based on signs and symptoms along with a history of exposure to risk factors, since laboratory findings are nonspecific and serologic tests may be negative even in the presence of infection. One of the limitations of serological testing is the absence of antibodies during the acute phase of the disease, as IgM is usually not detectable until the second week after symptom onset, resulting in low sensitivity during the early acute phase [19]. In this case, the diagnosis of leptospirosis was confirmed by a positive real-time PCR in a blood sample. Serial serologies remained negative at admission, on day 3, on day 40, and at 5 months. This is a common finding that complicates diagnosis.

The authors discuss possible reasons for the absence of seroconversion, including the timing of sample collection in relation to the phase of infection (which may precede antibody development), early antibiotic therapy that can inhibit the production of IgM/IgG antibodies, immunosuppressive states, limitations of the commercial kit used, and the wide diversity of *Leptospira* serovars, which might not be detected by the serological assay employed. Thus, serological results should always be interpreted in conjunction with the clinical presentation and other diagnostic tests.

In general, antibodies in leptospirosis become detectable between 3 and 10 days after symptom onset, and may not be present during the first week of illness. Given the limitations of serological testing in the early phase, it is recommended to collect a second sample during the convalescent phase—between 2 and 6 weeks after symptom onset—to demonstrate seroconversion [6,7,12]. The presence of pancytopenia and cholestasis can aid in the early diagnosis of febrile syndromes in patients with relevant risk factors. This is particularly important because seroconversion may occur later, between the 6th and 12th day of illness, or may never occur, with serological tests remaining persistently negative [8]. In this case, serology remained negative even during the convalescent phase, when repeated on day 40—within the expected 2 to 6-week window.

Early initiation of antibiotic therapy before seroconversion may suppress antibody production, contributing to the negative serological results observed in this patient [12]. Immunosuppression was ruled out through a negative HIV test and normal serum immunoglobulin levels. Immunosuppression does not explain the absence of seroconversion

in this case, as the patient exhibited IgG responses in other positive serologies (cytomegalovirus, Epstein-Barr virus, *Toxoplasma gondii*, and parvovirus).

Due to the lack of availability of different commercial kits, the JusChek® immunochromatographic assay was used, which detects qualitative IgM and IgG antibodies against *Leptospira interrogans* in human whole blood, serum, or plasma samples. This kit offers 93.8% sensitivity and 98.7% specificity when compared to the ELISA test. It is based on a membrane pre-coated with mouse anti-human IgG and IgM antibodies in the test line region. During the procedure, the sample reacts with recombinant *Leptospira interrogans* antigens and migrates by capillary action across the membrane. A colored line appears in the presence of antibodies, indicating a positive result. A control line ensures that the test was performed correctly, with adequate sample volume and proper membrane absorption.

Limitations of the JusChek® test include potential user error in execution or interpretation, lack of linear correlation with antibody titers (as it is a qualitative test), a required hematocrit range of 25%–65%, and the possibility of false-negative results. A negative result indicates that detectable antibodies are absent but do not exclude leptospiral infection, especially if the sample was collected too early or if antibody levels were below the assay's detection threshold. Furthermore, it must be considered that *Leptospira interrogans* is not the only pathogenic species. Therefore, the infecting strain in this case may have been a different *Leptospira* species, undetectable by the serological assay used.

Among pathogenic *Leptospira* species, *Leptospira interrogans* is the most relevant etiologic agent in humans. The taxonomic unit "serovar" (or serotype) is based on the surface expression of lipopolysaccharides. Structural differences in the carbohydrate portion of these lipopolysaccharides determine the antigenic diversity of the numerous serovars. Serovars share antigenic determinants and are grouped into serogroups. At least 25 serogroups and over 300 serovars have been described, which explains the pathogen's complexity and represents a diagnostic challenge [13].

The practical importance of the serovar is reflected from an epidemiological perspective, as certain serovars may establish commensal relationships with specific animal hosts while being pathogenic to others. Therefore, serological tests that do not detect all *Leptospira* serotype variants may yield negative results even in the presence of infection [6,12,19,20]. In this case, the serological test may have failed to detect the serotype that infected the patient, meaning that a mismatch between the infecting serotype and those targeted by the assay could have contributed to the absence of seroconversion.

Early detection of leptospirosis requires rapid and sensitive diagnostic tests. PCR amplifies specific DNA sequences. In this case, direct detection of *Leptospira* was performed using real-time PCR, with 93% sensitivity and 98% specificity, targeting the LipL32 gene, which encodes an outer membrane lipoprotein found exclusively in pathogenic *Leptospira serovars*. This method allowed for rapid confirmation of infection in the early days of illness. Real-time PCR is validated as an effective diagnostic tool in the early phase of infection, with excellent performance during the bacteremic phase, typically occurring within the first week of symptoms. A single positive real-time PCR result was sufficient to establish a definitive diagnosis of acute-phase leptospirosis before seroconversion [14,15,18,19,20,21]. However, the sensitivity of PCR is directly dependent on the disease phase at the time of sample collection relative to symptom onset. As leptospires are only transiently present in body fluids, a negative PCR result does not exclude leptospirosis [14,15,18,19,20,21].

The clinical presentation of leptospirosis is often confused with other causes of febrile syndromes. The absence of pathognomonic signs means that diagnosis relies on clinical suspicion and epidemiological context, particularly when PCR is not available. The main advantage of real-time PCR lies in its high sensitivity and specificity, making it essential during the initial phase of the disease, when serologic tests may still yield negative results.

Broader implementation of real-time PCR, considering its cost-effectiveness and feasibility in different healthcare settings, is crucial to expedite confirmatory diagnosis of leptospirosis [16,17].

The choice of laboratory testing should consider both the stage of disease progression and test availability. During the first week of illness, PCR is the only sensitive and specific test available. However, in low-resource regions, lack of access to PCR remains a significant barrier due to the high cost of equipment and the need for trained personnel [19]. From a public health standpoint, reporting leptospirosis based on molecular methods such as PCR has important implications. It facilitates early diagnosis and timely therapeutic intervention, which can positively impact patient survival. It is essential that healthcare professionals remain vigilant, and report suspected or confirmed cases as early as possible, enabling epidemiological surveillance and infection control measures. Occupational exposure is a major risk factor, and alert systems are critical to reducing this risk. Currently, no vaccine is available for leptospirosis [13]. PCR also enables identification of the infecting serovar, which is highly relevant for public health, as it allows tracking of infection sources and animal reservoirs and supports the development of preventive strategies and infection control measures [19].

The epidemiological context plays a central role in raising clinical suspicion for leptospirosis. When serologies are negative, early PCR testing of blood samples becomes a key diagnostic tool. This clinical case contributes to expanding knowledge on the diagnosis and management of leptospirosis, highlighting the importance of maintaining clinical suspicion in nonspecific presentations in patients with relevant risk factors. This approach guides diagnostic investigation, enables early treatment, and contributes to favorable clinical outcomes.

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