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Confronting Leptospirosis: A Tropical Illness Presenting with Thrombotic Microangiopathy and Multiorgan Dysfunction

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ABSTRACT

This case report outlines the presentation and clinical course of a 28-year-old lady with previously unremarkable health, who developed symptoms including fever, headache, gastrointestinal distress, and jaundice. Her condition rapidly deteriorated, culminating to multisystem involvement in the form of severe anaemia, acute kidney injury, thrombocytopenia, and acute respiratory distress syndrome (ARDS). The aetiology was confirmed as leptospirosis. Despite optimum therapeutic measures, including mechanical ventilation and plasmapheresis in view of suspected thrombotic microangiopathy, the patient succumbed to the complications of severe ARDS. This case underscores the imperative of early identification and tailored management strategies for intricate multi-system involvement in conditions like leptospirosis.

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Introduction

Leptospirosis, caused by the spirochete bacteria of the genus Leptospira, stands as a significant zoonotic disease with global implications. This infectious ailment is characterized by a broad range of clinical manifestations, spanning from mild febrile illness to severe multiorgan dysfunction. The burden of leptospirosis is particularly pronounced in tropical and subtropical regions, where environmental conditions facilitate its transmission. With an estimated one million severe cases occurring annually worldwide, this disease represents a substantial public health concern [1].

Historically, leptospirosis has been classified into two main species, the pathogenic Leptospira interrogans and the non-pathogenic L.biflexa. The disease is commonly associated with rodents, particularly rats, which serve as primary reservoirs. However, domestic dogs, cattle, pigs, and wild mammals can also contribute to its transmission. Given its diverse reservoirs and wide distribution, leptospirosis poses a challenge in terms of prevention and control [2].

Among the diverse complications associated with severe leptospirosis, thrombotic microangiopathy (TMA) has emerged as a rare yet significant haematological phenomenon. TMA encompasses a spectrum of disorders characterized by thrombocytopenia, microangiopathy, and subsequent organ damage. One notable manifestation of TMA is thrombotic thrombocytopenic purpura (TTP), which manifests with a complex set of symptoms including fever, neurological disturbances, renal failure, anaemia, and thrombocytopenia [3].

Bacterial infections, including leptospirosis, have been observed in patients presenting with TMA and admitted to intensive care units (ICUs). Such infections can potentially act as triggers for TMA, complicating the clinical picture and management approach. Therefore, a comprehensive evaluation for underlying infections becomes crucial in the care of TMA patients, whether the condition arises idiopathically or in association with other medical conditions [4].

Case Description

A 28-year-old married female, employed as a homemaker presented to the emergency department with a six-day history of sudden-onset high-grade intermittent fever accompanied by chills, malaise, myalgia, and a holo cranial dull aching headache. The patient

reported no diurnal fever variation, photophobia, phonophobia, seizures, cough, dyspnoea, dysuria, vaginal discharge, or genital bleeding. Concurrently, she experienced acute-onset loose stools with around six episodes per day for the past three days, characterized by non-bloody and non-foul-smelling stool consistency. Additionally, she encountered 2-3 episodes of non-bilious, non-projectile, non-bloody vomiting. Over the course of three days, she noticed a gradual yellowish discoloration of the sclera and a decrease in urine output, accompanied by passage of highly coloured urine. There were no reported episodes of clay-coloured stool, malena, hematuria, joint swelling, joint pain, or photosensitivity. Her family history was negative for similar symptoms. Travel history was negative, and no pets were present at home. However, she did have frequent exposure to water bodies near her residence. She had previously sought medical attention at a local hospital where she was found to have leucocytosis and elevated levels of urea and creatinine. Conservative management involving antibiotics and intravenous fluids was initiated for a day.

Subsequently, she developed progressive dyspnoea without chest pain, orthopnea, paroxysmal nocturnal dyspnoea (PND), cough, or palpitations. Upon presentation at emergency, the patient exhibited hypotension, tachycardia, and tachypnoea. General examination revealed pallor, mild icterus, and multiple ecchymotic patches on her trunk and upper limbs. No clubbing, cyanosis, oedema, or lymphadenopathy was observed. Heart sounds were normal on auscultation, while vesicular breath sounds were unremarkable except for intermittent bilateral axillary and interscapular crepitations. Other systemic examinations yielded normal results. Arterial blood gas analysis indicated high anion gap metabolic acidosis. In view of worsening respiratory distress, the patient was intubated in the emergency setting and subsequently admitted to the medicine intensive care unit (ICU) for further management. During her hospital stay, she experienced bleeding from the endotracheal tube and developed severe acute respiratory distress syndrome (ARDS) with a PF ratio of less than 100.

