Spotted Fever Group Rickettsioses in Himachal Pradesh

SK Mahajan*, R Kashyap*, N Sankhyan**, V Sharma***, JM Rolain+, BS Prasher++, D Raoult+

Abstract

Rickettsiae are in many places of the world emerging or reemerging pathogens. The spotted fevers group (SFG) composes a large group of tick- and mite–borne zoonotic infections that are caused by closely related rickettsiae. The SFG rickettsiae of Southeast Asia are yet to be identified. Earlier reports have documented the endemicity of rickettsioses among adults in the Himalayan belt but no confirmed case of spotted fever have been reported from this region of India. We present two cases of SFG rickettsioses; from the northern hilly region of India that were confirmed using specific microimmunofluorescence assay.

INTRODUCTION

Rickettsiae are in many places of the world emerging or reemerging pathogens. The spotted fevers group (SFG) composes a large group of tick- and mite–borne zoonotic infections that are caused by closely related rickettsiae. The SFG rickettsiae of Southeast Asia are yet to be identified.1

Tick-borne spotted fever: R conorii (Mediterranean spotted fever) and R. slovaca cause spotted fever in Europe, whereas Rocky Mountain spotted fever (R. rickettsii) occurs in America. Numerous other tick-borne SFG rickettsioses have been reported in recent years. R. africae is seen in sub-Saharan Africa, Indian tick typhus (R. conorii) is prevalent in India. Flinders island spotted fever (R. honei), Oriental or Japanese spotted fever (R. japonica) and R. helvetica are known in Japan and Thailand. R. sibirica (North Asian tick typhus), R. mongolotimonae and R. helionfigangii cause disease in China, Mongolia, former USSR (Asian republics, Siberia), Armenia and Pakistan.2

Flea-borne spotted fever: It caused by R. felis, suspected to be endemic globally and is an incompletely defined emerging disease.2 The infections due to several SFG rickettsiae, at present classified as nonhuman pathogens, will increase the size of this group of new emerging diseases.3

Rickettsioses are generally believed to have reemerged from many parts of India. The serological testing of residents of southern India presenting with fever of unknown etiology in 1996-1998 confirmed that spotted fever, epidemic/endemic typhus and scrub typhus continue to occur in southern India and an extensive study on tick-borne rickettsioses in the Pune district of Maharashtra revealed that Indian tick typhus exists as a zoonosis.3,4 Earlier reports have documented the endemicity of rickettsioses among adults in the Himalayan belt5 but no confirmed case of spotted fever have been reported from this mountainous region of north India.

Case Reports

Case 1: Forty seven years old female, from rural background, presented with high grade, continuous fever accompanied chills and rigor of 12 days duration. There was history of headache, myalgia, generalized body aches, pain in abdomen and decreased urinary output. The patient was in altered sensorium for last one day. On examination, patient was behaving irrelevantly, not obeying verbal commands. Eyes were congested, patient was jaundiced and signs of meningeal irritation were present. Muscle tenderness and abdominal wall tenderness was also present. There was no lymphadenopathy, eschar, abnormal bleeding from any site. Rest of the systemic examination was normal. Complete blood count was normal, random blood sugar was 132 mg%, liver function tests showed total bilirubin 3.0 mg%, unconjugated 1.8 mg%, SGOT and SGPT were 30 and 38 IU respectively along with alkaline phosphatase 782 IU. Serum urea was 143 mg% and Creatinine 2.7 mg%. Proteinuria was detected on urinary examination. CSF examination revealed proteins 115 mg%, sugar 45 mg%, 38 WBC's were present and 80% were neutrophils. Patient was empirically put on injection Ceftriaxone 1 gm IV, BD and Cap. Doxycyclin monohydrate, 200 mgs, OD through
feeding tube and IV fluids. Peripheral blood smear for parasites, Widal agglutination test, blood and urine culture, all were negative. Weil-Felix agglutination test showed titers 1: ≥ 160 to Proteus OXK antigen. After 48 hours of hospital stay she was afebrile, Ceftriaxone was stopped after 7 days of hospital stay but Doxycyclin was continued for next 10 days. Liver and renal function tests improved and returned to normal in next 6 days. She was discharged from hospital after two weeks stay.

Case 2: A 15-year-old girl, previously in good health, presented with high-grade fever of 12 days duration. Fever was accompanied by chills, rigors, myalgias and marked prostration. Apart from fever there was mild diffuse pain abdomen and occasional non-projectile, non-bilious vomiting for the last 15 days. There was no history of rash, bleeds, altered sensorium or other symptoms. On general physical examination, she was conscious, afebrile and oriented. There was no jaundice, lymphadenopathy, rash, eschar or bleeds from any site. Generalized muscle tenderness was present. Rest of the general and systemic examination was normal. Complete blood counts were normal and peripheral smear was negative for parasites or abnormal cells. Liver and renal function tests were normal. Widal agglutination test, blood and urine culture, were negative. Weil-Felix agglutination test showed titers 1:80 to Proteus OXK antigen. Patient was empirically put on injection Ceftriaxone 1 gm IV, BD and Cap. Doxycyclin monohydrate 100 mgs, OD. Subjectively general wellbeing improved dramatically within 24 hours and she became afebrile after 36 hours of hospital stay. Doxycyclin and Ceftriaxone were continued for a total of 5 and 7 days respectively. She was discharged from hospital after 8 days of stay.

