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Research Article

CASE SERIES OF RICKETTSIAL DISEASES IN A TERTIARY CARE CENTRE SOUTH INDIA

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ABSTRACT
Objective of the work was to describe the diverse presentation, diagnosis, management and complications of various rickettsial diseases referred to M S Ramaiah Medical College and Hospitals in a period of one year. All cases of febrile illness diagnosed as rickettsial fever over a period of 1 year were analysed. The diagnosis was based on the presence of fever with rash and positive weil-felix test with a single titre >1:320 or rise of four fold or more on repeat testing. Twenty cases of rickettsiae were seen over a period of 1 year (January 2011 to December 2011). Common symptoms were fever and rash. Eschar was seen in 5 cases (25%). Weil-felix test was positive in all 20 cases(100%). Liver enzymes were elevated in 8 cases(40%). Multiple organ dysfunction syndrome (mods) was present in 1 case (5%), headache (8 cases, 40%), meningism (6 cases, 30%), pneumonitis (5 cases,25%) thrombocytopenia (14 cases,70%) and renal impairment (6 cases, 30%) were some of the important complications. There was a good response to doxycyline in nearly all patients. All those patients with history of fever and rash and negative for malaria, dengue and leptospirosis have to be tested for rickettsial disease especially if they are from rural background. The weil felix test can be of great use to diagnose rickettsial fevers, inspite of it being non-specific, when other serological tests are not available.

Key Words: *Rickettsiae, Scrub Typhus, Spotted Fever, Indian Tick Typhus, Typhus Fever and Weil –Felix Test*

INTRODUCTION
Rickettsial diseases are widely distributed throughout the world and many recent reports suggest to their continued presence in several parts of the Indian subcontinent, particularly that of scrub Typhus (Mahajan *et al.,* 2006, 2007; Sharma *et al.,* 2005; Sundhindra *et al.,* 2004; Mathai *et al.,* 2001, 2003). Rickettsial diseases are generally incapacitating notoriously difficult to diagnose, and untreated cases can have fatality rates as high as 30-35 per cent. Thus, the reported historical numbers of cases of infections with rickettsiae are probably not very accurate and are known to be severely underreported. When diagnosed properly, they are often easily treated but, lack of definitive diagnostic tools and the hazards of handling these microorganisms aggravate the difficulties of diagnosis and treatment. To date, the diagnosis of a rickettsial illness has most often been confirmed by serologic testing. Serologic evidence of infection occurs no earlier than the second week of illness for any of the rickettsial diseases; thus, a specific diagnosis may not be available until after the patient has recovered or died. Higher mortality rates are also correlated with delays in consulting a physician and delays in the administration of appropriate antibiotic therapy. Many of the recent reports of scrub typhus and other rickettsial diseases from the Indian sub-continent are based on clinical findings and the relatively nonspecific Weil-Felix test including the study by Kamarasu *et al.,* (2007). Using this test, a high occurrence of rickettsial infections was observed in Tamil Nadu. The earlier work undertaken in the laboratory of investigators showed reasonably high specificity but a low sensitivity associated with this Weil-Felix test. The poor sensitivity of the Weil-Felix test is now well demonstrated for the diagnosis of Rocky Mountain spotted fever (RMSF) Hechemy *et al.,* (1979), Marx (1983) Walker *et al.,* (1980), Kaplan *et al.,* (1986); Raoult *et al.,* (1984), murine typhus, epidemic typhus. Ormsbee *et al.,* (1977) and scrub typhus (Brown *et al.,* 1983). Although a good

correlation between the results of the Weil-Felix test and detection of IgM antibodies by an IFA is often observed, with the development of techniques that are used to grow rickettsiae, this test should be used only as a first line of testing in rudimentary hospital laboratories. In spite of all the drawbacks associated with it, the Weil Felix test still serves as a useful and cheapest available tool for the laboratory diagnosis of rickettsial diseases. A four-fold rise in agglutinin titres in paired sera is diagnostic for infection with these febrile agents. However, with a single serum sample available, the test is suggestive of infection only at a high cut-off titre (>1:320) at which the positive predictive value and the specificity is reliable. Kamarasu *et al.,* (2007) used antibody titres of 80 or more from single serum sample to indicate either spotted fever or scrub typhus infection. The positive predictive value and the specificity at this threshold titre may not be very high, even then may indicate possibility of infection. In India, they have been reported from Jammu and Kashmir, Uttaranchal, Himachal Pradesh, Maharashtra, Assam, Rajasthan, Kerala and Tamilnadu (Rathi *et al.,* 2010; Batra, 2007). Scrub typhus is a predominant variant in India (Rathi *et al.,* 2010; Joshi *et al.,* 2009). They are more prevalent in hilly areas of Himalayan belt. Mahajan *et al.,* (2006) .Tick borne fevers present with fever, headache, and rash. Rash may not be present in all the cases. They can closely mimic multiple illnesses like meningococcemia, enteric fever, dengue, Leptospirosis and sometimes even leukaemia (Joshi *et al.,* 2009)**.** In India tick borne fevers are still under-reported due to lack of clinical suspicion and availability of diagnostic tests. We describe case series of twenty patients with rickettsial diseases to emphasise that these are not as uncommon as thought previously. Physicians should always consider the Ricketssial fevers as one of their differential diagnoses in patients with pyrexia of unknown origin especially if associated with rash. Relevant investigations should be undertaken and timely initiation of anti Ricketssial therapy could prevent morbidity and mortality.

