

Co-infection of Dengue, Scrub typhus and Typhoid during Dengue outbreak in Nepal, 2022: A case report

Bibek Raj Bhattarai¹, Rajshree Bhujel², Sushant Pokhrel¹, Abhishek Mishra³, and Anamika Priyadarshinee⁴

¹Manmohan Memorial Institute of Health Sciences

²Tribhuvan University Central Department of Microbiology

³Tribhuvan University Teaching Hospital

⁴KISTMCTH

November 4, 2022

Abstract

In midst of recent dengue outbreak in Nepal, 2022, the risk of co-infection increases and may lead to fatal outcomes if the diagnosis of multiple infections is delayed. Thus, all available diagnostic approaches must be taken to decrease the burden of illness and lessen mortality.

Introduction

Dengue is a tropical disease which is primarily caused by *Aedes aegypti* and *Aedes albopictus*. It is particularly prevalent in tropical and subtropical regions, and has been expanding into new geographic areas throughout time¹. Scrub typhus, which is caused by the bacteria *Orientia tsutsugamushi*, is another disease to be concerned about due to its endemicity in Nepal. The lack of distinct clinical symptoms and diagnostic resources, scrub typhus is frequently under-diagnosed². Another endemic febrile sickness in Nepal is typhoid fever; causative agent *Salmonella typhi*, and causes multi-systemic illness when contaminated food and water is consumed³.

Monsoon and post-monsoon is a high risk season for spreading of typhoid, dengue, and scrub-typhus⁴. Even though, the co-infections among the organisms are rare due to multiple etiological agents and/or vector involved, the probability cannot be neglected. Here, we present a case of 58 years old female from Dang, a district with sub-tropical climate, having co-infection of dengue, typhoid fever, and scrub typhus during dengue outbreak in Nepal.

Case Report:

A 58-year-old woman presented with a continuous fever that persisted for 16 days. The patient stated that 16 days prior, she was in good health. Then she had a moderate grade fever of 103°F that wasn't accompanied by chills or rigor. She also reported experiencing 2 weeks of progressively worsening epigastric discomfort accompanied by a feeling of abdominal fullness. There was no history of rashes, chest pain, coughing, loose stools, nausea/vomiting. Additionally, the patient also stated that she had no prior history of thyroid disease, pulmonary TB, diabetes mellitus, or hypertension. She said that she does not smoke, although she does consume 200 ml of alcohol twice daily. The most recent intake was about two weeks ago.

On examination, the patient was presented as conscious, pale, icterus, had a low grade fever of 100.5°C along with bilateral pitting edema, oral ulcer, and abdominal tenderness in epigastric region. Vital checkup

of patient presented hypotension (BP = 80/60 mmHg), Tachycardia (PR= 116 beats per minute), Respiratory rate of 20 beats per minute, low level SPO₂ i.e. 89% in room atmosphere.

Considering the recent dengue outbreak in Nepal, 2022 and based on the patient's presenting symptoms, test for dengue (NS1 and IgG/IgM), and *Salmonella typhi* IgG/IgM was requested along with hematological and biochemical parameters. Furthermore, urine culture and routine examination as well as blood culture was also requested. Blood tests revealed Dengue Anti- IgM positivity along with thrombocytopenia, both of which are consistent with dengue infection. Moreover, bilirubin and liver enzymes were increased with subsequent hypoalbuminemia. The results of the *S. typhi* IgM test were positive, indicating possible concurrent *Salmonella typhi* and dengue infection. Hydration therapy with crystalloid fluid was initiated instantaneously. Additionally, 100mg hydrocortisone was also injected immediately. The patient received three doses of a 1000mg paracetamol tablet each day and two daily injections of the ceftriaxone, 1000mg. Domperidone 10 mg & Ondansetron 4 mg were given to the patient to treat the nausea and vomiting that accompanied the indigestion. Tables 1 and 2 documents the serological testing and subsequent hematological as well as biochemical profile respectively following patient hospitalization.

Three to four days following hospitalization, the blood parameters were initially checked. With the exception of normal platelets and a total WBC count, the aberrant blood values were concerning. Urine and blood cultures test requested during admission came out negative despite routine examination reported increase in pus and epithelial cells. No clinical improvements were noticed. Consequently, the follow-up tests for Dengue IgG/IgM and *S. typhi* IgG/IgM as well as several tests for tropical fever panel (Scrub typhus IgG/IgM, *Leptospira* IgG/IgM, tests for *Brucella* Ab, K-39 total Ab test for Leishmaniasis, and smear for malarial parasite) were required. Acute infection of Scrub typhus with IgM positivity was reported despite having no physical signs of eschar as seen in patients with scrub typhus infection. Additionally, positive IgG Ab for *Leptospira*, Dengue and *S. typhi* was also recorded. Leishmanial (K-39) Ab came back negative, but the test for *Brucella* Ab agglutination came back positive implying exposure of the patient to the bacteria but did not establish acute or previous infection. For the treatment, 100mg Doxycycline was immediately initiated. Follow up I serological testing and subsequent hematological as well as biochemical profile is documented in Table 1 and 2.