Keeping in view the clinical features and occurrence of similar cases of undiagnosed pyrexia in last few years, serum samples of both patients were stored at -20 degrees and after lyophilization, were sent to France for rickettsial antibody detection by micro-immunofluorescent assay. The titers of IgG and IgM shown to various rickettsial species are given in Table 1. Serology to Orientia tsutsugamushi was negative in both patients. Keeping in view the clinical features and serological findings, the diagnosis of SFG rickettsioses can be concluded in both patients.

**DISCUSSION**

Generally, the clinical symptoms of SFG rickettsioses begin 6-10 days after the bite and typically include fever, headache, muscle pain, macular or maculo-papular rash, local lymphadenopathy, and a characteristic inoculation eschar (‘tache noire’) at the bite site. However, the main clinical signs vary depending on the rickettsial species involved, and sometimes allow one to distinguish between the diseases, e.g. single eschar is found in Mediterranean spotted fever but multiple eschars are often seen in African tick bite fever. SFG rickettsioses range from mild to severe and fatal diseases. Rocky Mountain spotted fever (SFSF) is considered the most severe SFG rickettsiosis, whereas no severe complications or deaths have been reported with African tick-bite fever.7 The frequent absence of a history of tick bite is likely due to transmission of the disease by immature larvae or nymphs who are often not noticed.1 The disease is milder in children and severe disease occurs in patients with diabetes mellitus, alcoholism, old age and G-6-PD deficiency.1 The pathogenesis of these diseases is vasculitis caused by the proliferation of organisms in the endothelial lining of small arteries, veins, and capillaries.1,2,6

Whole cells of Proteus vulgaris OX-2 react strongly with sera from persons infected with SFG rickettsiae except RMSF and whole cells of P. vulgaris OX-19 react with sera from persons infected with typhus group rickettsiae as well as with RMSF. The poor sensitivity and specificity of the Weil-Felix test for the diagnosis of RMSF is well demonstrated.6 The rickettsial Immunofluorescence assay (IFA) is the “gold standard” technique. IFA adapted to a micro-method format (microimmunofluorescence) is the test of choice for the sero-diagnosis of rickettsial diseases, it has the advantage of ability to detect antibodies to a number of rickettsial antigens (up to nine 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.2,6 In cases of acute infections caused by SFG rickettsiae, a significant antibody titer is observed at the end of the first week, concomitant with the detection of IgM antibodies, whereas IgG antibodies appear at the end of the second week. In the case of re-infection, IgM antibody titers can be variable and previous antigenic conditioning by infection or vaccination can account for the apparent lack of IgM response in a few patients.6,7

In a study by Philip et al, microimmunofluorescence test was used to study antibody responses to various spotted fever group rickettsiae during RMSF. The degree of cross-reaction to other rickettsial strains varied from patient to patient, but a particular pattern of cross-reaction was consistently observed in the same patient.7 The interrelationship of species within a rickettsial biogroup is so intimate that confirmation of their identity is generally

<table>
<thead>
<tr>
<th>Table 1: Serology titers on microimmunofluorescence assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case</td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td>Case 1</td>
</tr>
<tr>
<td>Case 2</td>
</tr>
</tbody>
</table>

Significant titers: IgG = 1:28, IgM = 1:64
difficult. The geographical origin of the infection is one of the best indicators of species identity. The identification of the rickettsial species causing an infection may be achieved by IFA or a cross-absorption test. For IFA, multiple microimmunofluorescence assay titers of the sera against different species are required. Usually homologous antibody titers are higher than heterologous antibody titers. PCR assays and sequencing of PCR products can be used by reference centers to identify rickettsiae in blood and skin biopsies.

The characteristic rash was not present in both cases, which highlights that SFG rickettsioses can be ‘spotless’ also.\(^1\) In a study conducted at Duke University Medical Center, 10.8% of 93 laboratory-confirmed or probable cases of RMSF were without rash or fleeting or atypical skin eruptions. Data of these cases of Rocky Mountain "spotless" or "almost spotless" fever support the premise that human Rickettsia rickettsii infection has a broader spectrum than that indicated by its classic description.\(^6\)

In areas where rickettsial diseases have not been described, cross-reactivity among rickettsiae of different groups can also be exploited as a first line for serologic testing however rickettsiae from resident arthropods should be the recovered from resident arthropods, in order to characterize the strains for sero-epidemiologic testing.\(^6\) Thus further studies are needed for exact characterization of the organism/organisms prevalent in this area.

Acknowledgements

We are thankful to Dr. Rakesh Sehgal, Director, CRI Kasauni and Mr. BD Negi, Chief Laboratory Technician, Department of Microbiology, I.G. Medical College, Shimla, for their help in lyophilization of blood samples.

REFERENCES


Announcement

DIPSI 2008

The 3rd National Conference of Diabetes in Pregnancy Study Group in India on 9th and 10th February 2008 at Nagpur.

For further details, please contact : Organising Secretary, Dr. Sunil Gupta, Diabetes Care n’ Research Centre, 42, Lendra Park, Ramdaspesh, Nagpur - 440 012.
Mobile : 09823152111, 09822717917, 09326108569
Tel. (+91) 0712 2428 111, 222, 333, 444 Fax : 0712-2428 555 Email : mail@dcrcindia.com

Please visit our Website : www.dcrcindia.com