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# SEVERE LEPTOSPIROSIS WITH APYREXIA AND AN ATYPICAL PRESENTATION: RAPID PROGRESSION TO MULTI-ORGAN FAILURE

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## ABSTRACT

*Introduction:* Leptospirosis is a common zoonotic infection in tropical regions with diverse clinical manifestations. Fever occurs in 89–100% of cases, while afebrile cases are extremely rare and seldom reported in the literature, accounting for less 1% of severe leptospirosis cases, posing a diagnostic challenge in clinical practice.

*Case description:* we report on a 43-year-old male farmer from northern Vietnam who was admitted with rapidly progressive jaundice and severe acute kidney injury following exposure to contaminated paddy field water. Notably, the patient remained afebrile throughout the disease course – an atypical presentation rarely seen in severe leptospirosis. The incubation period was extremely short (one day) with rapid progression to multi-organ failure within three days. Diagnosis was confirmed serologically with Leptospira IgM >100 U/ml and a more than 4-fold increase in IgG titre (from 10.4 to 72.3 U/ml) according to WHO criteria. The SOFA score at admission was 9 points. The patient responded well to combination antibiotic therapy, corticosteroids and renal replacement therapy, achieving complete recovery after 24 days.

*Conclusion:* This case emphasises the importance of not excluding leptospirosis even in the absence of fever, particularly in endemic areas with occupational risk factors. Markedly elevated bilirubin disproportionate to AST, ALT and rapidly progressive acute kidney injury are important suggestive signs.

## KEYWORDS

Leptospirosis, acute kidney injury, afebrile leptospirosis, Weil's disease

## LEARNING POINTS

- Distinguish between fever syndrome (systemic inflammatory symptoms) and pyrexia (elevated body temperature) – patients can have severe infections with fever syndrome but normal body temperature.
- A national early warning score (NEWS2) based on vital signs may fail to capture disease severity in afebrile presentations, while sequential organ failure assessment (SOFA) scores provide better risk stratification.
- Recognise the diagnostic pattern in severe leptospirosis: markedly elevated bilirubin (>580 µmol/l) with disproportionately mild liver enzyme elevation (AST <200 U/l) combined with rapidly progressive acute kidney injury.

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## INTRODUCTION

Leptospirosis is a zoonotic bacterial infection caused by spirochetes of the genus *Leptospira*, with worldwide distribution. Although incidence rates are increasing in developed countries, the disease burden primarily affects tropical, subtropical and developing regions, particularly Southeast Asia. It is estimated that there are approximately 1.03 million cases and 58,900 deaths annually worldwide[1]. In Vietnam, leptospirosis is one of the common infectious diseases in rural areas with high incidence rates in the Mekong Delta provinces[2].

The clinical manifestations of leptospirosis are highly diverse, ranging from asymptomatic infection to severe multi-organ dysfunction. Approximately 85–90% of cases present with mild symptoms characterised by non-specific acute fever, while 10–20% progress to severe forms known as Weil's disease, characterised by jaundice, acute kidney injury and haemorrhage[3]. Fever is the earliest and most important sign, occurring in 89–100% of patients in studies, with temperature typically over 38.5°C during the acute phase[4].

The incubation period is usually 5–14 days (average 10 days) after exposure to the infectious source. The disease progresses through two phases: the septicaemic phase with high fever, headache, myalgia and sometimes flu-like symptoms; and the immune phase with damage to target organs including liver and kidneys, and pulmonary haemorrhage, which can be fatal[5].

We report a case of severe leptospirosis with atypical features including absence of fever, extremely short incubation period (one day) and rapid progression to multi-organ failure, to raise awareness about atypical presentations of the disease.

## CASE DESCRIPTION

A 43-year-old male farmer from a northern province of Vietnam had no significant medical history, no chronic diseases, no alcohol consumption and no family history of liver or kidney disease; he was fully vaccinated against hepatitis B. Approximately five days before hospital admission, he worked in rice fields and had direct contact with potentially contaminated paddy field water.

*Day 0 (exposure day):* Field work was finished at 5:00 PM.

*Day 1:* There was an onset of fatigue, generalised myalgia, poor appetite and mild nausea. Body temperature was measured at home: 37°C on a digital thermometer.

*Days 1–3 (examination at the district hospital):* initial laboratory tests showed mild elevation of aspartate aminotransferase (AST) 54 U/l, alanine transaminase (ALT) 62 U/l and creatinine 101 µmol/l.

