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Case study of a 68-year-old male with leptospirosis and scrub typhus coinfection associated with acute kidney infection and jaundice

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Abstract
Leptospirosis and scrub typhus are bacterial zoonotic diseases and important causes of acute febrile illness in India. Both are responsible for high morbidity and mortality. Their common epidemiology creates an opportunity of dual infections with these diseases. In the current study, we present a brief medical case report of a 68-year-old male patient who was admitted to the emergency ward of RG Kar Medical College and Hospital on early September this year (9.9.2022). The patient was reported to have fever for seven days along with symptoms of weakness, vomiting and urinary incontinence. These were associated with enlarged liver and spleen along yellowish discoloration of urine and scleral icterus. In addition, the patient was diagnosed with acute kidney infection along with thrombocytopenia and generalized septic symptoms. Enzyme linked immunosorbent assay (ELISA) detected IgM antibodies to both leptospirosis and scrub typhus in the serum of the patient indicating dual infection with the bacterial diseases. The patient showed complete recovery on treatment with antibiotics. The current study adds further to previously published reports on co-infection of leptospirosis and scrub typhus. As both leptospirosis and scrub typhus present with similar clinical features, co-infection of these two diseases is not uncommon. Accordingly, cases of dual infections must be considered seriously and choice of therapy should include those drugs that cover for both the infections.

Keywords: Leptospirosis, Scrub Typhus, Acute Kidney Infection, Jaundice, Pancreatitis, ELISA

1. Introduction

Leptospirosis is a world-wide occurring zoonotic disease, caused by infection with pathogenic spirochetes of the genus Leptospira. Although traditionally considered as an occupational risk among persons exposed to contaminated water or infected animal urine, leptospirosis is recognized as a common cause of febrile illness in tropical environments world-wide [1, 2]. Mammals (wild/domestic) harbour the bacteria and shed these in the urine; they may disseminate the organism to a water source (streams and springs). The organism enters the human body through cuts or abrasions on the skin or through intact mucosa of the mouth, nose or conjunctiva. The clinical manifestations of leptospirosis range from a mild catarrh like fever, chills, nausea, muscle aches to icteric disease such as Weil's syndrome, which are characterized by renal failure, liver impairments and hemorrhages and have a high mortality rate. As clinical symptoms and signs of this infection resemble those of many other infectious diseases including viral hemorrhage fever and dengue fever, clinical findings need to be confirmed by laboratory diagnostic techniques.

Scrub Typhus, or tsutsugamushi fever, is a zoonotic disease that is accidentally transmitted to humans. It is frequently found in people with outdoor exposure in tropical and subtropical Asian regions [3]. The causative organism, *Orientia tsutsugamushi*, belongs to family Rickettsiaceae and is transmitted to humans by the bite of larval trombiculid mite or chigger. The bite from an infected chigger may be followed by a systemic illness ranging in severity from inapparent to fatal. Many scrub typhus cases go undiagnosed, particularly those in which an eschar cannot be found. Most common symptoms are fever, headache, body ache and sometimes rashes. The diagnosis of scrub typhus infection has relied on the detection of *Orientia tsutsugamushi* antibodies during the acute phase of the disease.

Most cases of leptospirosis are subclinical or have a mild clinical illness. The clinical picture of leptospirosis completely overlaps scrub typhus; fever, headache, conjunctival suffusion, myalgia, meningism, meningo-encephalitis, acute respiratory distress syndrome, hepatorenal dysfunction, rash and multi-organ dysfunction syndrome. Even though both these diseases are endemic in India, they are less commonly reported from New Delhi and surrounding areas [4-8]. Because outdoor activity is a shared risk factor for acquisition of leptospirosis and scrub typhus, coinfection with these two diseases is not uncommon [9, 10]. Most laboratories in India diagnose both scrub typhus and leptospirosis using IgM ELISA. Their common epidemiology creates an opportunity of dual infections with these diseases [9]. They also have a common seasonal pattern. Dual infection has been reported from Thailand and Taiwan [9, 11]. Case reports of serological dual infection have been reported from India as well [12-14]. The mortality rate for both scrub typhus and leptospirosis is up to 30%, if effective treatment is not given timely and appropriately [15, 16].

Most laboratories in India diagnose both scrub typhus and leptospirosis using IgM ELISA. Simultaneous detection of antibodies to leptospirosis and scrub typhus has been reported in a few cases. In this study, we present a brief medical case report of a 68-year-old male patient diagnosed with leptospirosis and scrub typhus dual infection. The clinical symptoms of the patient included fever, weakness, vomiting, urinary incontinence, associated with jaundice, acute kidney infection and thrombocytopenia. The patient showed gradual to complete recovery following treatment with antibiotics and associated medicines.