Investigations

The patient's complete blood count (CBC) revealed a severe drop in haemoglobin levels, with a haemoglobin concentration of 4.9 g/dL, coupled with a pronounced decrease in platelet count to 6000/µL. Alongside, there was evidence of mild elevation in neutrophil count (neutrophilic leucocytosis) and an elevated C-reactive protein (CRP) level of 206 mg/L, indicating heightened inflammation. Notably, the patient developed oliguric acute kidney injury (AKI), manifested by elevated levels of urea (174 mg/dL) and creatinine (5.5 mg/dL). Conjugated hyperbilirubinemia, a marker of disrupted liver function, was also observed. (Table 1). Ultrasonography of the abdomen did not reveal any notable abnormalities. Initial investigations, encompassing tests for tropical fevers and blood cultures, were undertaken. Initial serological results for malaria, dengue IgM, NS1 antigen, scrub typhus, and enteric fever were negative. Subsequently the patient had a positive result for IgM leptospira with a high titre (IgM ELISA: 21.64 NTU). The Modified Faine score, a diagnostic tool for leptospirosis, was calculated, while her lactate dehydrogenase (LDH) levels soared to 2060 IU, denoting ongoing active hemolysis. Workup for autoimmune haemolytic anemia was negative. Additionally, parameters of coagulation, including prothrombin time (PT-INR), activated partial thromboplastin time (aPTT), and fibrinogen, remained within reference ranges.

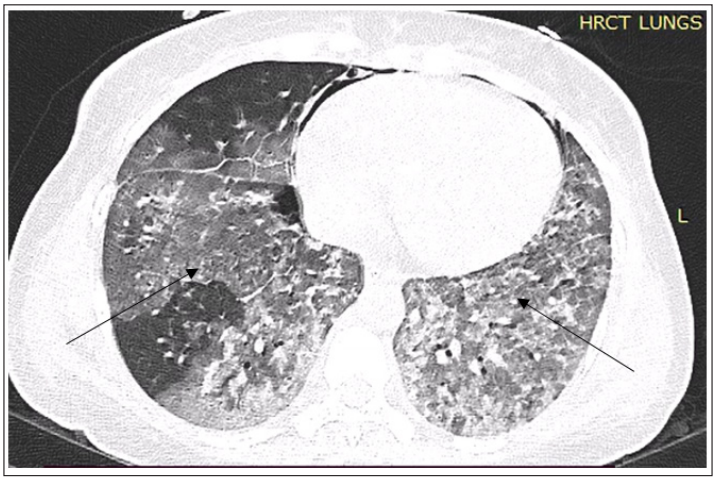
Peripheral blood smear analysis showcased a diminished platelet count, accompanied by microcytic micro-chromic red blood cells (RBCs) and the presence of 5 to 6% schistocytes-a characteristic sign of intravascular haemolysis. In light of these findings, a firm diagnosis of thrombotic microangiopathy (TMA) was established. Consequently, an extensive evaluation was initiated to discern potential underlying etiologies. Immunologic assessments, inclusive of complement component C3 and C4 levels, yielded normal results. Antinuclear antibody (ANA) screening via indirect immunofluorescence assay (IFA) turned out negative. However, due to financial constraints, the determination of ADAMTS13 levels, a vital marker in TMA cases, unfortunately could not be pursued. Subsequent high-resolution computed tomography (HRCT) imaging of the chest unveiled an array of significant pulmonary findings, including multiple centrilobular nodules, patchy areas of consolidation, and smooth thickening of interlobular septae affecting both lungs-an intricate constellation of features indicative of acute respiratory distress syndrome (ARDS).

