CASE REPORT

# CO-INFECTION OF DENGUE, LEPTOSPIROSIS AND MURINE TYPHUS: A RARE CASE IN ENDEMIC REGION

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**Abstract.** Tropical diseases often present as fever with non-specific symptoms known as acute undifferentiated febrile illness. This poses a substantial diagnostic problem made more difficult in the setting of co-infection, although these are seldom reported. Here, a case report is presented of a 31-year-old Thai man with fever for seven days, whose clinical picture and laboratory results were not compatible with a classic syndrome of a single tropical disease. Subsequent comprehensive investigations revealed co-infection of dengue infection (without warning signs), leptospirosis and murine typhus. Empirical antibiotic treatment with doxycycline was prescribed and the patient was discharged on Day 3 after admission.

**Keywords:** co-infection, dengue, leptospirosis, murine typhus, tropical disease

## INTRODUCTION

Acute undifferentiated febrile illness (AUFI) is one of the most critical health problems in tropical areas. Dengue, leptospirosis and rickettsia are the more common etiologies of AUFI in Thailand (Luvira *et al*, 2019). Unfortunately, from clinical presentations these infections are difficult to distinguish from one another and share a similar geographic distribution throughout the Asian Pacific area (Wangdi *et al*, 2019).

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In Thailand, dengue can be found in all regions of the country, with outbreaks occurring during the rainy season (May to September). Symptoms of dengue range from AUFI to dengue hemorrhagic fever/dengue shock syndrome; no specific treatment is currently unavailable (Rajapakse *et al*, 2012). Leptospirosis is predominately found in agricultural settings and presents a wide variety of clinical courses ranging from subclinical to a severe form, Weil's disease, and while early antibiotic treatment is crucial, diagnosis of the pathogen is challenging due to non-specific manifestations, low accuracy of clinical diagnosis and lack of point-of-care laboratory testing (Chierakul, 2014). Murine typhus is distributed worldwide but is under-recognized (Civen

and Ngo, 2008). The triad of murine typhus manifestations is fever, headache and rash, but complications and mortality are lower than dengue and leptospirosis (Lee and Rose, 2018).

This report presents a case of triple infection of dengue, leptospirosis and murine typhus. Clinical clues towards detection of co-infection are discussed.

## CASE REPORT

A 31-year-old Thai man presented with high grade fever, retro-orbital pain and nausea for the previous seven days. Two days before admission, he developed dry cough and severe myalgia accompanying with high grade fever, but no history of bleeding or rash. The patient resided in an urban area of Bangkok and reported taking two weeks previously a two-day trip to Yala, a southern province. The patient reported absence of allergic symptoms, previous illness, current prescribed medication or consumption of herbal concoction. Body temperature was 39.2°C, respiration rate of 22/min, pulse rate of 123/min, and blood pressure of 140/83 mm Hg. Physical examination revealed no abnormality except generalized maculopapular rash on trunk and positive tourniquet test. Jaundice, edema, eschar, lymphadenopathy and hepatosplenomegaly were not found. The patient was admitted due to high grade fever and poor oral intake. Basic laboratories tested on the date of admission (Day 7 post-onset of fever) showed normal white blood cell count and kidney function while the liver function test had slightly increase of total bilirubin, serum aminotransferases, alkaline phosphatase (Table 1). Chest radiography was normal.

At presentation, the differential diagnosis of AUFI was dengue, leptospirosis, malaria and rickettsia. Common etiology of rickettsia in Thailand is *Orientia tsutsugamushi* and *Rickettsia typhi*, causative agent of scrub typhus and murine typhus respectively. Malaria was excluded from negative (both thick and thin smear) blood smear. Rapid diagnostic tests for dengue NS1 antigen and IgM/IgG (LumiQuick Diagnostics Inc, Santa Clara, CA), rickettsia IgM/IgG (LumiQuick Diagnostics Inc, Santa Clara, CA) and leptospirosis IgM (Leptorapide®; Linnodee, Doagh, Northern Ireland) (as described in Luvira *et al*, 2019) resulted in positive IgG test for *R. typhi* (GenBio, San Diego, CA). Hemoculture (BACTEC™ 9050 system; Becton, Dickinson and Co, Franklin Lakes, NJ) showed no growth. The patient received empirical treatment with oral doxycycline (200 mg in the first dose followed by 100 mg twice a day for seven days). Rash disappeared on Day 1 after admission; fever was no longer detectable after 48 hours of antibiotic treatment and general conditions improved on Day 3 after admission at which time the patient was discharged. Laboratory results returned to hospital normal ranges at week 2 following treatment (Day 21 post-onset of fever) (Table 1).

PCR assays and serology tests were performed for detection of the causative agents (except *Plasmodium* spp.) as previously described (Luvira *et al*, 2019). PCR assays produced positive results for dengue virus serotype 1 and *Leptospira* but negative both scrub and murine typhus, the latter defined from a four-fold increase in an immunofluorescence assay (Department of Medical Science, Ministry of Public Health, Thailand). Thus, the patient had a combined infection of dengue, leptospirosis and rickettsia (murine typhus).