2. Materials and methods

A 68-year-old male patient was admitted to the emergency ward of RG Kar Medical College and Hospital on early September this year (9.9.2022). The patient was reported to be suffering from fever for seven days along with symptoms of weakness, vomiting and urinary incontinence. The patient showed yellowish discoloration of urine and scleral icterus associated with enlarged liver and spleen. The patient registered blood pressure= 94/62 mm Hg, capillary blood glucose (CBG)=148 mg/dl and oxygen saturation (SpO2) =97%. Serum of the patient was tested for leptospirosis at Virus Research & Diagnostic Laboratory (VRDL), Department of Microbiology, RG Kar Medical College and Hospital, Kolkata, after obtaining ethical clearance from the institution and informed consent. Serum IgM antibodies to leptospirosis were detected by ELISA method following standard kit protocol (J. Mitra & Co. Pvt. Ltd.) according to the manufacturer's instructions. The patient was also tested further for coinfection with scrub typhus. Similar to that of leptospirosis, IgM antibodies to scrub typhus were detected by ELISA method following standard kit protocol (J. Mitra & Co. Pvt. Ltd.). Calculations were done as per kit instructions as follows:

Sample O.D. ratio = Sample O.D. ÷ Cut off Value

[Cut off Value =0.569 for Leptospira IgM, and 0.372 for Scrub Typhus IgM, respectively]

Calculation of Leptospira or Scrub Typhus IgM units=sample O.D. ratio×10

3. Results

The preliminary clinical investigation report of the patient at the time of admission is summarized in Table 1.

Table 1: Laboratory investigation of patient sample recorded on 9.9.2022

Laboratory investigations	Patient history (recorded on 9.9.2022)
a) Laboratory parameters (with reference values in parenthesis)	
Hemoglobin (12.0-15.0 g/dl)	10.8
Total leucocyte count (4000-11000/mm3)	9800
Platelet count (150,000-400,000/mm3)	69,000
Total bilirubin (0.1-1.0 mg/dl)	29.0
Direct bilirubin (0-0.3 mg/dl)	14.6
Serum urea (10-40 mg/dl)	190
Serum creatinine (0.5-1.5 mg/dl)	3.0
Sodium (135-145 mmol/l)	132
Potassium (3.5-5.0 mmol/l)	3.6
b) Other investigations	
MPDA	Negative
Dengue NS1	Negative
HBsAG	Non-reactive
Anti-HCV antibody	Non-reactive

The clinical investigation report of the patient recorded on the following day (10.09.2022) is summarized in the below table (Table 2).

Table 2: Laboratory investigation of patient sample recorded on 10.9.2022

Laboratory investigations	Patient history (recorded on 10.9.2022)
a) Laboratory parameters (with reference values in parenthesis)	
Total Protein (6-8 g/dl)	5.6
Albumin (3.2-5.0 g/dl)	2.4
Total Bilirubin (0.1-1.0 mg/dl)	35.8
Direct Bilirubin (0-0.3 mg/dl)	16.7
Alanine Transaminase (5-35 IU/L)	145
Aspartate Transaminase (5-35 IU/L)	176
Alkaline Phosphatase (adult 110-310 IU/L)	181
Urea (10-40 mg/dl)	204
Creatinine (0.5-1.5 mg/dl)	2.8
Sodium (135-145 mmol/l)	131
Potassium (3.5-5.0 mmol/l)	3.1
Calcium Total (9-11 mg/dl)	8.5
Phosphate (2.5-4.5 mg/dl)	3.3
S Lipase (37ºC) (< 60 U/L)	257
S Amylase (IFCC 37ºC) (28.0-100.0 U/L)	385
C-Reactive Protein (< 0.6 mg/dl)	3.6
b) Other investigations	
MPDA	Negative
Dengue NS1	Negative
HBsAG	Non-reactive
Anti-HCV antibody	Non-reactive

*MPDA=Microarray pooled DNA analyzer; Dengue NS1=Dengue non-structural protein 1; HBsAG= Hepatitis B surface antigen; HCV= Hepatitis C virus

From preliminary clinical examination of laboratory parameters above (Table 1, 2), the patient was provisionally diagnosed to have jaundice, acute kidney infection along with thrombocytopenia and generalized septic symptoms. The clinical symptoms possibly indicated a severe form of leptospirosis [17] and accordingly the serum of the patient was tested for leptospirosis as well as scrub typhus

infection. ELISA results indicated the patient was positive with dual infection for both the bacterial diseases.

4. Discussion

Clinical manifestations specific for leptospirosis usually appear transiently in the early septicemic stage. Jaundice and acute renal dysfunction have been found to be associated with patients with the severe form of leptospirosis (Weil's syndrome) [1, 2]. Abnormal liver function mainly with elevated Aspartate Transaminase and Alanine Transaminase levels was found to be associated with patients with scrub typhus [18]. An increase in liver enzymes can also occur in the severe form of leptospirosis. In patients with leptospirosis, jaundice is clinically reflective of hyperbilirubinemia resulting from intrahepatic cholestasis [1]. Icterus is present in only 5-10% of leptospirosis cases but its presence signifies a severe progression. Renal failure in both scrub typhus and leptospirosis is non-oliguric and recovers completely. The incidence of renal failure in scrub typhus ranges from 18% to 66.4% [19-21] while it is 16 to 40% in cases of leptospirosis [1].

