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(CASE REPORT)

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PCR-Negative Leptospirosis: A Case Report

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Abstract

Pathogenic spirochetes of the genus *Leptospira* produce Leptospirosis, an emerging zoonotic infection that is frequently observed in tropical areas and frequently manifests as an undifferentiated fever. Because of its preliminary level of laboratory tests and generalized clinical signs, early diagnosis is still difficult.

We describe a 63-year-old male farmer patient who developed a high-grade fever, myalgia, thrombocytopenia, altered liver function, and hemodynamic abnormalities. Initial *Leptospira* IgM ELISA and Polymerase Chain Reaction (PCR) results were negative despite a high level of clinical suspicion, and repeated serological testing revealed seroconversion with positive IgM, validating the diagnosis. The patient required critical care management with mechanical ventilation, inotropes support, and broad-spectrum antibiotics along with doxycycline.

This case highlights the diagnostic dilemma of early Leptospirosis, especially in patients who have already been exposed to antibiotics or tests performed during the leptospiremic phase before antibody development. Careful clinical evaluation and repeated serological testing are necessary to confirm the diagnosis. In endemic areas, timely empirical treatment with doxycycline will save the patient.

Keywords: Leptospirosis; Microscopic Agglutination Test; Enzyme-Linked Immunosorbent Assay; Polymerase Chain Reaction; Zoonotic Infection

1. Introduction

Leptospirosis is a zoonotic or acute febrile disease caused by pathogenic spirochetes of the genus *Leptospira* from the Leptospiraceae family. Although this zoonotic disease occurs all over the world, it occurs more frequently in tropical and sub-tropical regions. Humans are usually infected either by direct proximity with a diseased animal or indirectly by exposure to soil and water polluted by infected animals. [1]

The pathogenesis starts when pathogenic *Leptospira* organisms enter the human body through intact mucous membranes, especially through skin breaks like abrasions, cuts, the mouth or the conjunctiva. Then it spreads by circulating throughout the body via bloodstream without causing any localized skin infections and only contributes to systemic disease or injury in the affected person. [2] Leptospirosis can present clinically in a variety of ways, from moderate, self-limiting fever to severe symptoms such as renal injury, liver dysfunction, pulmonary bleeding, and multiple organ failure. This broad clinical spectrum frequently causes misdiagnosis and treatment delay due to other differential diagnoses with other prominent febrile disorders such as malaria, dengue fever, viral hepatitis, and rickettsial infection. Therefore, proper diagnosis and suitable therapy are based on laboratory results. [1,3]

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Diagnosis of Leptospirosis based on a combination of clinical suspicion and laboratory confirmation. The gold standard diagnosis is the blood and urine PCR test, and the Microscopic Agglutination Test (MAT) for the detection of *Leptospira* DNA is most useful in the early phase of the disease. An Enzyme-Linked Immunosorbent Assay (ELISA) for IgM and IgG antibodies can be done, and its effectiveness depends on the severity of the disease. Before the initiation of antibiotic therapy, the sensitivity of *Leptospira* PCR is about 70-90%, whereas following early antibiotic exposure, the sensitivity declines significantly to around 30-60%; however, the specificity remains consistently high at 95-100% in both situations. Culture can be used to identify the organism, and it has a limitation that it is slow and has low sensitivity. [3,4,5] Treatment is according to the severity of the disease condition and includes empirical therapy as well as doxycycline. [6,7]

2. Case presentation

A 63-year-old male farmer patient presented to the emergency department with complaints of high-grade fever with chills, fatigue, myalgia, headache, and seizure-like episode for 4 days. History of trauma of right eye in 2021 and renal stone in 2015.

He was taken to a local hospital and managed with **intravenous Ceftriaxone 1gm,** and the patient went into hypotension (blood pressure: 90/50 mmHg) and decline in Glasgow Coma Scale (GCS: E1 V1 M1). He was intubated and referred to our hospital for further management.

The patient was admitted to the Medical Department Critical Care Unit for intensive monitoring and further management. On admission, his vital signs were as follows: blood pressure: 100/70 mmHg, heart rate: 100 bpm, respiratory rate: 28/min, temperature: 97.8 °F, and oxygen saturation: 95% on BiPAP support.

Initial laboratory investigations showed an elevated leukocyte count (14540/µL), thrombocytopenia, deranged liver enzymes, renal dysfunction with serum creatinine: 1.05 mg/dL and disproportionate hyperbilirubinemia. Cardiac biomarkers were elevated, including NT-pro BNP (16264.8 pg/mL), troponin I (0.180 ng/mL), and procalcitonin (34.17 ng/mL).

He started with an empirical antibiotic like intravenous Meropenem 2gm every 8 hours and oral Doxycycline 100mg twice daily with inotropes and other medications.

