

Recent cases of co-infection of scrub typhus and leptospirosis: A short clinical study

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Abstract

Scrub typhus and leptospirosis are bacterial zoonotic diseases causing high morbidity and mortality. Both are important causes of acute febrile illness in India. The common epidemiology of both the diseases creates an opportunity of dual infections with these diseases. The present study was conducted at RG Kar Medical College and Hospital to determine simultaneous infection of leptospirosis and scrub typhus in sera of febrile patients and evaluate the cases of serological dual infections. IgM antibodies to both leptospira and scrub typhus were detected by Enzyme linked immunosorbant assay (ELISA). During the study period (August 2022-October 2022), serum samples of patients were received for serology for scrub typhus. Out of these samples, 5 patients diagnosed for scrub typhus infection also had IgM antibodies to leptospira, thus indicating co-infection of both diseases. The current study adds further to few previously published reports on co-infection of scrub typhus with leptospirosis. As both leptospirosis and scrub typhus present with similar clinical features, co-infection of these two diseases is not uncommon and requires further confirmation at molecular level. Accordingly, cases of dual infections must be considered seriously and choice of therapy should include those drugs that cover for both the infections.

Keywords: Scrub typhus; Leptospirosis; Co-infection; Serology; ELISA; IgM antibodies

1. Introduction

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 [1]. The causative organism, *Orientia tsutsugamushi*, belongs to family Rickettsiaceae and is transmitted to humans by the bite of larval trombiculid mite or chigger. A cigarette burn-like sore, called an eschar, sometimes develops at the site of infection. Swollen lymph glands are also common. 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. As very few health facilities have accessible accurate diagnostic tests, the diagnosis of scrub fever must be based on clinical features. However, this is difficult because the clinical symptoms and signs are similar to those of many other febrile diseases, such as murine typhus, leptospirosis, and dengue virus infection. The diagnosis of scrub typhus infection has relied on the detection of *Orientia tsutsugamushi* antibodies during the acute phase of the disease.

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 [2, 3]. Mammals (wild/domestic) harbour the bacteria and shed these in the urine; they may disseminate the organism to a water source (streams and springs). In India outbreaks have been reported from the Andaman Island, Tamil Nadu, Karnataka, Maharashtra, Andhra Pradesh and Orissa especially after heavy rains [4]. The organism enters

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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.

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 [5-9]. Because outdoor activity is a shared risk factor for acquisition of leptospirosis and scrub typhus, coinfection with these two diseases is not uncommon [10, 11]. 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 [12]. They also have a common seasonal pattern. Dual infection has been reported from Thailand and Taiwan [12, 13]. Case reports of serological dual infection have been reported from India as well [14-16]. The mortality rate for both scrub typhus and leptospirosis is up to 30%, if effective treatment is not given timely and appropriately [17, 18].

Most laboratories in India diagnose both scrub typhus and leptospirosis using IgM ELISA. Simultaneous detection of antibodies to leptospira and scrub typhus has been reported in a few cases. The present study was conducted to detect antibodies to leptospira in patients diagnosed with scrub typhus. We report five cases of coinfection with scrub typhus and leptospirosis.

2. Material and methods

A clinical study was conducted at Virus Research & Diagnostic Laboratory (VRDL), Department of Microbiology, RG Kar Medical College and Hospital, Kolkata from August 2022-October 2022 to determine simultaneous infection of leptospirosis and scrub typhus. After obtaining ethical clearance from the institution and informed consent, sera of the adult patients, having symptoms of acute fever, rash, headache, malaise, with or without eschar, were clinically suspected as scrub typhus and tested for scrub typhus serology. Serum IgM antibodies to scrub typhus were detected by ELISA method following standard kit protocol (J. Mitra & Co. Pvt. Ltd.) according to the manufacturer's instructions. A value of IgM units greater than 11 was considered positive for scrub typhus IgM antibodies (as per kit instructions). Scrub positive patients with additional symptoms like abdominal pain, joint pain or jaundice were further tested for coinfection with leptospirosis. Similar to that of scrub typhus, IgM antibodies to leptospirosis were detected by ELISA method following standard kit protocol (J. Mitra & Co. Pvt. Ltd.). The clinical features, laboratory parameters and other data were entered in the excel spreadsheet (Microsoft Office, Redmond, Washington, USA) and subsequent analysis was carried out.

3. Results and discussion

In the present study, we found five clinical cases of co-infection with scrub typhus and leptospirosis. The IgM units for scrub typhus and leptospirosis for each case are summarized in Table 1.

Calculations were done as per kit instructions as follows:

$$\text{Sample O.D. ratio} = \text{Sample O.D.} \div \text{Cut off Value}$$

[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

The clinical investigation reports obtained for two cases with co-infection (no. 4 and 5) are summarized in Table 2.

