Short Communication

Delayed Diagnosis of Scrub Typhus in Dengue Epidemic: A Case Report

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Abstract

We report a case of scrub typhus presenting with fever and thrombocytopenia highlighting the wide variation in clinical presentations leading to delayed diagnosis in dengue epidemic. Fever and thrombocytopenia are the most common clinical presentations in viral hemorrhagic fever but other diseases like malaria, typhoid, leptospira, rickettsial and other arboviral diseases, should also be considered in differential diagnoses. A high clinical suspicion of scrub typhus and early differentiation from other diseases is important as lethal complications can occur because of delay in diagnosis and treatment.

Keywords: Scrub typhus, Dengue, Thrombocytopenia.

Introduction

The typhus and 'spotted' fever are caused by bacteria of the family Rickettsia ceae, which are obligate intracellular, Gram-negative, non-flagellate small pleomorphic coccobacilli.[1] Scrub typhus is an acute febrile illness caused by Rickettsia *tsutsugamushi.* Dengue fever is a common infection in India that often presents as acute febrile illness with thrombocytopenia and skin rash. It is important to rapidly delineate the cause of fever in regions where several infections like dengue, typhoid, malaria, scrub typhus, leptospira, and chickungunya are also seen. Scrub typhus is grossly under diagnosed in India due to its non-specific clinical presentations, limited awareness and low index of suspicion.

Clinicians should be aware of this condition during the outbreaks of hemorrhagic fevers such as dengue fever, chikungunya fever, leptospirosis and other viral fevers like zika virus. This infection also manifests clinically as high grade fever, body ache, skin rash, not subsiding with antipyretics. The typical rash and eschar may not always be present.[2] Most often there will be generalized or localized, tender lymphadenopathy. The severity of scrub typhus varies from sub-clinical illness to severe illness with multi-organ system involvement, which can be serious enough to be fatal, unless diagnosed early and treated. The mortality due to the disease is 7–30% in delayed treatment or multiple organfailure.[3]

Case Report

A 45-year-old male, a manual laborer presented with complaints of high-grade continuous fever of 10 days duration, associated with headache. He also had myalgia and multiple joint pains without signs of inflammation (arthralgia) for the past 5 days. He was diagnosed as case of suspected dengue fever because of ongoing epidemic in Delhi. The patient was given symptomatic treatment for 6 days in a private hospital without any relief in symptoms. Because of persistent fever, myalgia and joint pains he was referred to higher center.

On examination in medical emergency, patient was found to be conscious and oriented to time, place and person. His oral temperature was 104° F. His pulse rate and blood pressure was 100/min and 120/70 mmHg, respectively.

He was having significant calf muscle tenderness on both sides. He had yellow discoloration of his bulbar conjunctiva of both eyes. Respiratory, cardiovascular, gastrointestinal and central nervous system examinations were within normal limits.

Blood tests revealed a total leucocyte count of 12,400/µL with 50% neutrophils, 45% lymphocytes, 5% eosinophils, and platelet count of 35,000/mm^3. The erythrocyte sedimentation rate was 32 mm/1^{st} hr. Total bilirubin was 4.6 mg/dL with direct fraction of 3.8 mg/dL. The SGOT, SGPT and ALP were 369, 302 and 204 U/L respectively.

His blood urea was 42 mg/dL and serum creatinine was 0.8 mg/dL. His serum CPK total was 2400 U/L (normal range 50–200 U/L).The serology (IgM and IgG) and NS1Ag for dengue was negative. Peripheral smear and card test for malaria was negative too. HBsAg and anti-HCV were also non-reactive. C-Reactive protein level in the serum was 2.8 mg/dL (normal is less than 1 mg/dL). Chest X-ray, electrocardiogram and routine urine examination were normal.

The patient was re-examined in wards and found to have an ulcer, with necrotic base, of 6 mm size in the region of left upper thigh Fig. 1). There were also multiple, tender, discrete, 1.5×1.5 cm sized palpable lymph nodes in bilateral inguinal region. The diagnosis was revised provisionally to scrub typhus infection. He was started on tablet Doxycycline 100 mg twice daily and serology for scrub typhus was sent.

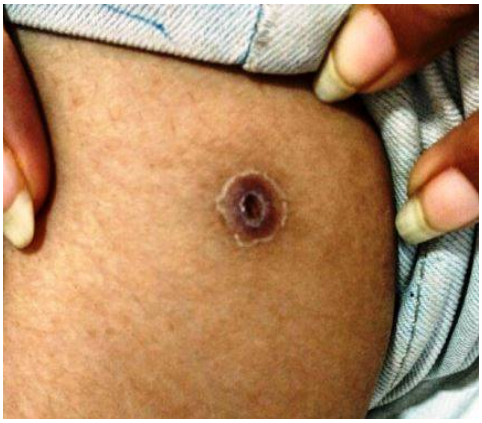

Figure 1.An Eschar on Upper Part of Thigh with Central Necrosis

Leptospira antibody test, done in the second week, was negative. Weil-Felix test, done on the 14^{th} day after the start of symptoms, was positive in titer of proteus OX K:1/320, proteus OX 2:1/20 and proteus OX19:1/20. ELISA (IgM) for scrub typhus was also positive. Patient became afebrile 2 days after starting Doxycycline and other symptoms also improved over next few days. He was discharged on the 6^{th} day after admission in a stable condition.