*Day 3:* clinical deterioration displayed progressive jaundice, icteric sclera, nausea and frequent vomiting. Repeat laboratory tests revealed: total/direct bilirubin: 487/289 µmol/l; urea: 45 mmol/l; creatinine: 856 µmol/l; mild elevation of liver enzymes disproportionate to bilirubin elevation.

A diagnosis of acute liver failure with acute kidney injury was made and the patient was transferred to the National Hospital for Tropical Diseases.

*Day 4 (admission status at our hospital):* the patient was alert (Glasgow Coma Score, GCS 15), haemodynamically stable (blood pressure: 125/84 mmHg, pulse: 85 bpm), temperature 37°C, $SpO_2$ 98% without oxygen support, with no signs of peripheral vasoconstriction or hypothermia. The national early warning score (NEWS) was 0 points (low risk), and the sequential organ failure assessment (SOFA) score was 9 points (severe organ dysfunction) *(Table 1)*. A physical examination revealed a deeply jaundiced patient, conjunctival congestion and markedly decreased urine output (200 ml/24h). A cardiac examination showed regular heart sounds without murmurs. Lung examinations were clear without rales. Abdomen examination was soft with hepatomegaly 2 cm below the costal margin and no splenomegaly. A neurological examination showed no signs of meningeal irritation.

*Days 4–7:* supportive treatment and ceftriaxone 2 g/24h, intermittent haemodialysis filtration daily.

*Day 7:* due to suspected leptospirosis (epidemiological factors plus high bilirubin/ALT ratio), doxycycline 100 mg twice daily and methylprednisolone 1 mg/kg/day were added, Leptospira IgM and IgG tests were ordered.

*Day 9:* leptospira IgM: >100 U/ml (strongly positive), Leptospira IgG: 10.4 U/ml

*Day 13:* leptospira IgG: 72.3 U/ml (more than 4-fold increase, confirmed diagnosis according to WHO criteria). Final diagnosis: acute severe leptospirosis (Weil's disease) without fever.

*Treatment response and outcomes:*

*Days 8–12:* significant improvement with urine output increasing to 3,000 ml/24h, kidney function: urea 26.6 mmol/l, creatinine 420 µmol/l, procalcitonin was decreased to 2.2 ng/ml.

*Day 24:* complete recovery with resolution of jaundice and icteric sclera, urine output 2,000 ml/day, no proteinuria, creatinine 156 µmol/l (near normal); the patient remained afebrile throughout treatment (temperature 36.2–37.1°C) *(see Table 2 and Fig. 1)*.

The treatment regimen was doxycycline for 14 days and methylprednisolone for 10 days (tapered); total number of dialysis sessions: 8.

After 24 days of inpatient treatment, the patient achieved complete recovery with resolution of jaundice, urine output 2,000 ml/day and no oedema, and he was afebrile with stable vital signs. He was transferred to a lower-level facility for continued monitoring.

Temperature monitoring protocol and measurement methodology:

- *Home (day 1):* digital thermometer (axillary route) 37.0°C;
- *District hospital (days 1–3):* mercury thermometer, axillary measurement every six hours;
- *Our hospital (days 4–24):* medical-grade mercury thermometer, axillary measurement.