Regular follow-up and no adjustments to the prescription were made. Subsequent follow-up showed no improvement in the liver enzyme levels - ALP value of >1600 U/L; bilirubin levels had dropped from the first follow-up but had remained clinically higher. Low hemoglobin level, low hematocrit %, low RBC indices, lymphocytosis, neutropenia, increase in bilirubin, and liver enzymes were seen throughout the follow-up course. Platelets level fluctuated during the course but eventually returned to normal. Patient was discharged when she was hemo-dynamically stable and symptomatically better. All the follow-up laboratory investigations performed until discharge was represented in Table 2.

The patient was informed upon discharge of any potential warning indications. It was advised to stay hydrated and to use insect repellent and/or mosquito nets. The patient was given a full explanation of how to take the prescribed prescriptions on a regular basis.

Discussion

The case illustrates the acute multi-bacterial infection of *Salmonella typhi* and *Orientia tsutsugamushi* in patient with Dengue fever. All the diagnosis was made on the basis of rapid serology test kit. Rapid serology kits can be questioned for their accuracy, but due to lack of resources in the settings and deteriorating condition of patient, the need for quick diagnostic approach was needed. Clinical laboratory parameters also played a vital role for taking the medical decision in addition to rapid serological tests. Other tests such as ELISA and/or polymerase chain reaction would lead to more confirmatory identification but were not accessible.

Dengue infection was diagnosed based on IgM positivity. Manufacturer (SD Bioline Dengue Duo, Abbott, Santa Clara, USA) reported sensitivity of 94.2% and specificity of 96.4% for diagnosis of acute IgM dengue infection. *Salmonella typhi* IgG/IgM (Bioline Diagnostics LLP, Delhi, India) was also identified based on

IgM positivity with sensitivity and specificity of 91% and 99.3% respectively. Suspecting the possible cross-reactivity of Rapid *Salmonella typhi* IgM in dengue fever, which is also concluded with the study performed by Bhatti et al, follow-up test was requested⁵. Three to four days following the initial test, a follow-up test showed that both the IgG/IgM tests for *S. typhi* and dengue were IgG positive. The study performed by Bhatti et al concluded cross-reactivity based on positive *S. typhi* IgM but negative IgG on dengue patients using rapid kits but our test showed positive IgM-Ab on initial test and subsequent IgG positivity on follow-up⁵. ImmuneMed Scrub Typhus Rapid test kit was used for qualitative detection of IgM/IgG Ab specific to *Orientia tsutsugamushi*. The sensitivity and specificity was 97.3% and 99.7% respectively.

Our patient works primarily in agricultural fields in Dang district of Nepal. Her work may have had her be exposed to ticks and mites. Furthermore, climatic condition as well as seasonal factors also played a role in co-infection⁴. Various studies and case reports have been documented regarding co-infection of Dengue virus and scrub typhus⁶, scrub typhus and enteric fever⁷ as well as dengue and enteric fever⁸ in Nepal. Few cases of all three i.e. dengue, scrub typhus and *S. typhi* co-infection was reported in India⁹. A study conducted by Murdoch DR et al did not observe any eschar in patient with scrub typhus-typhoid co-infection which is also consistent with our non-finding of eschar⁷. Thrombocytopenia, transaminitis, hyperbilirubinemia along with subsequent hypoalbuminemia was seen in our patient which is also consistent with dengue-scrub infection as conducted by Basheer A et al¹⁰. Another study in scrub- typhoid and dengue- typhoid co-infection revealed low hemoglobin level, thrombocytopenia, and increase in transaminases level^{11,12}.

Conclusion

Multiple co-infections may result in a febrile sickness with overlapping spectrum of symptoms that can be difficult to detect and treat. Nepal is prevalent to numerous endemic diseases such as dengue, scrub typhus and typhoid fever. Rapid diagnostic tests as well as subsequent correlation with other laboratory parameters can be useful in early treatment of patient and subsequently decrease the burden of co-infection and mortality.

Author's contribution

BRB, AP and SP contributed in data collection. BRB, RB and AM contributed to the writing of the manuscript. BRB and RB helped editing of the manuscript and critical reviewing. All authors have read and approved the final version of the manuscript.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Acknowledgments

The author acknowledges patient and her son's willingness to share medical history for educational, research, and publication purposes.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest.

Ethics approval

Our institution does not require ethical approval for reporting individual cases.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and accompanying medical data.

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Table legend

Table 1: Serological tests of patient demonstrating infection with multiple micro-organisms

Table 2: Hematological, Biochemical and Urine analysis of patient during admission and subsequent follow-up until discharge.