MATERIALS AND METHODS

Patients admitted with acute febrile illness to M.S. Ramaiah Institute of health sciences, Bengaluru, India, between 1st January 2011 to 31st December 2011, were evaluated. Detailed clinical examination including a careful search for eschar was made in all patients. Basic laboratory tests were done in these cases (complete blood count, peripheral smear, urine analysis, urea, creatinine, glucose, liver function tests). Additional investigations including blood culture, chest X-ray, Widal, peripheral smear for malaria parasite, serology for leptospirosis and serology for dengue were also done in all patients. In addition Weil Felix test was done in all these patients. Other investigations were done as indicated (USG abdomen, urine culture) to establish the cause of fever. Patients diagnosed to have Rickettsial disease on the basis of eschar and positive Weil Felix test were included in the study

RESULTS

Twenty patients were diagnosed to have Rickettsial disease during the study period of 1 year. The age ranged from 16 to 21 years. There were 8 females and 12 males. Most of the patients were from the rural areas of Karnataka.

Table 1 shows the signs and symptoms in these 20 cases. Fever, rash and headache were the common symptoms. Common signs seen were lymphadenopathy and hepatosplenomegaly. Eschar was seen in 5 patients. Leucocytosis was seen in 10 patients (50%). Thrombocytopenia was seen in 14 patients (70%). SGOT and / or SGPT were elevated in 8 patients (40%). Raised bilirubin (≥ 1.2 mg/dl) was found in 2 patients (10%). Abnormal CSF was found in 5(25%) patients and renal failure (creatinine > 1.5 mg/dl) was present in 6 patients (30%).

Table 2 shows the diagnostic criteria used in our study. The diagnosis was based on the presence of the characteristic eschar and / or positive Weil Felix test (≥ 1:80 titer). Eschar was present in a total of 5 patients – all had positive Weil Felix test also, Weil Felix test was positive in all of 20 cases – out of these, 5 had eschar also, whereas in the other 15 cases Weil Felix test alone was positive. Out of the 20

Table 1: Signs and Symptoms

Characteristics	Number of patients (20)
Mean age	22 years (16-21)
Male: Female	1.5:1
Activities of patients	
Farmer	10 (50%)
Recreation	2
Wild life photographer	1
Play on grassland	2
Rural areas (no significant history)	5 (25%)
Presenting features	
Fever	20(100%)
Rash	20(100%)
-maculopapular	12(60%)
-purpuric	8(40%)
Eschar	5(25%)
Hepatomegaly	15(75%)
Splenomegaly	10(50%)
Lymphadenopathy	10(50%)
Headache	8(40%)
Meningism	6(30%)
Investigations	
Haemoglobin(gm/dl)	10.31 (8.1-13.7)
Total leucocyte count(cells/cumm)	10,999(3600-17000)
Leucocytosis >11,000	10(50%)
Platelet count	1,27000(25000-4,80,000)
Thrombocytopenia <1.5 lac	14(70%)
Chest X-ray	
Pneumonitis	5(25%)
Liver function tests	6(30%)
Raised SGOT	8(40%)
Raised SGPT	4(20%)
Serum Bilirubin	2(10%)
Renal function tests	
Raised urea	3
Serum Creatinine	6(30%)
CSF analysis	
Elevated protein	5
Polymorphonuclear pleocytosis	4
Mononuclear pleocytosis	2
Weil- Felix reaction	
Raised OX K (Scrub typhus)	8(40%)
Raised OX 2(Indian Tick Typhus)	8(40%)
Raised OX 2 & OX 19	4(20%)

patients with the positive Weil Felix test, the titres were as follows: 1 in 320 or more in 10 patients, 1 in 160 in 6 patients and 1 in 80 in 4 patients. Weil felix test showed 8 of them to have scrub typhus,8 of them Indian tick typus and 4 of them spotted fever. All patients were treated with Doxycycline at a dose of 100mg twice a day .Mean duration of admission was 10 days (7-18 days). One patient died on day 18 of admission due to Multiorgan dysfunction syndrome (MODS).