| Parameter | Value | Points |
|---|---|---|
| **NEWS2** | | |
| Oxygen saturation (% room air) | 98 | 0 |
| Supplemental oxygen | None | 0 |
| Systolic blood pressure (mmHg) | 125 | 0 |
| Heart rate (bpm) | 85 | 0 |
| Temperature (°C) | 37.0 | 0 |
| Alert, vocal, pain and unresponsive score | Alert | 0 |
| Total | | 0 points (low risk category) |
| **SOFA score** | | |
| Respiratory (PaO2/FiO2 ratio) | >400 | 0 |
| Coagulation: platelets (×109/l) | 101 | 1 |
| Liver: total bilirubin (µmol/) | 582 | 4 |
| Cardiovascular | No vasopressor requirement | 0 |
| Central nervous system: GCS | 15 | 4 |
| Renal: creatinine (µmol/l) | 894 | |
| Total | | 9 points (severe organ dysfunction) |
| **Parameter** | **Value** | **Reference range** |
| **Haematology** | | |
| Haemoglobin (g/l) | 108 | 120–160 |
| WBC (×$10^9$/l) | 15.8 | 4–10 |
| Neutrophils (%) | 84 | 50–70 |
| Lymphocytes (%) | 12.3 | 20–40 |
| Platelets (×$10^9$/l) | 101 | 150–450 |
| **Renal function** | | |
| Urea (mmol/l) | 47 | 2.5–7.5 |
| Creatinine (µmol/l) | 894 | 44–120 |
| Estimated glomerular filtration rate (ml/min/1.73$m^2$) | 8 | > 90 |
| **Liver function** | | |
| Total bilirubin (µmol/l) | 582 | 3.4–21 |
| Direct bilirubin (µmol/l) | 432 | 0–8 |
| AST (U/l) | 122 | 8–33 |
| ALT (U/l) | 241 | 4–36 |
| Albumin (g/l) | 28 | 35–54 |
| Prothrombin time (%) | 104 | 70–140 |
| **Other parameters** | | |
| Lactate dehydrogenase (U/l) | 456 | 135–214 |
| Creatine kinase (U/l) | 334 | 38–174 |
| Procalcitonin (ng/ml) | 4.33 | <0.25 |
| C-reactive protein (mg/l) | 98 | <5.0 |
| **Urinalysis** | | |
| Protein | 3+ | Negative |
| RBC | Positive | Negative |
| WBC | Positive | Negative |
| **Test** | **Result** | **Interpretation** |
| **Viral hepatitis panel** | | |
| HAV IgM | Negative | No acute hepatitis A |
| HBsAg | Negative | No hepatitis B infection |
| HCV Ab | Negative | No hepatitis C infection |
| HEV IgM | Negative | No acute hepatitis E |
| **Other infections** | | |
| Blood cultures (two sets) | Negative after five days | No bacteraemia |
| Malaria testing | Negative | No malaria |
| Dengue NS1 | Negative | No dengue infection |
| Dengue IgM | Negative | No recent dengue |
| Imaging | Chest X-ray and abdominal ultrasound were normal | - |

**Abbreviations:** WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; RBC, red blood cell; HAV IgM, hepatitis A virus immunoglobulin M; HBsAg, hepatitis B surface antigen; HCV Ab, hepatitis C virus antibody; HEV IgM, hepatitis E virus immunoglobulin M; Dengue NS1, dengue non-structural protein 1; Dengue IgM, Dengue virus immunoglobulin M.

*Table 1. Severity assessment, early warning scores and laboratory results on admission (day 4).*

Standardised protocol at our institution:

- *Location:* axillary (standard method at our facility);
- *Duration:* thermometer placed for a minimum of 5 minutes;
- *Conditions:* dry axilla, patient rested for ≥15 minutes before measurement;
- *Frequency:* every 4 hours (06:00, 10:00, 14:00, 18:00, 22:00, 02:00);

*Personnel:* trained nursing staff following standard protocol.

Temperature trends over time:

- *Days 1–3 (district hospital):* 36.8–37.1°C (axillary);
- *Days 4–7:* 36.5–37.0°C (axillary);
- *Days 8–15:* 36.2–37.1°C (axillary);
- *Days 16–24:* 36.4–37.0°C (axillary).

Quality assurance:

- Mercury thermometers calibrated according to Ministry of Health regulations, Vietnam;
- Continuous monitoring by an experienced nursing team.

The maximum recorded temperature throughout the entire illness course was 37.1°C, with consistent readings between 36.2 and 37.1°C during the 24-day hospitalisation period.

Fever syndrome assessment – despite the absence of pyrexia (temperature ≥38°C), the patient exhibited several components of the fever syndrome including:

- Generalised myalgia (present from day 1);
- Fatigue and malaise (present from day 1);
- Anorexia (present from day 1);
- Notably absent: rigors, sweats, subjective feelings of hot/cold alternation, headache.

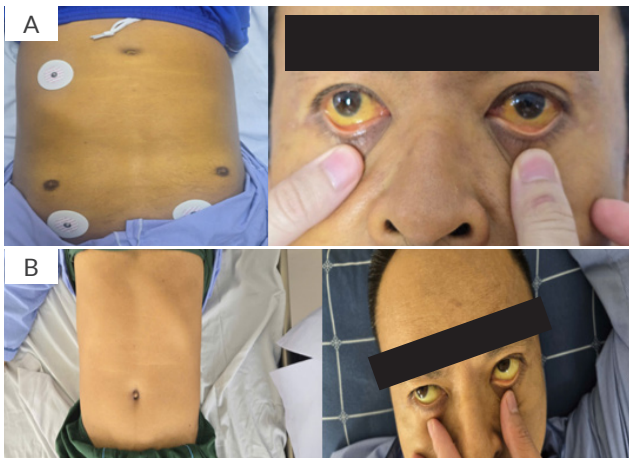



*Figure 1. Patient's skin and eyes A) on admission day and B) after 20 days of treatment.*

