Rickettsial Diseases in Haryana: Not an Uncommon Entity

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Abstract
Rickettsioses have not been reported from the plains of North India and Haryana in particular. Here we are reporting three cases of scrub typhus and one case of Indian tick typhus in the state of Haryana, all of which presented with fever and multi organ dysfunction, rash and without eschar. All were successfully treated with doxycycline.

Introduction
Recent reports from India and other neighboring countries suggest that there is a resurgence of rickettsiosis particularly scrub typhus which is associated with significant morbidity and mortality. In India cases series are available from Himalayan region and south India. Rickettsial diseases are rarely diagnosed in India because of nonspecific clinical presentation, low incidence of accompanying eschar, low index of suspicion and lack of adequate diagnostic facilities. By reporting cases from Haryana, this article intends to draw attention of readers that rickettsial diseases may not be a rare entity in plains and should be actively investigated as a potential cause of fever of unknown origin.

Case 1
A 40 year old female from rural background presented with high grade intermittent fever of 20 days duration. She also complained of generalized swelling, petechial rash over both upper and lower limbs, darkening of tips of bilateral fingers & nose and dyspnoea. On examination she was febrile, tachypnoeic, had tachycardia, icterus, generalized edema, petechial rashes over bilateral forearms, legs, palms and soles. There was hyperpigmentation at the tips of nose, fingers and toes suggestive of microinfarcts (Fig. 1a). On systemic examination she was conscious, with slow and slurred responses to commands. Hepatosplenomegaly was also present. Rest of systemic examination was normal. She was admitted with differential diagnosis of typhoid fever, meningococcemia or gram negative bacterial sepsis. She was given empirical treatment with intravenous Inj. Ceftriaxone 2 gm B.D.

Investigations showed Hb 14.5 gm%, TLC 18000/ mm³ with normal differential count, thrombocytopenia (70,000/ mm³). Bl. Urea 94 mg%, S. creatinine 2.0 mg%, S. bilirubin 3.0 mg%, AST 389 IU/L, ALT 227 IU/L, S. alkaline phosphatase 289 IU/L and Prothrombin Time index of 37%. Widal test, peripheral blood smear for malarial parasite, blood culture, urine culture, leptospiral & dengue serology and chest X-ray were all negative.

The condition of the patient deteriorated and she developed hypotension on day 5. In addition to fluids and inotropic support she was started on oral Doxycycline (100 mg twice daily) because of fever and multiple organ dysfunction syndrome (MODS) with rash & microinfarcts. There was good clinical response to doxycycline and patient became afebrile, normotensive without support and fully conscious with in 72 hours of starting treatment with doxycycline. Serology reports demonstrated IgM antibodies against O. tsutsugamushi (ELISA) confirming the diagnosis of scrub typhus. On follow up after 4 weeks patient was asymptomatic (Fig. 1b).

Case 2
A 22 year old female of urban area presented with high grade fever, headache and joint pain since 2 days with rashes all over the body since 1 day. On examination she was febrile, drowsy and had tachycardia & pleomorphic (macular, papular, petechial and occasionally vesicular) rashes all over the body including palms and soles (Fig. 2) with bilateral conjunctival hemorrhages. On systemic examination she had neck rigidity and positive Kernig's sign. She was treated empirically on the lines of pyogenic meningitis (meningococcemia) with intravenous Ceftriaxone and Dexamethasone. Investigations revealed leucocytosis with hyperkalemic metabolic acidosis.
neutrophilia on complete hemogram. CSF examination showed protein- 350 mg%; sugar- 50 mg% (corresponding blood sugar- 80 mg%); Total cell count-21,900/mm³ with 98% neutrophils & no organisms on gram staining. CSF DNA PCR for Hemophilus, meningococcus and pneumococcus was negative. All other investigations including leptospiral serology were normal apart from mildly deranged liver and renal function tests. Patient’s condition improved initially with resolution of drowsiness, but fever and headache still persisted. On 3rd day she deteriorated and developed hypotension and unconsciousness after which she was started on oral doxycycline because of pleomorphic rash along with fluids and inotropic support. Her clinical condition improved markedly within 48 hours with restoration of normotension and consciousness. Doxycycline was continued for 2 weeks. Serology reports later revealed IgM antibodies against O. tsutsugamushi (Scrub typhus).

Case 3

A 60 year old female from rural background presented with high grade continuous fever since 8 days. There was history of hematuria, headache, multiple joint pain, abdomen discomfort with generalized myalgias. On examination she was conscious and had generalized edema, tachycardia, tachypnoea and hypotension. There was maculopapular rash over trunk and bilateral limbs including palms and soles (Figs. 3a & 3b) along with generalized muscle tenderness. There was no lymphadenopathy, eschar or bleeding from any site. Systemic examination showed crepitations in right infrascapular area and hepatosplenomegaly. She was admitted with differential diagnosis of Gram negative sepsis, rickettsiosis, or chikungunya fever and given empirical treatment in the form of Inj. Ceftriaxone 2 gm BD and Tab Doxycycline 100 mg BD. She had an evidence of multiorgan dysfunction syndrome including acute lung injury, renal dysfunction and evidence of disseminated intravascular coagulation. Chest X-ray showed interstitial infiltrates and blunting of costophrenic angle on right side. There was hypoxia with respiratory alkalosis on ABGA.

