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Case Report

Triple co-infection involving Dengue Fever, Scrub Typhus and Acute Brucellosis - a rare and surprising entity

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Abstract

We report a case of a 28 year old patient presenting with the chief complaints of fever attributed to multiple co-infections. Co-infections have been infrequently reported in literature, dual co-infections being the most common variety. Dengue Fever, Scrub typhus and Acute Brucellosis are commonly found in North India, however they have never been reported to occur simultaneously in the same patient. Cross-reactivity amongst the tests for these infections is unlikely as well. This highlights the possibility of the multiple co-infections in patients presenting with mixed or un-improving symptoms as well as those with laboratory values disproportionate to each tropical illness. Physicians should hold high index of suspicion for co-infections if the same is noted in patients with fever.

CASE REPORT

A 28-year-old female living in Uttarakhand presented with complaints of high-grade fever with rigors, fatigue and retro-orbital pain for a duration of nine days. She complained of generalised joint pains as well as backache which was acute in onset.

She did not report any rash or insect bites but reported that she lived in a heavily wooded area and reared cattle for a living. Further still, no history of trauma was reported with reference to her back ache.

She was examined after a thorough history taking. She was febrile with a temperature of 104 degrees Fahrenheit and dyspnoeic with a respiratory rate of 24 cycles per minute and an oxygen saturation of 94% on room air; her remaining vitals were within normal limits.

General examination revealed mild pallor, icterus, and mild periorbital oedema alongside pitting-type pedal oedema until the ankles. She had a generalised erythematous rash but no petechiae or eschar. Swollen, tender joints were noted as well. Chest auscultation exhibited bilateral basal crepitations with normal heart sounds. Abdominal examination exhibited splenomegaly measuring two centimetres below the costal margin and a tender liver. On examination of her back, there was diffuse pain over her lower back with no pin-point tenderness or neck stiffness. The rest of her examination was unremarkable.

Table 1. *Her laboratory findings were listed in this table*

Investigations	Findings
Haemoglobin(g/dl)	11.6
PCV(%)	35.8
Platelets(n x 10^9/L)	28
Total Leucocyte Count(n x 10^9/L)	11.9
ESR(mm/hour)	35
PT/INR	11 seconds/1.06
APTT	30 seconds
S. Creatinine(mg/dl)	0.7
S. Urea(mg/dl)	8
Random Blood Sugar(mg/dl)	90
S. Potassium(mEq/L)	3.7
S. Sodium(mEq/L)	139
Total. Bilirubin(mg/dl)	5.09
Direct Bilirubin(mg/dl)	3.5
Indirect Bilirubin(mg/dl)	1.59
Alanine Aminotransferase(U/L)	144
Aspartate Aminotransferase(U/L)	506
Alkaline Phosphatase(IU/L)	363
Lactate Dehydrogenase(U/L)	409
S. Albumin(mg/dl)	4.0

Abdominal ultrasound examination revealed mild ascites and mild splenomegaly, and chest radiography exhibited bilateral pleural effusion which was evaluated by aspiration and found to be transudative. Transthoracic echocardiogram was normal. An X-ray of her lumbosacral spine was obtained for her back ache and was found to be normal.

The patient was evaluated for tropical fevers commonly found in the region such as Scrub Typhus, Dengue Fever and Malaria. Her Scrub Typhus and Dengue fever Rapid testing came back positive. Dengue Fever was further confirmed with IgM and NS1 antigen ELISA testing and Scrub Typhus with IgM testing, both of which were positive. The patient was started on oral doxycycline 100mg twice daily alongside supportive care and platelet count monitoring. Serology for Hepatitis B (HBsAg), Hepatitis C virus (Anti HCV antibodies), Hepatitis A virus (HAV- IgM), Hepatitis E Virus (HEV- IgM) and ELISA for Human Immunodeficiency virus antibodies were negative. Rheumatological markers such as antinuclear antibodies, Rheumatoid factor, Typhidot and Direct Coomb’s test were also found to be negative as well.

However, the patient did not exhibit any improvement after 2 days of proper antibiotic therapy and complained of persistent back aches. Due to her relevant history of cattle rearing and symptomology, the patient was evaluated for Brucellosis and Brucella tube agglutination test serology was sent which too rendered a positive result.

Oral doxycycline was continued and intravenous gentamicin was added to the patient’s regimen for a duration of one week. She started improving and exhibited marked improvement in both clinical and laboratory parameters. The patient was then discharged and advised to continue prescribed antibiotics for a period of six weeks.

DISCUSSION

Scrub typhus is a rickettsia infection that is commonly found in India, especially in the sub-Himalayan regions and southern states. It is transmitted by Trombiculidae, a type of mite usually found in woodlands and damp areas with vegetation. If diagnosed early, it is easily treatable; however, in certain cases may be potentially fatal. predominantly found in wooded areas and forests.

Humans may acquire the infection on via “chigger bite” on passing through infested areas. The bites, though barely noticeable at first may leave behind a typical eschar assisting with the diagnosis. The infection is introduced into the bloodstream via the bite and the rickettsia on proliferation causes damage to the vasculature leading to widespread plasma leakage and eventual circulatory collapse. The initial presentation is relatively general with fever and headache being the commonest manifestations (1-3).

Dengue fever is endemic to Southeast Asia as well with outbreaks occurring periodically during the monsoon. It is a mosquito-borne viral illness caused by the genus Flaviviridae. It has four major serotypes and the vector, in this case, is the Aedes mosquito. The disease may be transmitted via a mosquito bite and incubate into either a flu-like illness which may be self-resolving or may progress to more lethal versions such as dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) which are often fatal (4-6).