Table 1 Calculation of Leptospira and Scrub Typhus IgM units obtained from IgM Microlisa Test (for leptospirosis and scrub positive samples)

Serial No.	Name of patient	Age/Sex	Hospital Registration No. (RG No.)	Leptospira IgM units	Scrub Typhus IgM units
1	Subnodu Sarkar	66Y/Male	2200769025	27.7	70.51
2	Anjana Shau	42Y/Female	2200703532	19.36	17.79
3	Dulal Saha	68Y/Male	2200745360	32.09	14.22
4	Asraful Mondal	27Y/Male	2200781696	23.81	58.09
5	Rajjak Molla	33Y/Male	2200822319	28.03	63.79

Table 2 Laboratory investigation of patient samples with co-infection

Laboratory investigations	Case no. 4	Case no. 5
(a) Laboratory parameters (with reference values in parenthesis)		
Hemoglobin (12.0-15.0 g/dl)	10.7	11.9
Total leucocyte count (4000-11000/mm ³)	7600	8200
Platelet count (150,000-400,000/mm ³)	1,25,000	1,80,000
Serum bilirubin (0.2-1.2 mg/dl)	0.6	1.0
Direct bilirubin (0-0.2 mg/dl)	0.2	0.9
Serum alkaline phosphatase (40-120 IU/L)	86	97
Aspartate transaminase (\leq 40 IU/L)	27	42
Alanine transaminase (\leq 40 IU/L)	30	31
Serum urea (15-40 mg/dL)	27	28
Serum creatinine (0.2-1.1 mg/dL)	0.8	0.9
Sodium (120-145 mEq/L)	134	137
Potassium (3.5-5.5 mEq/L)	3.6	4.2
Albumin (4.0-5.5 g/dL)	2.5	3.1
(b) Other investigations		
MPDA	Negative	Negative
Dengue NS1	Negative	Negative
VDRL	Non-reactive	Non-reactive
RPR	Non-reactive	Non-reactive
HIV-I, II	Non-reactive	Non-reactive
HBsAG	Non-reactive	Non-reactive
Anti-HCV antibody	Non-reactive	Non-reactive
Brucella SAT	Negative	Negative
Widal tube test	Negative	Negative
Peripheral blood smear for malaria parasite	Negative	Negative
Blood culture for <i>Salmonella</i> spp.	Negative	Negative

*MPDA=Microarray pooled DNA analyzer; Dengue NS1=Dengue nonstructural protein 1; VDRL= Venereal disease research laboratory test for syphilis; RPR=Rapid plasma regain for syphilis; HIV=Human immunodeficiency virus; HBsAG= Hepatitis B surface antigen; HCV= Hepatitis C virus

4. Discussion

Scrub typhus is a seasonal disease with high incidence in the post monsoon season. The incidence of scrub typhus probably increases in this season because of the increase in growth of scrubs which enables the increase in mite populations. Most of the scrub typhus patients presented in the months of September to November. Similar observations were recorded in other studies [19, 20]. The incidence of leptospirosis increases after the rainy season because of the ensuing waterlogging caused. Several epidemics of leptospirosis have been reported during the monsoons [21-23]. Cases of leptospirosis have also been reported from Delhi, mostly slums during the months of August and September [24, 25]. Five cases of leptospirosis were reported in an earlier study in a rural medical college in Himachal in the month of September 2014 [26].

In the present study, we report five cases of leptospirosis and scrub typhus co-infection in the months August-September 2022. In 2003, a case of concurrent infection of scrub typhus and leptospirosis was reported in a patient with acalculous cholecystitis [27]. In 2012, another case of co-infection with scrub typhus and leptospira was reported by Wei et al. However, both the cases responded well to management [28]. A similar case was reported from the Himalayan region in India in 2012 [29]. In a recent study, co-infection of leptospira and scrub typhus were reported in 11 patients by ELISA [30]. Borkakoty et al. found scrub typhus IgM and leptospira IgM positive simultaneously in 25% cases of patients with pyrexia of unknown origin [31]. There are various tests for diagnosis of leptospirosis like loop mediated isothermal amplification assay, polymerase chain reaction (PCR) and ELISA [32]. The advantage of ELISA is that it can be performed easily with less infrastructure and technical expertise and is inexpensive compared to microscopic agglutination test (MAT).

Elevated bilirubin or creatinine levels could not be significantly related to isolated infection by leptospirosis or dual infection. This was also shown in a study done by Lee et al. where fever, headache, jaundice and oliguria were not significantly related to leptospirosis versus dual infection of leptospirosis and scrub typhus [33].

Early diagnosis is important because there is usually an excellent response to treatment and timely anti-microbial therapy may prevent complications. As *Orientia tsutsugamushi* lacks a proper cell wall instead have a slime layer, the cephalosporin group of antibiotics is virtually ineffective against scrub typhus [34]. It was also reported that doxycycline is an effective therapy for patients with leptospirosis [35]. Therefore, doxycycline/azithromycin is recommended to treat patients with scrub typhus/leptospirosis and seasonal therapy may be life-saving in these regions when clinical suspicion is high. Rifampicin and azithromycin are alternatives in cases resistant to doxycycline [36]. However, there is a need for individual diagnosis, as both the infection requires specific treatment protocol and meticulous supportive therapy is essential to prevent complications. Scrub typhus infection may be prevented by wearing proper dresses and use of insect repellent cream containing N, N-diethyl-m-toluamide to minimise exposure to infected mites [37]. Simultaneously, animal exposure may be avoided which harbour leptospires and use boiled water for drinking.

5. Conclusion

Since both leptospirosis and scrub typhus present with similar clinical features, co-infection of these two diseases may occur and it requires different methods for confirmation of these cases. Molecular confirmation of leptospirosis and scrub typhus is required along with ELISA for detection of IgG antibodies, to further validate our results. The present report, however, will be beneficial for undertaking future detailed surveillance, patient management, developing effective public health responses and public awareness to scrub typhus and leptospirosis.

Compliance with ethical standards

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Disclosure of conflict of interest

The author has no potential conflicts of interest to disclose.

Statement of ethical approval

The studies on patient samples were carried out after obtaining ethical clearance from the institution and informed consent

Statement of informed consent

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

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