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Case Report

Leptospirosis Presenting with Features of Thrombotic Microangiopathy

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Leptospirosis is an exceptionally rare infectious disease in the Republic of Ireland. Leptospirosis can present with or mimic thrombotic microangiopathies (TTP/HUS). A 48-year-old male presented to a peripheral hospital with a short history of diarrhoea, anaemia, hyperbilirubinemia, raised lactate dehydrogenase, thrombocytopenia, and severe acute kidney injury and was transferred to our tertiary care kidney centre. A form of acute thrombotic microangiopathy (TMA) was suspected. However, no schistocytes were seen on the blood film, and the reticulocyte count was depressed. A kidney biopsy was performed before initiating any potential treatment which revealed acute interstitial nephritis (AIN). Leptospirosis was considered and subsequently serologically confirmed. The patient was managed with antimicrobials and supportive therapy. Acute kidney injury is common in leptospirosis and is often due to AIN. Initial presentation can mimic TMA; however, a differential diagnosis of leptospirosis should be considered even in nonendemic areas due to re-emergence of the disease.

1. Background

Systemic infections can mimic the features of thrombotic microangiopathies (TMAs) [1]. Leptospirosis is a common tropical zoonotic infection, but its incidence in the Republic of Ireland (ROI) is less than 0.4/100,000 population. In its fulminant form, leptospirosis can present with multiorgan failure, pulmonary haemorrhage, acute liver injury, acute kidney injury (AKI), and haematological abnormalities being a prominent feature which may overlap with other disorders such as TTP [2]. The reported kidney biopsy findings in leptospirosis-associated AKI suggest acute interstitial nephritis (AIN) with acute tubular injury as being the most common histopathological lesion [3]. We report a rare case of leptospirosis with a clinical presentation of features consistent with TMA and an acute kidney injury with a kidney biopsy showing features of AIN.

2. Case Presentation

A 48-year-old Caucasian man presented to the emergency department with lethargy, malaise, myalgias, nausea, calf pain, loss of appetite, and decreased urine output. This was preceded by 1 episode of nonbloody diarrhoea and fever following consumption of chicken at a barbeque 10 days beforehand.

He had no significant past medical or surgical history. He was not on any regular medication but had used an antibiotic metronidazole prior to hospital admission. He denied the use of any over-the-counter, herbal, or illicit drug use. He had no history of known allergies. He smoked 5–10 cigarettes per day for the last 10 years and consumed 20–30 units of alcohol per week. He worked in information technology and had no recent history of travels or contact with pets or animals.

He had a blood pressure check while seated 131/85, heart rate 88 beats per minute, respiratory rate 16 per minute, temperature 36.7 celsius, and oxygen saturation 98% on ambient room air. His further physical examination showed pallor and jaundice with no evidence of conjunctivitis or neurological manifestations. He had no other remarkable findings on systemic examination. His initial investigation results are shown in Table 1.

His laboratory features showed AKI KDIGO stage 3, thrombocytopenia, anaemia, hyperbilirubinemia, raised lactate dehydrogenase (LDH), and active urinary sediments suggesting an acute TMA. He was transferred to our hospital for further investigations and treatment with a working diagnosis of an acute TMA and a possible requirement for haemodialysis and plasmapheresis.

On arrival to the tertiary care hospital, his haemodynamic status was stable. He had relatively preserved urine output without any urgent indication for the initiation of renal replacement therapy. With a recovering kidney function and no schistocytes on a blood film (schistocytes on blood film are usually seen in TMA), it was decided not to commence plasmapheresis. A kidney biopsy was performed to clarify the underlying diagnosis. He was commenced on antibiotics for a presumed abdominal or urinary source of infection.

The kidney biopsy showed no features of TMA but severe AIN. The inflammation included eosinophils; Grocott's methenamine silver stain was negative for leptospira organisms (Figures 1, 2(a), and 2(b)). Eosinophilic-rich AIN is typically seen due to a drug reaction; however, clinical and laboratory features suggested a systemic cause, particularly leptospirosis. Despite being extremely rare in ROI, diagnostic tests for leptospirosis were sent.

Our patient did not recall a history of exposure to any animals. He had a fall in a small lake about 2 weeks prior to symptoms onset. The lake water was likely the source of his leptospira infection.

He had a serological test IgM positive for leptospirosis, and his microscopic agglutination test (MAT) result confirmed leptospirosis (Table 2).

3. Management

In this case, patient's acute kidney injury improved without renal replacement therapy or plasmapheresis. He was commenced on intravenous fluid and empirical penicillin antibiotic treatment for presumed abdominal or urinary source of infection. His creatinine, bilirubin, and platelet trends are presented in Figure 3.

Our patient's kidney biopsy showed AIN with no significant medication exposure prior to kidney biopsy. In view of improvement in kidney functions, a decision was made not to commence steroids treatment and to await leptospirosis results.

Once his diagnosis of leptospirosis was confirmed, the antibiotic regimen was switched to doxycycline 100 mg twice a day for a duration of one week. The patient had a follow-up in a clinic after two weeks with resolution of all his symptoms and normal blood results.