Microbiological investigations including *Leptospira* PCR were not detected, and *Leptospira* Ab, IgM, ELISA was also negative. Blood, urine, and endotracheal (ET) mini bronchoalveolar lavage (Bal) culture reports showed no growth. Scrub typhus and dengue were tested and were not detected. USG abdomen and pelvis was taken and shows hepatomegaly with fatty changes and bilateral medullary renal disease.

Leptospira Ab, IgM, serum, ELISA was again negative, and the third sample became positive on 06 December 2025, confirming the diagnosis. Seroconversion was observed on day 10 of illness, and the presentation was suggestive of severe leptospirosis with multiorgan involvement. The patient's general condition improved and discharge with symptomatic medication.

Serial laboratory parameters are summarized in Table 1

Table 1 Serial Laboratory Parameters

INVESTIGATION	29/11	02/12	06/12	24/12	Reference range
Hemoglobin (g/dL)	14	13.3	13.5	12.6	12-16
TLC (/µL)	14540	10090	6850	5150	4000-11000
Platelet count (x10^5/µL)	0.66	1.65	2.56	1.94	1.5- 4.5
Total bilirubin (mg/dL)	-	2.35	1.8	0.67	0.2-1
Direct bilirubin (mg/dL)	-	0.7	0.46	0.14	0-0.2
Indirect bilirubin (mg/dL)	-	1.65	1.34	0.53	0.2-1
Total protein (g/dL)	-	6.38	6	6.79	6-8

Albumin (g/dL)	-	3.63	3.32	3.51	3.5-4.8
AST (IU/L)	-	42	48	24	10-40
ALT (IU/L)	-	63	64	31	10-40
ALP (IU/L)	-	90	88	85	30-120
Serum creatinine (mg/dL)	1.05	0.7	0.85	0.81	0.6-1.3
Sodium	141	143	138	140	135-145
Potassium	4.18	3.51	3.76	3.86	3.5-5.3
ESR (mm/hr)	-	-	-	39	0-15
CRP (mg/L)	163.20	-	7.6	-	0-10
Procalcitonin (ng/mL)	-	34.17	-	-	0-0.5
NT-pro BNP (pg/mL)		16264.8	-	-	0-125
Reticulocyte count (%)	1.4	1.17	2.53	1.7	0.5-2.5
Lactate Dehydrogenase (U/L)	747	-	-	-	208-378
Leptospira IgM ELISA	Negative (3.4)	Negative (3.90)	-	Positive (13.48)	-
PCR	Not detected	-	-	-	-

TLC- Total Leukocyte Count; ESR- Erythrocyte Sedimentation Rate; CRP- C-Reactive protein; AST- Aspartate Aminotransferase; ALT- Alanine Aminotransferase; ALP- Alkaline Phosphatase

3. Discussion

Leptospirosis is a re-emerging zoonotic infection that exhibits a broad range of clinical features, from mild fever to severe multi-organ dysfunction. Achieving an early, accurate laboratory evaluation is one of the biggest challenges to its treatment. Its non-specific symptoms, which overlap with other endemic illnesses like dengue, malaria, and viral fever, make early identification difficult. In our case report, we describe a patient who presented with clinically suspected symptoms (high-grade fever, myalgia, headache, and other typical symptoms) of Leptospirosis whose initial laboratory data showed negative results for both *Leptospira* IgM and PCR. These findings illustrate the diagnostic difficulty that occurs in regular clinical practice.

The PCR test is the gold standard test used to detect Leptospirosis. One of the major challenges in detecting Leptospirosis is that the patient has undergone antibiotic exposure before hospital admission. This early antibiotic exposure can destroy the bacterial cell wall, which significantly lowers the sensitivity of PCR and other molecular assays. Musso and La Scola explained the time-sensitivity nature of molecular tests in Leptospirosis and the reduction of diagnostic accuracy following antibiotic administration [8]. *Leptospira* PCR demonstrates a sensitivity of about 70-90% prior to antibiotic therapy, which may decline to 30-60% after early treatment, while specificity remains high at 95-100% [5]. This likely explains the early negative molecular findings in our case report.

Similarly, serological testing is inherently limited by time. IgM ELISA, the most used serological test to detect Leptospirosis. Panwala et al. reported that IgM antibody typically remains undetected till several days after infection, and early testing frequently shows false-negative results. Repeated serological screening increases the accuracy of the test, especially if the initial test is conducted within the first week of symptoms [9]. This trend was exactly observed in our patients, with only one third of the IgM tests demonstrating seroconversion, and the first two being negative.