## DISCUSSION

This case illustrates a fundamental clinical concept that is often overlooked in infectious disease practice: the distinction between fever syndrome and pyrexia. Fever syndrome encompasses the constellation of symptoms resulting from systemic inflammatory response including myalgia, fatigue, anorexia and malaise, while pyrexia specifically refers to elevation of core body temperature above the normal range (over 38°C). Our patient demonstrated classic fever syndrome components without pyrexia, a presentation that challenges traditional diagnostic paradigms. The absence of thermoregulatory dysfunction (normal temperature, heart rate and respiratory rate) despite severe systemic inflammation (C-reactive protein 98 mg/l, procalcitonin 4.33 ng/ml) suggests selective impairment of hypothalamic pyrogenic pathways while other inflammatory cascades remained intact. This dissociation has important clinical implications. Traditional early warning scores such as NEWS2, which heavily weight vital sign abnormalities, failed to capture disease severity (NEWS2 = 0) compared to organ-

| Treatment day | Day 1 | Day 5 | Day 13 | Day 24 | Reference range |
|---|---|---|---|---|---|
| RBC (T/l) | 3.84 | 3.42 | 3.13 | 2.50 | 4.2–5.9 |
| Haemoglobin (g/l) | 108 | 95 | 88 | 71 | 120–160 |
| WBC | 15.8 | 15.1 | 15.1 | 6.8 | 4–10 |
| Neutrophils (%) | 84.6 | 47.3 | 49.0 | 46.1 | 50–70 |
| Lymphocytes (%) | 12.3 | 46.0 | 44.2 | 40.1 | 20–40 |
| Platelet count (×10⁹/l) | 101 | 177 | 478 | 356 | 150–450 |
| Prothrombin (%) | 104 | 74 | 110 | 100 | |
| Urea (mmol/l) | 47.2 | 26.6 | 30.0 | 7.2 | 2.5–7.5 |
| Creatinine (µmol/l) | 894 | 420 | 461 | 156 | 44–120 |
| Total bilirubin (µmol/l) | 582 | 470 | 196 | 61.7 | 3.4–21 |
| Direct bilirubin (µmol/l) | 432 | 379 | 138 | 43.4 | 0–8 |
| AST (U/l) | 122 | 69 | 38 | 39 | 8–33 |
| ALT (U/l) | 241 | 115 | 57 | 62 | 4–36 |
| Albumin (g/l) | 28 | 22 | 40 | 38 | 35–54 |
| Procalcitonin (ng/ml) | 4.33 | 2.55 | - | - | <0.25 |
| Ammonia (µmol/l) | 34 | - | - | - | 11–32 |
| Na+ (mmol/l) | 126 | 130 | 138 | 135 | 135–145 |
| K+ (mmol/l) | 4.4 | 4 | 4.2 | 3.8 | 3.5–5 |

**Abbreviations:** WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; RBC, red blood cell; Na+, sodium ions; K+, potassium ions.

*Table 2. Peripheral blood laboratory characteristics.*

specific dysfunction scores such as SOFA (score = 9) *(Table 1)*. This discordance explains why afebrile severe infections can be missed or underestimated in clinical practice, particularly in resource-limited settings where biochemical markers may not be readily available. This case adds to the limited literature on afebrile severe bacterial infections and emphasises that the absence of fever should not exclude consideration of serious infectious diseases, particularly in endemic areas with appropriate epidemiological risk factors. This case also emphasises the importance of biochemical markers over vital signs in certain clinical scenarios.

An important differential consideration in afebrile severe infections is whether the absence of fever results from impaired peripheral perfusion or septic shock with hypothermia. In our patient, careful assessment demonstrated normal perfusion parameters: capillary refill time of less than 2 seconds throughout hospitalisation; strong, equal peripheral pulses bilaterally; warm, well-perfused skin despite jaundice; normal mental status (GCS 15) indicating adequate cerebral perfusion; oliguria secondary to acute kidney injury rather than hypoperfusion. Critically, the patient never developed hypothermia (temperature never under 36°C) and maintained stable thermoregulation (36.2–37.1°C range) throughout the clinical course. This pattern excludes shock-related temperature dysregulation and supports the hypothesis of selective impairment of pyrogenic pathways while maintaining normal thermoregulatory capacity. The normal cardiovascular parameters (heart rate 85 bpm, blood pressure 125/84 mmHg, no vasopressor requirement) further confirm that the afebrile presentation was not secondary to circulatory compromise but rather represents a genuine dissociation between inflammatory response and temperature regulation in this patient's presentation of severe leptospirosis.