Table 1: Investigation results.

Test	Results (reference range)
Creatinine	623 (59–104 μmol/L)
Urea	22 (2.8–8.1 mmol/L)
Sodium	125 (133–146 mmol/L)
Potassium	3 (3.5–5.3 mmol/L)
Hb	8.8 (13–17.5 gm/dL)
WBC	8.42 (4–11·10^9/L)
Platelets	73 (140–400·10^9/L)
Neutrophils	6.59 (2–7.5·10^9/L)
Lymphocytes	1.02 (1–4·10^9/L)
CRP	80 (0–5 mg/L)
ALT	48 (0–41 I.U./L)
AST	44 (0–40 U./L)
Alkaline phosphatase	75 (40–130 I.U./L)
GGT	41 (0–59 I.U./L)
Bilirubin	134 (0–21 μmol/L)
LDH	355 (135–225 I.U./L)
Reticulocyte count	8 (10–80 10^9/L)
Fibrinogen	4.5 (1.9–3.5 g/L)

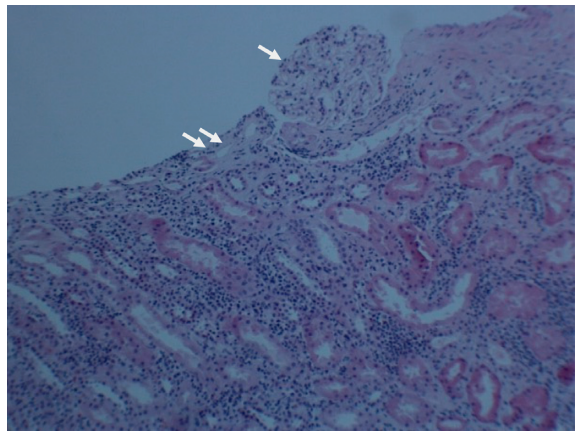
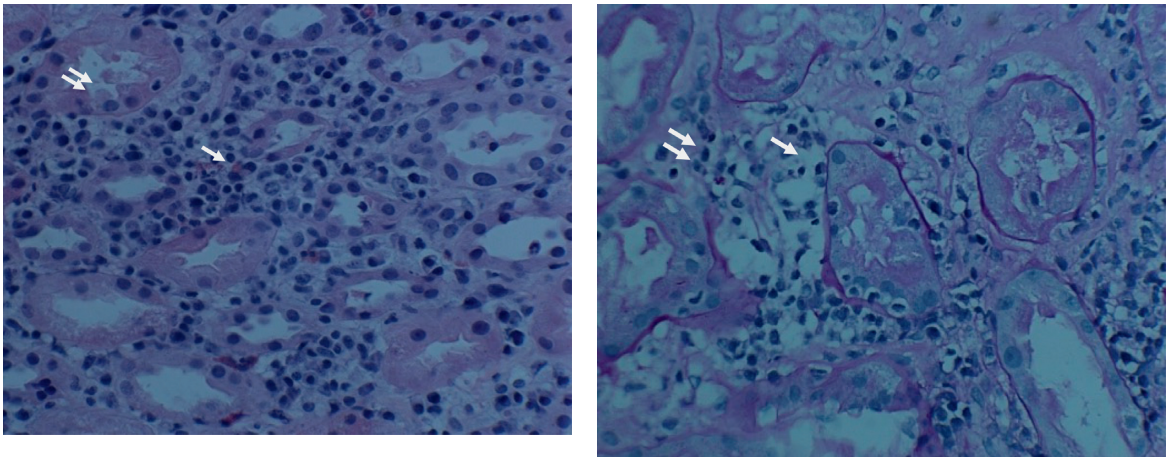


Figure 1: Hematoxylin and eosin staining (H&E)* with 100 magnification. The image shows a normal glomerulus (single arrow) and arteriole (double arrow) moderate tubulointerstitial inflammation and oedema.

4. Discussion

Leptospirosis is a zoonotic disease caused by a spirochete of the genus *Leptospira interrogans* [4]. Rodents and other animals (pigs, goats, cattle, horses, and dogs) are the natural reservoirs of this disease. The transmission of this infection results from contact with contaminated water, soil, or direct contact with animal urine or blood. An outbreak of leptospirosis was reported in triathlon athletes who were infected from the lake water [5]. In our case, the patient probably got infected when he accidentally fell into the lake.

The spirochetes cause infection by entering through skin abrasions, conjunctiva, and oral mucosal route as they cannot penetrate through intact skin [4]. The disease is commonly prevalent in the tropical region but does have a worldwide distribution. The domestic animal vaccination and eradication of rodents are important control measures which prevent the spread of infection. There is no current vaccine available for human use.



(a) (b)

Figure 2: (a) Hematoxylin and eosin staining (H&E)* with 400 magnification. The image shows tubulointerstitial inflammation with lymphocytes, plasma cells, and some eosinophils (single arrow) interstitial oedema with wide spacing of the tubule (double arrow). (b) Periodic acid Schiff (PAS)* with 600 magnification. The image shows moderate tubulitis with lymphocytes in the wall of the tubule (single arrow) and tubule destruction (double arrow) with fragmented tubular basement membrane.

