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Neonatal Scrub Typhus Mimicking Sepsis with Multisystem Involvement : A Rare Case Series

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Abstract
Scrub typhus is a common rickettsial infection of human caused by Orientia tsutsugamushi contracted through the bite of an infected mite. India is endemic for this disease and it is often found in pediatric population presented with fever, rash, hepatomegaly, edema, lymphadenopathy and eschar. But Scrub typhus is extremely rare in neonates and often we do not consider this diagnosis initially ,as the presentation is almost sepsis like . Here we reported a series of three cases of neonatal scrub typhus who presented with high grade unremitting fever with varying features of hepatosplenomegaly, convulsion, respiratory distress, oliguria, jaundice, while only one had eschar on chest. Laboratory investigations revealed thrombocytopenia, altered hepatic and renal function, CSF pleocytosis with negative sepsis screen and blood culture. They treated initially as sepsis, meningitis or pneumonia without much improvement. Then IgM scrub typhus report came positive and the neonates start recovering dramatically within few days of using doxycycline (in two cases) or azithromycin (in one case)with gradual normalization of clinical and laboratory parameters. So scrub typhus should be considered as a differential diagnosis in every sick neonates with persistent fever and other signs of sepsis, specially in endemic countries like India. Rarity of the neonatal scrub typhus presented as sepsis with multisystem involvement prompted us to report these cases.

INTRODUCTION

Scrub typhus, the most common rickettsial infection caused by Orientiatsutsugamushi, is contracted through the bite of an infected trombiculid mite, where humans are accidental hosts[1]. India is endemic for scrub typhus due to its location in the Tsutsugamushi triangle. Though often found in pediatric population presenting with fever, rash, hepatosplenomegaly, edema, lymphadenopathy and eschar, but Scrub typhus is extremely rare in neonates and often we do not consider this diagnosis initially[2]. Manifestations in neonate mostly mimic sepsis and so often the diagnosis is missed or delayed leading to multi organ dysfunction syndrome (MODS)[3,4]. Incidence in neonates is 1.6% as per Ganesh[5] and <50 cases of neonatal scrub typhus have been reported so far in literature, with a mortality rate of 18% 6,7. Pathognomonic eschar at the bite site has been reported in only 18% of published neonatal scrub cases. Here we present a series of three cases of neonatal scrub typhus with varying presentations.

Case Report:

Case 1: A 22 day old, male neonate presented with high grade fever for 7 days with hepatosplenomegaly and a blackish maculopapular rash on the right chest wall. High C-reactive Protein (CRP) (34mg/dl), thrombocytopenia(70,000/cumm)and raised liver enzymes (SGPT=248 IU/lt, SGOT= 248 IU/lt) noted. On the second day, baby developed left sided focal clonic convulsions controlled by phenobarbitone. CSF mimic aseptic meningitis(55cells/HPF).On the third day, he developed shock with a Downe's score of 4/10, requiring ionotropic support and continuous positive airway pressure (CPAP). Platelet become 40,000/cumm with diffuse pneumonitis on Chest X-ray. Then scrub typhus IgM report came positive and I.V doxycycline was added at the dose of 2.2mg/kg twice daily for the next 10 days. The baby became afebrile within a period of 48 hours. Blood and urine culture, USG brain, TORCH profile normal. Dengue IgM, MP, MPDA were negative as well. On the eighth day, platelets count raised to 1,60,000/cumm and inotropes and CPAP were gradually withdrawn. Hepatosplenomegaly reduced and baby discharged in stable condition. This case showed multisystem involvement in a scrub typhus (hepatitis, pneumonia, meningitis) along with eschar.

Case 2: A 26 day old, female neonate presented with high grade fever for 5 days and repeated vomiting for last 2 days along with hepatosplenomegaly and conjugated hyperbilirubinemia. The baby was empirically started on Piperacillin/tazobactam and Amikacin with no improvement. Sepsis screen and CSF normal and Dengue IgM, MP, MPDA were negative. On the fourth day, scrub typhus IgM report came positive, syrup Azithromycin (10 mg/kg/day) for 5 days started. She became afebrile within 2 days. Blood and urine culture showed no growth. This case showed scrub typhus with sepsis like presentation along with jaundice.

Case 3: A 19 day old male neonate presented with high fever for 5 days, refusal to feed for 2 days and respiratory distress with a Downe's score of 3/10 and hepatosplenomegaly. He had oliguria with glomerular filtration rate 15 ml/min /1.73 m^2. Blood reports revealed raised WBC, thrombocytopenia, urea-30 mg/dl, creatinine-1.5 mg/dl, CRP-80mg/dl and elevated liver enzymes. Dengue IgM, MP, MPDA were negative.

