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Case Series

Scrub typhus: emerging as a co-infection of acute undifferentiated febrile illness in children in a District hospital of Eastern India

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ABSTRACT

Scrub typhus, a zoonosis, caused by *Orientia tsuttsutgamushi* is transmitted to man through bite of infected trombоculid mite. It is endemic in India as other other South-east Asia countries of Tsuttsutgamuhi triangle and affects children as well. It generally presents as an acute febrile illness with non-specific features like headache rash, lymphadenopathy resembling many other commonly prevalent febrile infections. An eschar, though pathognomonic of Scrub typhus, is often missed clinically. Therefore, a high index of clinical suspicion is essential to establish a diagnosis of Scrub typhus and hence it remains usually under-diagnosed in any undifferentiated febrile illness. In this case series including three cases, we decided to rule out Scrub typhus as a co-infection when there was persistence of fever associated with thrombocytopenia even after ongoing treatment of the primarily diagnosed infection. An eschar was incidentally detected in one case only.

Keywords: Scrub typhus, Co-infection, Thrombocytopenia, Eschar, IgM ELISA

INTRODUCTION

Scrub typhus, the most commonly reported rickettsial infection, is caused by *Orientia tsutsutgamushi*, an obligate intracellular gram-negative bacterium. The disease is acquired by the bite of infected trombuculid larval mite called chiggers.[1,2]

Nearly one million people suffer from this disease every year in South-East Asian countries, popularly known as Tsutsutgamushi Triangle.[3] Since its first outbreak in West Bengal and Assam during World War II, scrub typhus has re-emerged as a widely significant public health issue in almost all over India specially in Northern, North-Eastern, Central and Southern states.[4,5]

Scrub typhus usually starts as a febrile illness with non-specific features like headache, rash, dyspnoea, organomegaly, lymphadenopathy etc., resembling dengue, malaria, enteric fever or seasonal viral infections alike.[6] Eschar, a necrotic lesion with a central black crust resembling a cigarette burn at the site of mite bite is pathognomonic of the disease and found quite unpredictably in 20-87% of cases.[7,8] Again it is often missed in dark skinned subjects during routine examination because it is painless and hence ignored by the patient while mostly found in covered regions like groin and axilla.[9] Moreover both incidence and studies of scrub typhus in children is much lower than in adult population.[10,11] Thus in absence of detection of characteristic eschar or eschar-like lesion Scrub typhus remains under-considered by clinicians as a probable primary diagnosis in any undifferentiated febrile illness in children.[12]

In this case series, persistent character of fever combined with thrombocytopenia, in spite of adequate treatment of the diagnosed primary infection, aroused a high index of

clinical suspicion of presence of a co-infection which was finally sought out to be Scrub typhus.

CASE SERIES

Case study 1: Scrub typhus with dengue

A 5-year-old child was admitted with high fever for 6 days associated with headache, myalgia, cough and oliguria. On clinical examination he had facial puffiness, bipedal edma, a rapid thready pulse, temperature 102˚ F, B.P. 70/50, respiratory rate 40/min, no signs of respiratory distress, bilateral occasional crepitations, no organomegaly, no lymphadenopathy, normal sensorium and no meningeal signs. He was so initially stabilised with IV isotonic fluids for hypotensive shock and monitored as per protocol for the management of hypotensive shock in suspected dengue fever. He was started empirically with IV ceftriaxone. Immediate investigations were aimed to rule out suspected infections and also to find out biochemical features suggestive of acute kidney or liver injury and bacterial sepsis, if any. The work up revealed Hb 8 gm%, TLC 16,200 (Poly 40% lympho 55%), platelets 60000 per cm, hematocrit 38, ESR 22, CRP 6.6, procalcitonin 1.26 ng/ml, malaria antgens for P. Vivax and *P. falciparum* negative, no malarial parasites on blood slides, Widal test for *S. typhi* and *S. paratyphi* negative, LFT (total serum bilirubin 0.4 mg/dl, SGPT 36 U/l, SGOT 101 U/L, ALP 204 U/L), blood urea 45 mg/dl, serum creatinine 1.6 mg/dl, serum Na 135 mEq/L, serum K 4 mEq/L, serum chloride 105 mEq/L and urine routine examination (albumin/occult blood/sugar/ketones/RBC Nil, pus cells 1-2/HPF). Next day his ELISA test for dengue IgM antibody came positive, USG abdomen showed no ascites but small bilateral pleural effusion with chest X-ray having nonspecific changes. On the 3rd day his blood culture report showed no growth of microorganisms. The child recovered from shock with improvement of edema and diuresis within 48 hours but his fever persisted at high grade even after 3 days of admission. His repeat CBC showed TLC 16800/cmm, platelets 70,000/cmm and hematocrit 30. Eventually on repeated search for clinical clues, the mother complained that the child had a mild itch over his genitalia for few days and a small burn-out eschar was detected hidden at the root of the penis underneath the shaft (Figure 1). The child was soon started with azithromycin @ 10 mg/kg per day as per national guidelines for rickettsial diseases and IV ceftriaxone was omitted. Next day his ELISA test for scrub typhus IgM antibody came out positive.[13] The child was afebrile and hemodynamically stable after 48 hours of azithromycin administration. His repeat CBC showed gradual increase of platelet count and fall of haematocrit. Finally, he was discharged on day 7 after completion of azithromycin course for 5 days with final (day 8) routine blood examination showing TLC 8540 (Poly 55%, lympho 40%), platelets 2,90,000/cmm, ESR 11 and hematocrit 22, blood urea 17 mg/dl and serum creatinine 0.6 mg/dl.

Figure 1: An eschar looking like a cigarette burn lesion on the under-surface of the root of penis of the patient (case 1).