Discussion

In epidemic of dengue, patients usually present with fever, rash, joint pains and thrombocytopenia; however, those patients who are having persistent fever even after 10 days of symptomatic treatment, an alternative diagnosis should always be considered like malaria, typhoid, leptospirosis, HIVor scrub typhus disease because there is overlapping of clinical signs and symptoms in these patients. In dengue epidemics, other mimickers as given above or dual infections are also seen which can cause diagnostic challenge or delay in diagnosis.

The clinical presentation of scrub typhus is notoriously non-specific. Like dengue, it also can occur during the monsoon season and in those who are engaged in occupational or recreational behavior which brings them into contact with mite-infested habitats. The painless chigger bite can occur on any part of the body but it is often located in areas that are often omitted on examination like genital region or axilla.[4] Our patient too had an eschar at the upper part of thigh, which was missed at initial evaluation in private hospital and in our emergency too. An eschar forms at the bite site in about half of primary infections which begin as small papules, which undergoes central necrosis and acquire a blackened crust to form lesions resembling a cigarette burn but its absence does not rule out scrub typhus. The fever starts abruptly and is of high grade and associated with severe headache, pain in joints and muscles and other features of systemic organ involvement. Characteristically, generalized lymphadenopathy with hepato-splenomegaly may be seen in these patients.[5] Laboratory diagnosis of scrub typhus is based on serological and molecular diagnostic tests. Weil Felix test has a low sensitivity and specificity but may be

helpful in resource-limited clinical settings.[6] This test is based on the fact that some of the antibodies that are formed in the body during a rickettsial infection react with certain strains (OX-2, OX-19 and OX-K) of Proteus *vulgaris* and cause them to clump (agglutinate). This test should be done in the second week of the patient's illness. Another test like the indirect immunofluorescence assay (IFA) is highly sensitive and is considered 'gold standard' but its use is limited by the cost and availability. Polymerase chain reaction (PCR) can detect acute infection with Orientia *tsutsugamushi*.[7] A rapid immunochromatographic assay which uses recombinant major outer membrane protein antigen of Orientia *tsutsugamushi* to detect IgM, IgG and IgA antibodies has been shown to be reliable and suitable for use in developing countries but is expensive and not available everywhere.

Scrub typhus is diagnosed late due to lack of diagnostic facilities and a low index of suspicion among clinicians as the signs and symptoms are non-specific. The complications in scrub typhus develops after first week of illness and are directly related to the blood load of O. tsutsugamushi.[8] Therapeutic trial with antibiotic therapy is warranted where index of suspicion is high.

Tetracycline (500 mg given four times a day) or Doxycycline (200 mg once a day for seven days) is the treatment of choice. Chloramphenicol (500 mg given four times a day) is an alternative. Rifampicin (900 mg per day for a week) has been found effective in patients who respond poorly to conventional therapy. Macrolides may be used in children and pregnant women.[9] In our case, the patient presented late, about 10 days after his first symptom. Initially he was empirically treated for dengue and malaria fever but on detailed clinical examination, we found an eschar in inguinal area and final diagnosis of scrub typhus was confirmed by serology test. This again highlights the importance of thorough clinical examination in modern clinical era and resource-limited developing countries like ours.

Conclusion

Scrub typhus is endemic in many parts of India and all clinicians should be well aware of the disease. Fever is the most common feature of scrub typhus and in endemic areas it is one of the causes of "fever of unknown origin". Scrub typhus clinically mimics other infections like dengue, typhoid, malaria, and leptospira as all of them may be associated with high-grade fever, thrombocytopenia, liver and other organ failure. It also has been seen that even after ruling out complicated malaria, leptospirosis and dengue fever, many of these cases remain undiagnosed, so high clinical suspicion is must in these situations. An eschar at the wound site is the single most useful diagnostic clue. So that it is very important to perform a thorough clinical examination to look for eschar and exclude other causes of fever.

Weil-Felix test is a commonly performed test in developing countries although it is not very sensitive. The gold standard serological tests for diagnosis are indirect immunofluorescence and ELISA tests. Therapeutic trial with antibiotics like doxycycline or azithromycin is warranted where index of suspicion is high. With prompt treatment, mortality related to this serious infection is negligible. At present, no effective vaccine for prevention has been developed for scrub typhus. It is known to occur all over India and clinicians should be aware of this potentially serious and underdiagnosed but easily treatable disease.

Conflict of Interest: None

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