Table 1: Investigations

Investigation	01/08/23	02/08/23	03/08/23	04/08/23	05/08/23	06/08/23
Hb (g/dl)	4.9	5.5	5.9	7.5	6.8	8.7
TLC (x1000) (/ul)	13.8	7.49	6.24	6.79	4.94	3.97
Platelet (/ul)	6000	7000	20000	15000	86300	80000
DLC (N/L/M)	81/14.3/4.6/0	82.5/10.3/7.2	69/19/10.7	76/12.1/11.9	74/11/14.9	57/28/14/0.3
TB (mg/dl)	6.76	5.93	5.53	-	5.22	3.1
DB (mg/dl)	5.13	4.28	3.84	-	3.57	1.9
SGPT (u/l)	106	77	81	-	75	38
SGOT (u/l)	142	123	161	-	157	82
ALP (u/l)	151	184	160	-	189	230
GGT (u/l)	38	45	59	-	60	-
TP (g/dl)	4.3	4.9	4.8	-	4.8	7.7
Serum Albumin (g/dl)	2.6	2.9	2.7	-	2.7	2.9
Sr globulin (g/dl)	1.7	2.0	2.1	-	2.1	4.8
Urea (mg/dl)	170	143	217	-	220	147
Creatinine (mg/dl)	5.77	5.13	6.88	-	6.79	4.29

Na(mmol/l)	144	143	142	-	140	144
K (mmol/l)	3.9	3.8	3.8	-	3.63	4.63
Cl(mmol/l)	107	106	103	-	101	99
Ca (mg/dl)	6.3	7.4	7.7	-	7.7	9.4
Uric acid (mg/dl)	7.6	6.2	8.6	-	8.3	7
Phosphorus (mg/dl)	3.5	6.0	6.4	-	5.5	4.8
PT/INR		13/1.02	13/1.03	12.3/0.97	-	-
aPTT (s)	31.4	49.2	25.8	20.1	-	-
Fibrinogen		159.2	335.8	308	-	-
Folate	5.56	-	-	-	-	-
Reticulocyte count	1.13	-	0.26	-	-	-
TSH	0.183	-	-	-	-	-
FT3/FT4	0.69/1.28	-	-	-	-	-
CRP	-	-	-	206	-	-
LDH	2060 IU	-	1780 IU	-	-	-

Special Investigations:
ANA-IFA: Negative
C3: 128 (84-168 mg/dl) /C4: 30.6 (15-50mg/dl)
Urine R/M: RBC: 10-15 cells
Direct Coomb's test: Negative
Peripheral Smear: Normochromic Normocytic Anemia with Anisocytosis, Leucocytosis, Platelets decreased, 5-6% Schistocytes seen
HRCT Chest: Multiple Centrilobular Nodules Coalescing to Form Patchy Areas of Consolidation with Smooth Interlobular Septal Thickening in Bilateral Lungs. Features Suggestive of Ards.



Treatment

The patient's treatment regimen encompassed the administration of empiric broad-spectrum antibiotics, namely meropenem and doxycycline, supplemented with teicoplanin to cover Methicillin-Resistant Staphylococcus aureus (MRSA) infection. Given her critical respiratory status, she was placed on invasive mechanical ventilation using the Airway Pressure Release Ventilation (APRV) mode in accordance with the Acute Respiratory Distress Syndrome (ARDS) protocol. Notably, due to evidence of bleeding from the endotracheal tube and escalating oxygen requirements, the differential diagnosis of diffuse alveolar haemorrhage was considered, prompting the initiation of corticosteroid therapy.

Throughout her hospitalization, the patient underwent transfusion of various blood components, including packed red blood cells (PRBCs), random donor platelets (RDPs), and single donor platelets (SDPs). In light of her acute kidney injury (AKI), hemodialysis was instituted to provide renal support. A modified Plasmic score of 6, indicative of Thrombotic Thrombocytopenic Purpura (TTP), heightened clinical suspicion for an underlying thrombotic microangiopathy (TMA). Consequently, therapeutic plasmapheresis was initiated. Following a session of plasmapheresis, there was a notable amelioration in platelet counts, elevating to 80,000/µl. Regrettably, despite the comprehensive interventions employed, the patient's clinical trajectory remained unfavourable. Her respiratory status progressively deteriorated, leading to exacerbated hypoxemia and the development of acute hypoxemic respiratory failure, ultimately culminating in her demise due to severe ARDS.