Patient had marked clinical improvement with in 72 hours of starting treatment with doxycycline and was discharged after a week. Later serology reports revealed presence of IgM antibodies against R. conorii causative agent of Mediterranean Spotted Fever (aka Indian Tick Typhus in India) Table 1.

Discussion

Rickettsiosis particularly scrub typhus is endemic in Southeast Asia, Northern Australia and pacific islands. In
India it has been reported from Himalayan region particularly Shivalik foothills and southern part of country. Recently there are few case reports of Spotted Fever Group (SFG) rickettsiosis from Himachal Pradesh. These diseases are caused by bacteria of family Rickettsiaceae which are small, obligate intracellular, gram negative, non-flagellate, pleomorphic coccobacilli. Scrub typhus is caused by Orienta tsutsugamushi transmitted by bite of larval stage of trombiculid mites or chiggers. SFG comprise a large group of tick, mite and flea borne infections that are caused by closely related rickettsiae. Tick borne spotted fevers include diseases caused by R. conorii (Mediterranean spotted fever in Europe, Indian tick typhus in India), R. rickettsei (RMSF in America), R. africae (African tick bite fever), R. japonica (Japanese spotted fever), R. sibirica (North Asian tick typhus), R. mongoliensis & R. heilongiawangii (in China, Mongolia, former USSR and Pakistan). Mite borne spotted fever include Rickettsial pox (caused by R. akari) seen in America. Flea borne spotted fever includes disease caused by R. felis an emerging disease which has been documented in America and Europe.

The clinical features (Table 2) of these rickettsial diseases can be quite nonspecific especially in endemic areas. The common symptoms include fever, rash, headache, myalgia, dry cough and gastrointestinal disturbances simulating common flu. The characteristic eschar and rash may not always be present. The frequent absence of eschar in scrub typhus may be attributed to bite by larval stage of mite. None of our patients had eschar. Incubation period varies from 1–3 weeks but there was no history of mite/ tick bite in our patients.However, we speculate that most of these patients either had a bite of dogtick or larval stage of the mite. Endothelial cell invasion and injury leading to increased vascular permeability, edema, hypovolumia & ischemia is central pathophysiological mechanism of all rickettsiosis. This vascular injury leads to capillary leak syndrome manifesting as multiple organ dysfunction like interstitial pneumonia, myocarditis, encephalitis, hepatic dysfunction and/or prerenal azotemia. There is also focal occlusive end angiitis causing microinfarcts which may be readily visible in digits and tip of nose as seen in one of the reported cases. All of our patients had thrombocytopenia which is likely to be result of consumption of platelets in the process of intravascular microthrombosis. DIC and ARDS are also known complications of rickettsiosis but these are rare. Meningo-encephalitis is a well known accompaniment of severe rickettsiosis resulting in pleocytosis and increased proteins in CSF in one third of cases. Usually pleocytosis is mild (10-100 cells/mm³) with mononuclear predominance but on occasion there may be marked polymorphonuclear pleocytosis.

Our 3rd case represent this type of atypical CSF finding.

Diagnosis of rickettsial diseases is very difficult and requires high degree of clinical suspicion with confirmation coming either serologically or by isolation. Clinically diagnosis is made by typical clinical picture of fever, rash and eschar and response to one of the anti-rickettsial drugs. However there is low incidence of eschar in south East Asian patients. As isolation/ detection techniques are not routinely available, serological tests remains an important tool in diagnosis. Indirect immunofluorescence assay (IFA) is considered the test of choice. It has the advantage of ability of detect antibodies to a number of rickettsial antigens simultaneously with the same drop of serum and it allows the detection of IgG and IgM antibodies, however there is cross-reactivity with other members of the group. In cases of acute infections a significant antibody titre is observed at the end of the first week, concomitant with the detection of IgM antibodies.