Table 1
Clinical data of a patient with acute undifferentiated febrile illness admitted to the Hospital for Tropical Diseases, Mahidol University, Bangkok, Thailand.

| Laboratory test | Day 7 post-onset of fever | Day 21 post-onset of fever |
|---|---|---|
| CBC | | |
| Hct (%) | 38.1 | 38.7 |
| WBC/μl (N%, L%, atypL%) | 8,100 (76%, 11%, 3%), | 6,400 (59.1%, 31.1%, 0%) |
| platelet count/μl | 183,000 | 230,000 |
| Blood urea nitrogen/creatinine | 10.6 | 12.9 |
| DB (mg/dl) | 0.19 | 0.2 |
| TB (mg/dl) | 1.05 | 0.51 |
| ALP (IU/l) | 95 | 78 |
| ALT (IU/l) | 118 | 38 |
| AST (IU/l) | 98 | 22 |
| Malaria (thick and thin smear) | Negative | NA |
| Rapid diagnostic test | | |
| Dengue NS1 Antigen and anti-dengue IgG/IgM | Negative | NA |
| Leptospirosis IgM | Negative | NA |
| Rickettsia IgG/IgM Test | Negative | NA |
| ImmunoDOT test for *Rickettsia typhi* | Positive | NA |
| Blood culture | No growth (two specimens) | NA |
| Dengue PCR assay | Dengue virus serotype 1 | NA |
| Dengue ELISA | IgM negative; IgG positive | IgM negative; IgG positive |
| Leptospirosis PCR assay | Positive | NA |
| MAT | Negative (<1:100) | Negative (<1:100) |
| Scrub typhus PCR assay- | Negative | NA |
| Murine typhus PCR assay | Negative | NA |
| Scrub typhus IFA | IgM negative; IgG negative | IgM negative; IgG negative |
| Murine typhus IFA | IgM 1:100; IgG <1:50 | IgM 1:400; IgG 1:100 |

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; atypL: atypical lymphocytes; CBC: complete blood count; DB: direct bilirubin; ELISA: enzyme-linked immunosorbent assay; Hct: hematocrit; IFA: immunofluorescence assay; L: lymphocytes; N: neutrophils; NA: not applicable; PCR: polymerase chain reaction; TB: total bilirubin; WBC: white blood cell count; μl: microliter; mg/dl: milligrams per deciliter; IU/l: international units per liter .

## DISCUSSION

Concurrent infection with more than one pathogen in AUFI patients is not uncommon, but actual prevalence and impact on public health are underrated. A systematic review of the etiology of severe febrile illness in low- and middle-income countries concluded 17.9% of cases are due to more than one pathogen (Prasad *et al*, 2015). Co-infection of dengue and leptospirosis in tropical regions is between 1.3-4.1% as these diseases share a common distribution of endemicity (Kumar *et al*, 2012; Suppiah *et al*, 2017), with a higher mortality (29.6%) from dengue and leptospirosis co-infection compared to dengue (3.7%) or leptospirosis (14.6%) alone (Kumar *et al*, 2012). Prevalence of leptospirosis, rickettsia, brucellosis and typhoid co-infection is 187 per 1515 population in rural and agriculture regions of Egypt (Parker *et al*, 2007). Co-infection of leptospirosis and murine typhus was also reported in a laboratory-based surveillance study in Egypt (Parker *et al*, 2007).

Although signs of fever, myalgia, maculopapular rash, and mild thrombocytopenia can be found in all three diseases of interest, it is worth noting that clinical pictures of retro-orbital pain, nausea and positive tourniquet test suggest dengue infection. However, the long duration of fever (seven days) and a predomination of neutrophils are not compatible with classical dengue infection. In addition, elevated levels of aspartate aminotransferase compare to alanine aminotransferase, typical presentation in dengue infection (Kittitrakul *et al*, 2015; Luvira *et al*, 2019), was absent in the patient. A history of travel to rural areas, combined with severe calf pain, raises a suspicion of leptospirosis (Lee and Rose, 2018). Owing to its predominance as the cause of rickettsia in Bangkok and its similar presentation to dengue, murine typhus was also considered (Luvira *et al*, 2019). An empirical therapeutic treatment with doxycycline was prescribed owing to the length of time required for laboratory confirmation of these infections and malaria had been excluded (Suputtamongkol *et al*, 2010).

In clinical practice, co-infections could be underdiagnosed given several tropical diseases, such as dengue, mild form of leptospirosis and rickettsia, can resolve spontaneously. Nevertheless, early treatment is able to reduce duration of symptoms and complications, especially in leptospirosis (Civen and Ngo, 2008). Clinicians should be aware of co-infection in AUFI patients with atypical presentations, those with severe symptoms and patients who do not respond to treatment.

In conclusion, co-infection in tropical disease is a challenging problem that is much under-recognized. A vigilant attitude towards atypical clinical presentations and laboratory results is required to recognize such cases allowing appropriate empirical therapeutic treatment without waiting for lengthy laboratory confirmation of the causative pathogens and thereby avoiding possible complication and/or more severe outcome.

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## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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