Initial treatment choices typically rely on environmental exposure, occupation, and trends in symptoms instead of a single diagnostic result, and data from research on acute febrile illnesses indicates that laboratory confirmation can be delayed beyond clinical manifestation [10]. Relying only on early negative tests in an endemic area might cause treatment delays and raise the risk of serious side effects such as hepatic and renal impairment.

Our case report demonstrates that Leptospirosis should be approached as a clinical diagnosis in its early stage. This is crucial to take a thorough medical history, determine the exposure risk, and identify distinguishing characteristics. Repeated serological testing and careful clinical observation are essential when the investigation is inconclusive. More

precise diagnosis and immediate action are ensured by combining clinical examination with precisely scheduled laboratory testing, even after a negative Leptospira PCR.

Abbreviations

- PCR: Polymerase Chain Reaction
- ELISA: Enzyme-Linked Immunosorbent Assay
- MAT: Microscopic Agglutination Test

4. Conclusion

PCR is an important technique for the early diagnosis of Leptospirosis; however, negative results may be due to the timing of the sample collection or prior antibiotic administration. This case report demonstrates how crucial clinical assessment and knowledge are to making a diagnosis of Leptospirosis. Particularly in individuals who are received prior to antibiotic exposure, especially bactericidal agents or duration the early stage of their illness, preliminary negative IgM and PCR results may not rule out the disease. Treatment delays and increased risk of complications can result from relying just on laboratory confirmation. Laboratory tests need to be used as a supplementary measure to support the early diagnosis of Leptospirosis, which must depend mainly on clinical symptoms, signs, and exposure history. When initial results are negative but there is still a high degree of clinical suspicion, repeated serological testing is necessary. Empirical therapy should not be postponed while awaiting confirmatory laboratory data.

For all clinicians, particularly those working in endemic areas, the most important thing is that effective management of Leptospirosis depends more on clinical knowledge than on laboratory results.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

The authors certify that they have obtained consent from the patient and their details will be concealed with due effort.

References

[1] Thaipadunpanit J, Chierakul W, Wuthiekanun V, Limmathurotsakul D, Amornchai P, Boonslip S, et al. Diagnostic Accuracy of Real-Time PCR Assays Targeting 16S rRNA and lipl32 Genes for Human Leptospirosis in Thailand: A Case-Control Study. Ahmed N, editor. PLoS ONE. 2011 Jan 24;6(1): e16236. 10.1371/journal.pone.0016236

[2] Haake DA, Levett PN. Leptospirosis in Humans. Current Topics in Microbiology and Immunology [Internet]. 2014 Nov 12;387(25388133):65–97. 10.1007/978-3-662-45059-8_5.

[3] Esteves LM, Bulhões SM, Branco CC, Carreira T, Vieira ML, Gomes-Solecki M, et al. Diagnosis of Human Leptospirosis in a Clinical Setting: Real-Time PCR High Resolution Melting Analysis for Detection of Leptospira at the Onset of Disease. Scientific Reports. 2018 Jun 15;8(1). 10.1038/s41598-018-27555-2.

[4] Signorini ML, Lottersberger J, Tarabla HD, Vanasco NB. Enzyme-linked immunosorbent assay to diagnose human leptospirosis: a meta-analysis of the published literature. Epidemiology and Infection [Internet]. 2013 Jan 1;141(1):22–32. 10.1017/S0950268812001951.

[5] World Health Organization. Human leptospirosis: Guidance for diagnosis, surveillance and control [Internet]. www.who.int. 2003.

[6] Nicholas Philip John Day, DM, FRCP. Leptospirosis: Treatment and prevention. Morven S Edwards, MDJason Stout, MD, editor. Upto date. 2025.

[7] Varughese M, Anjali R, Mohan CA, Thomas P. A study to compare the role of various antibiotics in reducing the mortality and morbidity among patients with leptospirosis. Indian Journal of Medical Sciences. 2025 Feb 19; 77:92–7. 10.25259/IJMS_177_2024.

[8] Musso D, La Scola B. Laboratory diagnosis of leptospirosis: A challenge. Journal of Microbiology, Immunology and Infection [Internet]. 2013 Aug;46(4):245–52. 10.1016/j.jmii.2013.03.001.

[9] Tanvi Panwala, Mulla S, Patel P. Seroprevalence of Leptospirosis in South Gujarat Region by Evaluating the Two Rapid Commercial Diagnostic Kits Against the Mat Test for Detection of Antibodies to Leptospira Interorgan. National Journal of Community Medicine [Internet]. 2026 [cited 2026 Feb 24];2(01):64–70.

[10] Rao P, Sethi S, Sud A, Banga SS, Sharma M. Screening of patients with acute febrile illness for leptospirosis using clinical criteria and serology. The National medical journal of India [Internet]. 2005;18(5):244–6.