Fig. 1: Black maculopapular rash-eschar on the right mammary region in first case of scrub typhus

Fig. 2: Hepatosplenomegaly in 2nd case of scrub typhus

Fig. 3: Chest X-Ray showing right sided patchy consolidation in 3rd case of scrub typhus

Table 1. Summary of three cases of neonatal scrub typhus

Clinical History	Case 1	Case 2	Case 3
Age at admission	22 days	26 days	19 days
Clinical presentation	presented with high grade, A intermittent fever for 7 days.	presented with high grade fever for 5 days and vomiting for 2 days.	presented with fever for 5 days with lethargy and refusal to feed for 2 days
Clinical examination and course	hepatosplenomegaly, left sided focal clonic convulsions on 2ndday . On day3,developed shock, respiratory distress, required CPAP, downe's score of 4/10,dopamine till 20mcg/kg/min was required.	Icterus with hepatosplenomegaly, increase in the frequency of vomiting.	Temp 103°F with hepatosplenomegaly. On day 2, developed respiratory distress, downe's score -3/10. Chest X-ray showed right sided patchy consolidation Develops AKI with oliguria.
TLC/cumm	14000	16000	24000
Platelet	70,000	170000	85,000
CRP	34 mg/dl	12 mg/dl	80 mg/dl
LFT	Raised	conjugated hyperbilirubinemia	raised
RFT	normal	normal	urea-30 mg/dl, creatinine-1.5 mg/dl
TORCH	negative	negative	negative
Blood and Urine C/S	No growth	No growth	No growth
CSF	55/hpf, lymphcoytes	<5 cells/hpf	<5 cells/hpf
Scrub typhus IgM	Positive	Positive	Positive
Clinical management	IV Doxycycline 2.2 mg/kg twice daily for 10 days	Syp azithromycin 10 mg/kg/day for 5 days	IV Doxycycline 2.2 mg/kg twice daily for 10 days
Outcome	Baby became afebrile within 48 hours of doxycycline therapy. Gradual improvement in platelet count and regression of liver and spleen	Became afebrile within 48 hours of azithromycin therapy.	Baby became afebrile within 48 hours. Improvement in platelet count and decrease in liver and spleen size
Final diagnosis	Scrub typhus with hepatitis, pneumonia, meningitis(eschar present)	Scrub typhus with gastrointestinal manifestations	Scrub typhus with hepatitis, pneumonia, acute kidney injury.

Chest X-ray showed right sided patchy consolidation Empirical antibiotics and CPAP support initiated without improvement. Intravenous doxycycline started after positive scrub typhus IgM report. He improved dramatically within 2 days with reduced spikes of fever, increased GFR and fall in the creatinine. Blood report after 5 days showed improvement in platelet count along with decrease in the CRP. So this was a case of neonatal scrub typhus with manifestations of hepatitis, pneumonia and acute kidney injury.

Though rare, but still cases of neonatal scrub typhus have been reported in various literature[8,9]. In neonates it often present with sepsis like feature and demographic characteristics should be kept in mind for such cases where antibiotic response is poor. As untreated Scrub typhus can result in fatal consequences, early diagnosis and treatment is of utmost importance . Though American Academy of Paediatrics Committee on Infectious Diseases recommended doxycycline as the drug of choice but due to its possible adverse effects, azithromycin and clarithromycin may be better options for initial treatment[10,11].

In the present case series, three neonates with scrub typhus presented with high grade unremitting fever with varying features of hepatosplenomegaly, convulsion, respiratory distress, oliguria, jaundice, while only one had eschar on chest. Two of them required CPAP and one inotropic support. They treated initially as sepsis, meningitis or pneumonia without much improvement before ELISA IgM scrub typhus came positive. Then started recovering dramatically within few days of using doxycycline (in two cases) or azithromycin (in one case)with gradual normalization of clinical and laboratory parameters.

Jajoo *et al* (2017) reported scrub typhus in a 19 days old neonate presented with features suggestive of severe sepsis. Intravenous clarithromycin (15 mg/kg/day in two divided doses) was initiated with defervescence of fever and clinical improvement within 48 hours[12]. Vindhiya *et al* (2023) presented a case series of 5 neonatal scrub typhus. All of them had fever and high CRP, with either hepatosplenomegaly, shock, paralytic ileus, aseptic meningitis or pericardial and pleural effusion. Two out of five babies had pathognomonic eschar. Three babies were treated with doxycycline and two babies required intravenous azithromycin[13]. Perumal (2016) reported a case of neonatal scrub typhus presenting with multi-organ dysfunction and eschar, who recovered well with iv doxycycline therapy[14]. Deglurkar *et al* (2023) described scrub typhus in seven neonates. All cases had fever and thrombocytopenia, 85% had hepatosplenomegaly. 71% had transaminitis, 57% required respiratory support, 43% had multi-organ dysfunction, 29% had shock. They treated with doxycycline and showed quick recovery[15]. Narayanasamy *et al* (2022), reported a 26-day-old breast-fed infant presented with fever, vomiting, loose stools, abdominal distension and refusal of feeds where fever subsided within 48 hours of starting oral azithromycin[16].

CONCLUSION

The present case series highlights that neonates presenting with features of sepsis like fever, respiratory distress, organomegaly, oedema, thrombocytopenia or shock and showing no improvement on antibiotics with culture negative, should always be investigated for scrub typhus

especially in endemic regions like India. Prompt diagnosis is essential as the infection is easily treatable with specific antibiotics like doxycycline or azithromycin, while delay in management can lead to MODS and mortality.

Ethics Approval and Consent: Informed consent was taken from parent or legal guardian of the neonates to publish the case series.

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