Case study 2: Scrub typhus with malaria

A 7-year-old boy admitted with high grade fever for 7 days associated with vomiting but no pain abdomen, normal bowels and high colored urine for last 3 days was clinically irritable but oriented, febrile (101˚F) having BP 110/70, no organomegaly, no lymphadenopathy and no meningeal signs. Initial work-up with blood showed malarial antigen for *P. vivax* positive, Hb 6.8 gm/dl, TLC 4900 (poly 53%, lympho 47%), platelets 53,000/cmm, hematocrit 21%, ESR 22 CRP 12 U/L and dengue IgM ELISA test negative. Hence, chloroquin and primaquin were started on admission as per *P. Vivax* treatment guideline along with symptomatic measures for pyrexia and vomiting. His LFT and urine routine examination was normal. But on day 3 of treatment with antimalarials the patient showed no improvement clinically running persistent high fever and having routine hemogram showing Platelets remaining still low to 64,000/cmm, Hb 7 gm/dl, TLC 5300 (Poly 50%, lympho 44%) and ESR 25. On thorough search there was no suspected eschar like lesion found but azithromycin was started along with sending blood for Scrub typhus serology as per national guidelines.[13] Next day the patient was afebrile and his Scrub typhus IgM Elisa report came positive and Platelets showed a moderate rise to 84000/cmm. Finally, the child was discharged on day 7 on completion of a 5-day course of azithromycin when his platelets showed 2,55,000/cmm, Hb 9 gm/dl, ESR 12 and CRP 3 U/L. He was given primaquin @ 0.25mg/kg for a total of 14 days.

Case study 3: Scrub typhus with hepatitis A

An 8-year-old female child was admitted with fever associated with yellow discoloration of urine and conjunctiva for 10 days. On clinical examination she had high temperature (102˚F), jaundice, BP 105/75, tender hepatomeagaly, no lymphadenopathy, normal sensorium

and no meningeal signs. Her initial investigations revealed malarial parasite antigens negative, Hb-11.3 mg/dl, TLC-9400/cmm (Poly-44%, lympho-48%), platelets 56000, hematocrit 31%, ESR 30, LFT (total bilirubin 7.6 mg/dl, SGPT-1561 U/L, ALP-364 U/L), HBSAg negative, HBC IgM negative, HBA IgM positive, PT 12.5 seconds, INR 0.95 and only hepatomegaly on USG abdomen. She was empirically given IV ceftriaxone and treatment in line of hepatitis A. On day 2 her repeat platelet examination showed 48000/cmm but dengue IgM Elisa negative and Widal test negative. IV Ceftriaxone was withdrawn and azithromycin was started on thorough examination as per national guidelines, though no eschar was detected.[13] On day 3, her Scrub typhus IgM ELISA test came out positive. She became afebrile since day 5 onwards. She was finally discharged on day 8 after completion of 5-day azithromycin course with her platelets raised to 3.08/cmm and LFT having total bilirubin 1.7 mg/dl and SGPT 198 U/l.

DISCUSSION

Thrombocytopenia is a common haematological finding in many infections with overlapping clinical features and thus helps to rule out or establish their co-existence in a febrile illness.

Thrombocytopenia along with leucopenia with raised hematocrit occurs during the course of dengue infection.[14-17] Similarly, thrombocytopenia with or without leucopenia is also observed in malaria and enteric fever.[18-23] Thrombocytopenia with leucocytosis is commonly observed in Scrub typhus and leptospirosis.[24-29] Increased hepatic enzymes with or with hyperbilirubinemia may occur in dengue, Scrub typhus, leptospirosis and enteric fever.[14,17,24,26-33] Chikungunya is also associated with thrombocytopenia and leucopenia with lymphocyte preponderance but it was not considered in this study since none of the cases here had met the definition of clinical and epidemiological criteria as laid down in WHO and national guidelines.[34-36]

In this study thrombocytopenia associated with persistence of fever was common to all the three cases and thus stood as a high index of possibility of existence of a second infection with similar clinical spectrum. Antigens for malaria (vivax and falciparum) and dengue (NS1) were tested as a routine screening at the time of admission in all the cases due to their endemicty and current outbreak in this region.

In the first case presenting with fever with hypotensive shock, Dengue was initially diagnosed in the routine test for dengue. As the fever was persisting for 10 days, the possible co-infection of enteric fever was also ruled out by Widal test. Though shock was corrected within 48 hours, high grade fever was persistent and thrombocytopenia was associated with leucocytosis rather than leucopenia as commonly expected in dengue. Incidentally, an eschar-like lesion, though missed initially, was detected over the genitalia in the course of repeated clinical evaluation and Scrub typhus was serologically confirmed as a co-infection. Though shock with features of acute kidney injury of this child was presumed mainly due to dengue infection, scrub typhus too might be a contributing factor to its pathogenesis.[37-40]

In the second case diagnosed on routine screening as *P. Vivax* malaria, fever did not subside even after full course of antimalarial treatment. Enteric fever being excluded by subsequent Widal test, scrub typhus remained the next possible suspect and later confirmed as a co-infection.

The third case presenting with fever and jaundice was diagnosed as having hepatitis A infection at the very outset. But her persistence of fever coupled with moderate thrombocytopenia with a decreasing trend sparked the suspicion of a co-infection. On excluding dengue, malaria, enteric fever and leptospirosis, scrub typhus was finally diagnosed as a co-infection.

CONCLUSION

Scrub typhus should always be suspected in children as the probable co-infection whenever there is persistence of fever during the course of treatment of a primarily diagnosed infection, especially in a setting of thrombocytopenia. A thorough search for an eschar-like lesion combined by the IgM ELISA test for Scrub typhus antigen should always be done as a routine in every case of suspect.

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