Table 2: Criteria for Diagnosis

Criteria	No of patients (%)
Eschar alone	0(0%)
Eschar+Weil Felix	5(5%)
Weil Felix alone	15((75%)
Total	20

	Ox19	Ox2	Oxk
Epidemic typhus	++	+/-	-
Endemic typhus	++	-	-
Scrub typhus	-	-	++
spotted fever	+	+	-
Rickettsialpox	-	-	-
Q fever	-	-	-
Trench fever	?	?	?

Indian Scenario:

1206 cases of scrub typhus were reported in Himachal pradesh in 2 years (2009 & 2010) with 44 deaths. Kumerasu *et al.*, (2007) did extensive study on Rickettsial infections in Tamilnadu. Narendra (2011) reported 75 cases of spotted fever and scrub typhus in children in 2009 from Akola, Maharashtra and proposed clinical scoring system.

Table 3: Comparison of our study results with Rathi et al., (2011).

Clinical features	Rathi *et al.*, ., (2011)	Present study
Fever	100%	100%
Maculopapular rash	62%	60%
Purpuric rash	53%	30%
Eschar	7%	25%
Thrombocytopenia	68%	70%
Hepatomegaly	74%	75%
Lymphadenopathy	31%	50%
Pneumonitis	21%	25%
Meningism	28%	40%
Hyponatremia	48%	36%
Death	8%	5%

Table 3 compares our study results with Rathi *et al.*, (2011). All the clinical features were almost equal except we saw less of purpuric rash and more of eschar. We saw more of lymphadenopathy feature and Meningism when compared. We had slightly less incidence of death.