An elevated level of serum C-Reactive Protein (3.6 mg/dl) is a sign of acute inflammation due to infection. Elevated level of ferritin (990 ng/µl) is also indicative of inflammation and/ liver disease. High level of lipase may be associated with an infection in pancreas or chronic kidney disease. In an earlier study, leptospirosis-induced pancreatitis was reported for a 23-year-old man associated with acute kidney injury and high lipase level [22]. In a recent case study, acute pancreatitis due to leptospirosis was reported with increased level of serum amylase and lipase [23]. Clinical and laboratory manifestations are helpful in making differential diagnosis of leptospirosis and scrub typhus. Once leptospirosis or scrub typhus is diagnosed, clinicians should be alert to potential coinfection with the other disease because of shared risk factors for acquisition of these diseases. Several previous studies have reported coinfection of patients with scrub typhus and leptospirosis [9, 10].

The patient was treated with antibiotics, meropenem-500, doxycycline-100, rifaximin-550 and ceftriaxone. As *O. tsutsugamushi* lacks a proper cell wall, the cephalosporin group of antibiotics is virtually ineffective against scrub typhus [24, 25]. It was also reported that doxycycline is an effective therapy for patients with leptospirosis [26]. Rifampicin and azithromycin are alternatives in cases resistant to doxycycline [27]. The treatment of choice for severe leptospirosis is I.V penicillin or I.V ceftriaxone [28, 29] while that for scrub typhus is doxycycline. Azithromycin and doxycycline have both been shown to be effective in the treatment of scrub typhus, but the resolution of symptoms has shown to be faster in doxycycline compared to azithromycin [30]. Recent trials have demonstrated that the broad-spectrum third generation cephalosporins cefotaxime and ceftriaxone are also acceptable agents for patients with severe leptospirosis.

Clinical investigation of the patient following administration of antibiotics and additional medications (tab pan 40, tab zofer, lactulose, intravenous fluids) recorded on 14.09.2022 and 21.09.2022 are shown in Table 3. Treatment resulted in marked improvement in kidney function (decrease in the level of urea and creatinine to normal levels) along with gradual lowering of bilirubin levels (total and direct) and recovery from jaundice. The levels of liver function enzymes gradually reduced to normal levels with time and the patient recovered completely. A decrease in C-Reactive Protein to nearly normal level indicated a lowering of inflammation.

Table 3: Laboratory investigation of patient sample (recorded on 14.9.2022 and 21.09.2022, respectively) following medication

Laboratory investigations	Patient parameters (recorded on 14.9.2022)	Patient parameters (recorded on 21.9.2022)
(a) Laboratory parameters (with reference values in parenthesis)		
Total Protein (6-8 g/dl)	6.2	5.9
Albumin (3.2-5.0 g/dl)	3.4	2.8
Total Bilirubin (0.1-1.0 mg/dl)	15.7	4.9
Direct Bilirubin (0-0.3 mg/dl)	9.0	2.6
Alanine Transaminase (5-35 IU/L)	84	88
Aspartate Transaminase (5-35 IU/L)	54	56
Alkaline Phosphatase (adult 110-310 IU/L)	117	119
Urea (10-40 mg/dl)	58	40
Creatinine (0.5-1.5 mg/dl)	1.2	1.0
Sodium (135-145 mmol/l)	137	139
Potassium (3.5-5.0 mmol/l)	3.0	4.2
C-Reactive Protein (< 0.6 mg/dl)	0.7	-
(b) Other investigations		
MPDA	Negative	Negative
Dengue NS1	Negative	Negative
HBsAG	Non-reactive	Non-reactive
Anti-HCV antibody	Non-reactive	Non-reactive

5. Conclusion

In the current study, we present a case report of a 68-year-old male patient diagnosed with leptospirosis and scrub typhus coinfection. The patient was reported to have fever for seven days along with weakness, vomiting, urinary incontinence, enlarged liver and spleen, scleral icterus, acute kidney infection, thrombocytopenia and generalized septic symptoms. Treatment with antibiotics, meropenem-500, doxycycline-100, rifaximin-550 and ceftriaxone resulted in complete recovery of the patient. Since both leptospirosis and scrub typhus present with similar clinical features, co-infection of these two diseases is not uncommon. Accordingly, choice of therapy should include those drugs that cover for both the infections.

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7. Disclosure of conflict of interest

The author has no potential conflicts of interest to disclose.

8. Statement of ethical approval

The studies on patient samples were carried out after

obtaining ethical clearance from the institution and informed consent.

9. Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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