Discussion

Leptospirosis, a re-emerging zoonotic disease, has been spreading rapidly through rural areas of Northern India. A study at PGIMER Chandigarh pinpointed the monsoon months, from July to October,

as the prime period for its outbreak [5]. Traditionally, the culprit behind this disease has been two species of Leptospira: the pathogenic L. interrogans and the free-living L. biflexa. Rodents, especially rats, stand as its primary reservoirs, while other domestic animals like dogs, cattle, pigs, and even wild mammals also contribute to its transmission. This bacterium spreads like wildfire within the host's body, wreaking havoc across multiple organs and microcirculation. During its acute phase, Leptospira can be detected in the bloodstream through PCR, which is followed by the immune phase that utilizes serology and urine culture for diagnosis. To aid in its recognition, the WHO introduced Faine's criteria, based on clinical history, epidemiological aspects, and lab parameters [6]. The modified Faine's criteria, when combined with a rapid immunochromatographic assay, displayed an impressive sensitivity of 89.39% and a negative predictive value of 89.55%, solidifying its diagnostic prowess [6]. Beyond the fever and chills, leptospirosis often unveils its dark side—pulmonary manifestations striking 20% to 70% of patients [7]. These can range from a pesky cough to outright respiratory failure, replete with pulmonary haemorrhage and hyaline membrane formation [7,8].

Alarming is the fact that the hemorrhagic form of the disease claims a staggering 60% mortality rate. Yet, the clinical labyrinth of leptospirosis doesn't stop there. Its presentation spans from a mild febrile illness to the formidable Weil's disease, distinguished by the classic triad of jaundice, acute kidney injury (AKI), and haemorrhage [5]. The extent of liver involvement is key, especially when coupled with acute renal failure, with poorer outcomes often in tow [9]. Remarkably, 20%–70% of patients also grapple with pulmonary involvement, the severity of which can range from a mundane cough to respiratory failure due to pronounced pulmonary haemorrhage and hyaline membrane development [8,9]. What's more, the haemorrhagic form proudly boasts a mortality rate of up to 60% [9]. In this perplexing landscape, thrombotic microangiopathy (TMA) has emerged as a rare yet intriguing haematological complication. This elusive entity, bearing resemblance to thrombotic thrombocytopenic purpura (TTP) or hemolytic uremic syndrome (HUS), has confounded the medical world. In a report from Tepecik Research Hospital, Izmir, Turkey, leptospirosis manifested as TTP, with patient improvement following antibiotics and plasmapheresis [10].

Equally fascinating, the Department of Nephrology/Pathology in Ireland encountered a leptospirosis case mimicking TMA, where antibiotic therapy alone led to renal recovery, sparing the need for renal replacement therapy or plasmapheresis. The universe of TMA syndromes, encompassing microangiopathic haemolytic anaemia, thrombocytopenia, and organ injury, is a multifaceted realm. These syndromes can be genetic, originating from deficiencies in ADAMTS 13, or acquired, attributed to autoantibodies, complement-mediated pathways, metabolism derangements, or coagulation anomalies. While primary TTP can surface in adulthood, often triggered by stress, infection, or pregnancy, acquired TTP cases dominate the adult population. Notably, systemic infections, malignancies, autoimmune disorders, and pregnancy can mirror the clinical and pathological aspects of TMA. However, the resolution of these features occurs upon treating the underlying disorder. Plasmapheresis takes the lead in treatment, though immune TTP cases have spurred the exploration of steroids and rituximab.

Timely intervention is imperative, as primary TMA, particularly TTP, grapples with a daunting 90% mortality rate [3]. In navigating these uncharted waters, high clinical suspicion and swift action emerge as the beacon for improving patient outcomes. With each case revealing novel complexities, the medical community strives to decipher the intricate puzzle of leptospirosis and its enigmatic haematological manifestations as was depicted in our case.

Conclusion

This case report highlights the importance of early identification and tailored management strategies for intricate multi-system involvement in conditions like leptospirosis, which can manifest with a wide range of symptoms and lead to severe multi-system complications. Despite her previously unremarkable health, the patient's condition rapidly deteriorated, leading to a tragic outcome. Plasmapheresis has been reported to be beneficial in Weil's disease with kidney failure, as has been cortisone therapy in case of pulmonary leptospirosis. Thrombotic microangiopathy has been rarely reported during leptospirosis. It serves as a reminder to healthcare professionals to remain vigilant, especially in regions where the disease is endemic, and to consider leptospirosis in the differential diagnosis of patients presenting with a febrile illness and multi-system involvement.

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