Table 2: Investigation results.

Investigations	Result
Blood film	Target cells, hypersegmented neutrophils, and hypochromasia without schistocytes or spherocytes
Hep A, Hep B, Hep C, HIV, CMV	Negative
Vasculitis screen (ANCA, C3, C4, and CTD)	Negative
Urine analysis	Blood+ and protein+
Midstream urine (MSU)	No growth
Chest X-ray	Nil acute
Ultrasound kidneys	No evidence of obstruction or any other abnormality
Echocardiogram	No valvular or other abnormalities including evidence of infiltrative diseases
CT TAP	No mass, lymphadenopathy, or organomegaly incidental finding of liver haemangioma
Bone marrow biopsy	Maturation of all cell lines was unremarkable
Kidney biopsy	Acute eosinophil-rich tubulointerstitial nephritis
Microscopic agglutination test	Positive for leptospirosis
Serum protein electrophoresis	No abnormal bands

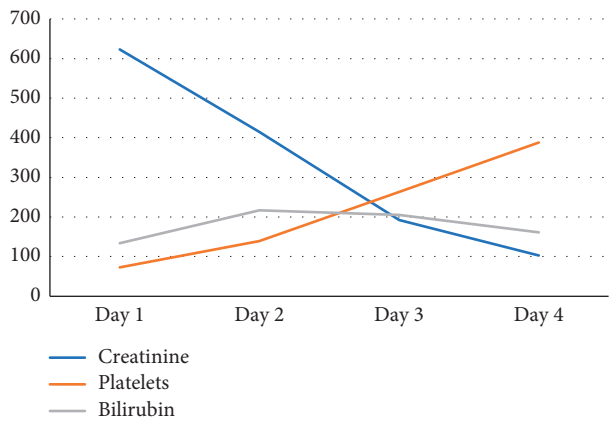


Figure 3: Trends of creatinine, platelets, and bilirubin.

The presentation of this disease is very variable with the spectrum of disease ranging from a mild self-limiting infection to a severe life-threatening infection with acute kidney injury, pulmonary haemorrhage, and haematological abnormalities (Weil's disease) which is associated with a mortality rate of over 20% [6].

Systemic infections can show similar features as acute thrombotic microangiopathy (TMA) with some reports of leptospirosis-induced TMA [1, 2]. A TMA (TTP/HUS) registry showed 7% of patients presented with features of TMA were subsequently diagnosed with a systematic infection [1]. A suggested approach to unmask an underlying aetiology for AKI with jaundice includes consideration of differential diagnosis, as shown in Table 3.

The kidney manifestations of leptospirosis mostly include microscopic haematuria, proteinuria, and

Table 3: Differential diagnosis of acute kidney injury with jaundice.

Acute thrombotic microangiopathy (TMA) includes TTP and HUS
Thrombotic thrombocytopenic purpura (TTP)
Haemolytic uremic syndrome (HUS)
Atypical haemolytic uremic syndrome (aHUS)
Hepatorenal syndrome
Rhabdomyolysis
Leptospirosis/Weil's disease
Malaria

nonoliguric AKI [7]. The electrolyte abnormalities of hyponatremia, hypomagnesaemia, and hypokalaemia are also seen in this disease attributed to kidney tubular damage associated with the disease [8]. The kidney injury usually has multifactorial aetiologies secondary to critical illness, AIN, direct nephrotoxic damage to tubule by leptospira organism or toxin, hyperbilirubinemia, and rhabdomyolysis [3, 8]. Few cases result in chronic kidney disease but rarely end up in dialysis-dependent chronic kidney disease [9].The common histologic changes in kidney biopsy include AIN, bile acid cast nephropathy, and acute tubular necrosis [10].

The treatment of this infection includes supportive care and antibiotic therapy. The antibiotics used for the treatment include penicillin, cephalosporin, doxycycline, and azithromycin [11]. Doxycycline is usually the preferred antibiotic unless contraindicated due to allergies or pregnancy [11].

5. Conclusion

Leptospirosis is an important consideration in patients presenting with suspected features of acute TMA (TTP/HUS). In nonendemic regions, the re-emergence of the disease results in new cases. The management is primarily antibiotics and supportive therapy. AKI commonly has nonoliguric association with hypokalaemia, and kidney biopsy shows AIN and acute tubular injury.

Additional Points

Learning Points. 1. Leptospirosis can mimic thrombotic microangiopathies and should be part of differential diagnosis even in a nonendemic area. 2. The most common histological finding on kidney biopsy is acute interstitial nephritis and acute tubular necrosis. 3. Acute kidney injury has often nonoliguric association with hypokalaemia and hyponatraemia. Active urinary sediment with blood and protein is commonly seen on urinalysis.

Consent

Written informed consent for the paper to be published (including images) was obtained from the patient. He understood that the information should be published without his name attached, but that full anonymity could not be guaranteed. He understood that the text and any pictures published in the article would be freely available on the Internet and may be seen by the general public. The pictures and text may also appear on other websites or in print and may be translated into other languages or used for commercial purposes.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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