This represents an atypical case of leptospirosis, which has three notable characteristics that pose diagnostic challenges for clinicians.

First is the extremely short incubation period (one day): unlike the classic incubation period of 5–14 days, the patient developed symptoms only one day after exposure to paddy field water. This may suggest a large bacterial inoculum or particular host susceptibility, causing rapid and severe disease progression from the onset. According to some recent case reports, the incubation period may be shorter in severe infections with high bacterial loads.

Second is the absence of fever throughout the disease course: fever is the most common symptom of leptospirosis, occurring in 89–100% of patients. The absence of fever in this case is extremely rare and may lead to misdiagnosis, particularly in Vietnam where hepatitis B prevalence exceeds 8% of the population. Some recent studies have reported afebrile leptospirosis cases, especially in elderly patients or those with immune disorders.

Third is the extremely rapid progression to multi-organ failure: the patient rapidly developed severe jaundice with acute kidney injury, with a critical condition occurring rapidly within a few days. Notably, the bilirubin-to-liver enzyme ratio was very high (bilirubin more than 580 µmol/l while AST was only 122 U/l) – a characteristic feature of severe leptospirosis due to mechanisms primarily involving cholestasis and haemolysis rather than hepatocyte necrosis[6].

Leptospirosis causes renal damage through complex mechanisms. The outer membrane protein LipL32 of Leptospira directly binds to toll-like receptor-2 (TLR-2) on renal tubular epithelial cells, activating intracellular inflammatory pathways including TNF-α production and nuclear factor kappa B activation, leading to acute and chronic kidney injury[7].

Jaundice in leptospirosis results from impaired bile excretion and cellular membrane damage, rather than widespread hepatocyte necrosis as seen in typical viral hepatitis[6]. Hepatic capillariasis causes oedema and obstruction of small bile ducts, leading to cholestasis. Damage to bile canaliculi, endoplasmic reticulum, Golgi apparatus and microvilli reduces bile excretory capacity. Mild haemolysis due to red blood cell damage also contributes to increased indirect bilirubin but is not the primary mechanism. A novel mechanism proposed by Miyahara et al. from hamster models suggests that Leptospira migrates through intercellular spaces, causing bile leakage from bile canaliculi into blood – contributing to the explanation of why conjugated bilirubin is markedly elevated while liver enzymes (AST/ALT) show only mild elevation, which is a characteristic suggestive sign in severe leptospirosis[8].

Diagnosis of leptospirosis is based on the combination of clinical manifestations, epidemiological history and confirmatory laboratory tests. In this case, the more than 4-fold increase in IgG titre (from 10.4 to 72.3 U/ml) according to WHO criteria provides definitive diagnostic evidence[9,10]. Elevated procalcitonin (4.33 ng/ml) is also suggestive of severe bacterial infection, although not specific for leptospirosis.

Treatment of severe leptospirosis includes specific antibiotics and aggressive supportive care. Recent studies suggest that combination therapy with ceftriaxone (for acute phase) and doxycycline (for prolonged phase) is effective. The role of corticosteroids in leptospirosis remains controversial, but some studies suggest potential benefits in severe cases with systemic inflammation. Intermittent haemodialysis is an important supportive measure in severe acute kidney injury.

Poor prognostic factors in severe leptospirosis include advanced age, acute kidney injury, coagulopathy, pulmonary haemorrhage and septic shock. This case had a favourable prognosis due to timely diagnosis and treatment. This case emphasises important clinical lessons for physicians:

1. Do not exclude leptospirosis even in the absence of fever, especially in endemic areas with occupational risk factors.
2. Elevated procalcitonin, elevated direct bilirubin and minimal liver enzyme elevation are important suggestive signs.

3. Carefully investigate epidemiological factors when encountering cases of acute liver/kidney failure of unknown aetiology.
4. Proactively initiate specific empirical antibiotic treatment in suspected cases.

## CONCLUSION

We report a case of severe leptospirosis with atypical presentation including absence of fever, extremely short incubation period and rapid multi-organ failure progression. This case adds evidence to the diverse manifestations of leptospirosis and emphasises the importance of clinical vigilance, careful epidemiological assessment and timely use of specific antibiotics to improve prognosis.

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