Such varied presentations may place Dengue fever as a common differential alongside other tropical illnesses and even be found to occur concurrently. It has been commonly reported in the literature that Dengue fever has occurred along with Leptospirosis and Malaria in the same patient. Salmonella Typhi and Dengue have been observed to occur simultaneously as well (7-9).

It is not unusual to find infections caused by multiple pathogens in the same individual in developing countries, especially during periods of an outbreak.

India’s tropical climate allows for outbreaks of both Dengue fever and Scrub Typhus. Both of these diseases peak in the monsoons and share common presenting features. However, despite these similarities dengue-scrub typhus co-infection has been reported sparingly (9, 10).

Brucellosis is a bacterial infection caused by its subtypes- “Brucella Melitensis, Brucella Abortus, Brucella Suis and Brucella Canis” (11). The disease is transmitted from infected animals, primarily cattle to humans by ingestion of “infected animal products, close contact with an infected animal or inhalation of aerosol”. The disease remains a significant health problem in the Mediterranean region, South-east Asia and Central America (12, 13). Brucellosis affects nearly every system and presents with a broad array of clinical manifestations, many of which overlap with Dengue fever which makes their distinction a diagnostic challenge (6, 11).

Both diseases present with non-specific fever and overlapping symptoms such as myalgia, arthralgia, and headaches including haematological manifestations such as thrombocytopaenia or pancytopenia. However, their concurrent existence has been rarely observed perhaps due to a low degree of clinical suspicion or lack of awareness.

Scrub Typhus and Brucellosis share clinical features with the more commonly found Dengue Fever, however, unlike Dengue fever, require specific antibiotic treatment for the recovery of the patient. Thus, making their identification vital in areas where co-infection may be suspected. Early identification vastly improves the patient’s prognosis and assists in reducing hospital stays. Scrub Typhus and Brucellosis co-infections with Dengue fever individually may have been reported in the literature, however, to find all three infections occurring concurrently have never been reported before, thus making our case report the first of its kind.

Besides the high index of clinical suspicion which led to the abovementioned diagnosis, a question that must be addressed is that of cross-reactivity.

The confirmatory diagnosis of brucellosis depends upon the isolation of organisms from blood or tissue samples. However, serology employing serum agglutination tests remains the most commonly used diagnostic tool due to availability and ease. A titre above 1:160 is considered positive for diagnosis (14).

The diagnosis of dengue fever also depends upon similar serology testing with a three to five-time rise of IgM titre within 3-5 days after infection is considered diagnostic (15).

Ayyub et al state in their work that “the combined Pan Bio Duo dengue IgM and IgG capture ELISA test is a commonly used accurate and rapid test for the detection of antibodies to dengue viruses in samples of human serum. The overall sensitivity of the test is 90- 100% in diagnosing primary infection while specificity for other flaviviruses is above 75% and non-flavivirus is about 100% thus making false positives rare (16, 17).

However, the likelihood of finding elevated IgM titres up to three months after active Dengue infection makes the test unreliable, by itself (18).

The usage of rapid NS1 antigen detection as well as NS1 antigen ELISA testing has shown some promise as a diagnostic tool for Dengue Fever. Non-structural protein NS1 is actively secreted in the bloodstream during Dengue Infection, thus making it a useful diagnostic marker (19).

The sensitivity of rapid NS1 antigen detection and NS1 antigen ELISA testing has been found to be “81.5% and 89.9%” respectively, while the specificity has been found to be “66.7% and 100%” respectively. Several studies such as Shrivastava et al and Ahmed and Broor have shown sensitivity and specificity of NS1 antigen ELISA testing to range from 76-97% and 98-10% respectively, thus suggesting its usefulness for the diagnosis of Dengue fever. Gaikwad et al found the concordance between NS1 antigen ELISA and RT-PCR was found to be 100% from day 3 to day 8. Thus implying that a positive NS1 antigen ELISA test could be considered equivalent to RT-PCR in resource-deficient settings (20-22).

Serological cross-reactivity is uncommon in Pan Bio Duo dengue IgM and IgG capture ELISA assay and the same has been amply re-affirmed in literature” as confirmed by Cuzzubo et al.

Further still, NS1 antigen cross-reactivity may occur amongst flaviviruses themselves but is otherwise found to be specific for Dengue fever (19).

Cross-reactivity of Brucella serum agglutination test with Pan Bio Dengue Duo IgM and IgG capture ELISA used for serological diagnosis of dengue fever has not been reported previously and is considered highly unlikely (17, 23).

ELISA detecting Orientia tsutsugamushi-specific IgM antibodies is considered highly discriminatory with “sensitivities and specificities of 92% and 92% respectively” as shown by Kannan et al. They go on to state that “sensitivity and specificity of Immunofluorescence Assay(IFA) were found to be 95% and 74% respectively and that of Rapid Diagnostic Tests(RDT) was 94 % and 92%” thus implying that false positives in this test would be a rarity as well (24).

In this case, positive IgM and NS1 antigen ELISA status for Dengue Fever as well as positive RDT and ELISA for Scrub Typhus determines the presence of concurrent infections thus confirming this case to be the first triple positive co-infection in literature (25).

However, one cannot rule out cross-reactivity due to the absence of a definitive diagnostic test in the form of virus isolation from blood or other body tissues or RT-PCR which was not available.

The possibility of concurrent tropical infections is a very real entity as evidenced by our case report. However, we find it under-reported or under-noticed due to the overlapping symptomology presented by most of these illnesses. As some of these infections have the potential to be fatal, we hope that our case report will highlight the importance of identifying laboratory or clinical anomalies as the initial clue for the existence of co-infections. Thus leading to a better outcome for the patient.

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