### Table 1 : Clinical and laboratory characteristics of cases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Rash</th>
<th>Eschar</th>
<th>Thrombocytopenia</th>
<th>LFT's</th>
<th>RFT's</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>Petechial</td>
<td>-</td>
<td>+</td>
<td>Deranged</td>
<td>Deranged</td>
<td>Scrub Typhus</td>
</tr>
<tr>
<td>Case 2</td>
<td>Maculopapular</td>
<td>-</td>
<td>+</td>
<td>do-</td>
<td>do-</td>
<td>Scrub Typhus</td>
</tr>
<tr>
<td>Case 3</td>
<td>Maculopapular</td>
<td>-</td>
<td>+</td>
<td>do-</td>
<td>do-</td>
<td>Indian Tick Typhus</td>
</tr>
</tbody>
</table>

### Table 2 : Clinical features of rickettsial fever

<table>
<thead>
<tr>
<th>Disease</th>
<th>Organism</th>
<th>Transmission</th>
<th>Incubation period (days)</th>
<th>Duration (days)</th>
<th>Rash (%)</th>
<th>Eschar (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mediterranean spotted fever</td>
<td>R. conorii</td>
<td>Tick bite: R. sanguineus, R. pumilio</td>
<td>5-7</td>
<td>7-14</td>
<td>97</td>
<td>50</td>
</tr>
<tr>
<td>Scrub typhus</td>
<td>Orientia tsutsugamushi</td>
<td>Mite Bite: Lepotrombidium deliense, others</td>
<td>9-18</td>
<td>6-21</td>
<td>50</td>
<td>35</td>
</tr>
</tbody>
</table>

### Table 3 : Drug treatment of rickettsial fever

<table>
<thead>
<tr>
<th>Age group</th>
<th>Treatment of choicea</th>
<th>Dosage</th>
<th>Duration</th>
<th>Alternate treatmentb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult</td>
<td>Doxycycline</td>
<td>100 mg BD</td>
<td>12 to 14 days</td>
<td>Chloramphenicol, Azithromycin, Clarithromycin</td>
</tr>
<tr>
<td>Children</td>
<td>Doxycycline</td>
<td>4 mg/kg/day</td>
<td>12 to 14 days</td>
<td>Chloramphenicol Azithromycin Clarithromycin</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Azithromycin</td>
<td>500 mg OD</td>
<td>12 to 14 days</td>
<td>Chloramphenicol Clarithromycin Rifampicin</td>
</tr>
</tbody>
</table>

a : In critically ill patients; Doxycycline dosage of 4.4 mg/kg/day upt to 200 mg every 12 hours; chloramphenicol in a loading dose of 15-20 mg/kg iv followed by 30-50 mg/kg/day daily in divided doses every 6 hours. b : Azithromycin 500 mg OD; Clarithromycin 500 mg BD; Chloramphenicol loading dose of 50 mg/kg followed by 50 mg/kg/day every 6 hours.
whereas IgG antibodies appear at the end of the second week. In the case of re-infection, IgM antibody titres can be variable and previous antigenic conditioning by infection or vaccination can account for the apparent lack of IgM response in a few patients. The sensitivity and specificity of IFA are 94-100% & 100% respectively. ELISA is claimed to be equally good as IFA.

Weil-Felix test (W-F) based on detection of antibodies to various Proteus antigens with cross reacting epitopes to antigens of genus Rickettsiae (except R. akari) has low sensitivity and specificity for diagnosis of these infections. Although there is often a good correlation between results of WF test and detection of IgM antibodies by IFA/ELISA, WF test should be used only in those settings where better tests are not available.

Doxycycline and tetracycline are drugs of choice. Doxycycline is given orally in a dosage of 200 mg/day in divided doses every 12 hourly whereas Tetracycline is administered orally in dosage of 25-30 mg/kg body weight/day in divided doses every 6 hours, without a loading dose.

Chloramphenicol is an effective alternative given orally in a loading dose of 50 mg/kg followed by 50 mg/kg/day in divided doses every 6 hours. Treatment in children is controversial, brief treatment with doxycycline may pose only a low risk of teeth discoloration, an adverse effect that once concerned many clinicians. Doxycycline can be given safely in children in a dose of 4 mg/kg/day in two divided doses. Doxycycline should be cautiously used in patients with an underlying liver disorder; however it can be safely used if the liver dysfunction is due to rickettsiosis. Macrolides can also be given as alternatives in pediatric age group. In critically ill patients in whom drug cannot be administered orally antibiotics should be given intravenously. In case of resistance of Doxycycline, Azithromycin (500 OD) or Clarithromycin (500 mg BD) may be used and may also become drug of choice in children, pregnant women. Rifampicin also appears to be effective and can be used in combination with erythromycin especially against R. conorii and in pregnancy.

**Conclusion**

Previously rickettsioses were documented from hilly areas of North India and southern part of country. To the best of our knowledge there is no case report from plains of North or West India. These cases are being increasingly seen in these areas and usually treated as cases of enteric or malarial fever. Chloramphenicol once used extensively for enteric fever also has activity against rickettsiae resulting in defervescence. Same is also true for Ciprofloxacin. The idea of this paper is to make aware the physicians that such infections do occur and Rickettsiosis should be kept in differential diagnosis of fever of unknown origin particularly if accompanied by rash and multiple organ dysfunctions. Rickettsiosis should not be excluded from list of differentials solely on basis of absence of eschar or rash.

**References**

5. Update on Rickettsial infections. Clinical Infectious Diseases. 2007;45:539-44.

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