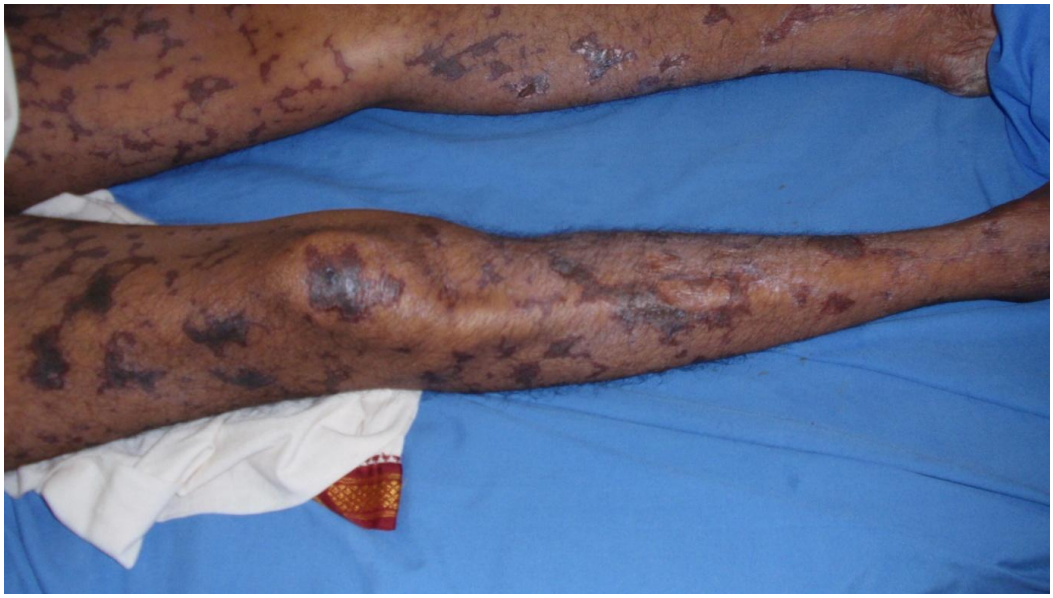

Figure 1: Ecchymotic Purpuric Hemorrhagic Rash

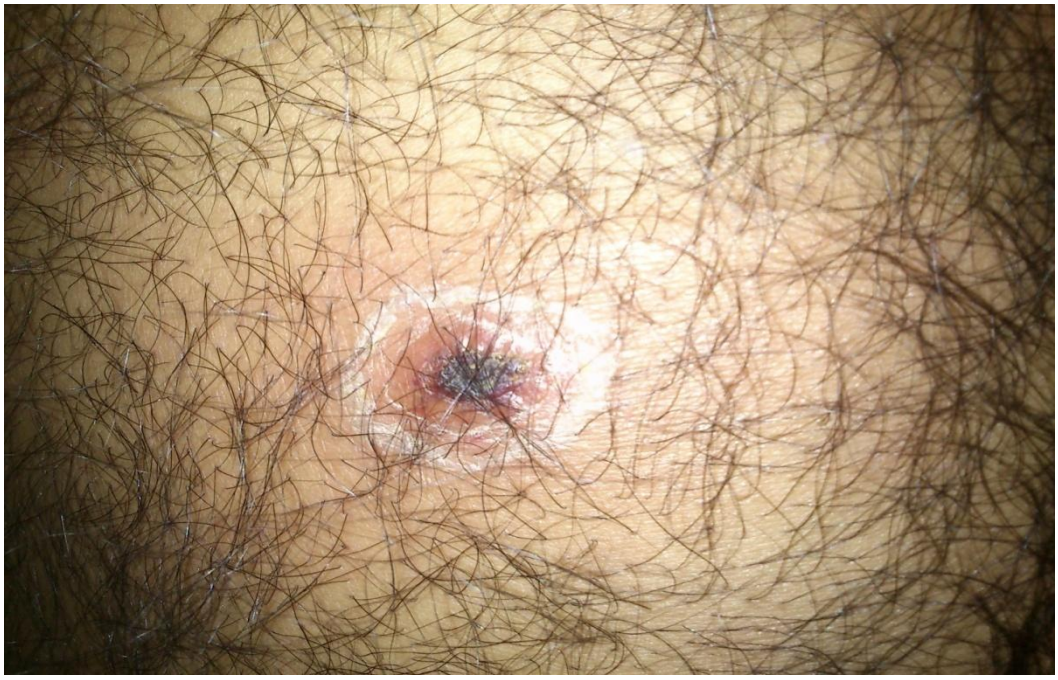

Figure 2: Typical Eschar at the Tick Bite Site

DISCUSSION

Rickettsiae are small gram negative, obligate, nonflagellate intracellular coccobacilli which infect humans through insects (Hackstadt, 1996). Animals are the hosts, but there can be transovarian transmission in insects. Rickettsia conori is the cause of Tick typhus in India and Mediterranean region (Oberoi *et al.,* 2010; Cowan, 2000). It is transmitted by brown dog tick *Rhipicephalus sanguineus.* They proliferate in endothelial cells of small blood vessels causing focal occlusive endangitis, particularly in skin, lungs, brain, kidneys, heart, and skeletal muscle and may cause venous thrombosis and peripheral gangrene. Incubation period ranges from 2 to 28 days followed by sudden onset of high grade fever sometimes with chills and rigors, headache, dry cough, body pains and vomiting. After 3 to 5 days, rash develops starting in ankles, spreading over to entire body involving palms and soles. Rash is usually maculopapular, petechial and haemorrhagic. An eschar (tachenoir) at the entry site is usually present. Rash may not be present in all the cases. They can have generalised lymphadenopathy, Hepatomegaly, Splenomegaly, deranged liver function tests, thrombocytopenia and pneumonitis. Complications like menigoencephalitis, hepato renal syndrome, acute renal failure, myocarditis, peripheral gangrene, venous thrombo embolism, secondary bacterial infections causing broncho pneumonia, parotitis, and otitis media can develop (Oberoi *et al.,* 2010). Differential diagnosis includes enteric fever, viral haemorrhagic fevers like dengue, leptospirosis, relapsing fever, measles, scarlet fever, staphylococcal toxic shock syndrome, typhoid, malaria (Joshi *et al.,* 2009) , collagen vascular diseases and vasculitis . Routine laboratory investigations are usually normal. Specific diagnosis is made by weil felix test, immunoflourescent assay, Elisa and polymerase chain reaction (Kamarasu *et al.,* 2007, Hechemy 1979; Moerman *et al.,* 2009). Weil-Felix test is heterophile antibody test against agglutinins to Proteus vulgaris OX2, OX 19 and OX k .Doxycycline is the drug of choice (Stephen *et al.,* 2008). Tetracycline, Chloramphenicol, macrolides, specially, clarithromycin, azithromycin and roxithromycin and floroquinolones, specially, ciprofloxacin, ofloxacin, pefloxacin and levofloxacin are also useful (Siberry *et al.,* 2007). Macrolides are used in pregnant women and children (Cascio *et al.,* 2001).

Conclusion

Rickettsial diseases have variable presentations and hard to diagnose. High clinical suspicion is required to make early diagnosis, treatment and prevention of fatal complications. These are not uncommon as thought previously. There are many case reports from north India, central India and rural parts of India showing increasing incidence of these tick borne diseases in India. All those patients with history of fever and rash and negative for malaria, dengue and Leptospirosis have to be tested for rickettsial disease especially if they are from rural background. The Weil-Felix test can be of great use to diagnose rickettsial fevers, inspite of it being non-specific, when other serological tests are not available[7]. Some of the cases had few interesting features like presence of hepatitis, pneumonitis and skin manifestations not typical of Indian Tick typhus. Early diagnosis and treatment can save patients. As illustrated in the figure one the rashes can be as typical as this and the eschar figure two which is a necrotic inoculation site with an erythematous rim can be seen in some Indian tick typhus and scrub typhus. The above case series of twenty in one year in a single institute clearly indicates that rickettsial diseases are not uncommon at all.

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