RESEARCH PAPER | Medical Education | Volume : 3 | Issue : 12 | Dec 2013 | ISSN - 2249-555X

Rickettsial Disease an unusual cause of severe febrile illness in ICU

KEYWORDS: Rickettsioses, rickettsial disease, typhus

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ABSTRACT *We report a case of a 45yrs male patient admitted in ICU with 12 days H/O fever, headache & myalgias. He had respiratory distress and hypotension requiring mechanical ventilation and inotopic support. Presentation mimicking usual viral or tropical fever but usual fever workup was nondiagnostic. Finally detected to have rickettsial fever. Responded wonderfully to appropriate specific treatment in 48 hours and recovered completely*

Rickettsial Diseases usually are transmitted to humans by arthropods. They are generally incapacitating and notoriously difficult to diagnose; untreated cases can have high fatality rates. Clinical suspicion is important. The Weil Felix and other serological tests are useful. Doxycycline is usually the drug of choice.

Introduction:
Rickettsioses usually are arthropod borne diseases.[1] Patients usually present as fever, rash, myalgia & various systemic features. High index of suspicion is required as untreated cases can have high mortality rates. Clinical presentation often mimics viral or tropical fever. Weil Felix & other serological tests are useful for diagnosis. Drug of choice is doxycycline.
Case: 45years/ male, apparently healthy farmer, presented with H/O sudden onset sickness for last 12 days. He complained of high grade intermittent fever with chills. Fever spiking daily. He suffered from severe headache and agonizing generalized muscle pains particularly more in thigh region. Pain was severe enough so as to disturb his daily routine. He gave H/O cough and breathlessness for last 2 days. Breathlessness worsened rapidly over few hours before admission. There were no other significant medical complains. He had no associated co-morbidities. He had taken treatment from local doctor in the form of analgesics, antipyretics, antibiotics (cephalosporins) but with little relief. At the time of admission he was conscious, well oriented. Tachycardia, tachypnoea were present. Blood Pressure was 100/70 mm Hg. He was dyspnoic and appeared quite sick. Breath sounds were equal. Crepitations were heard all over lung fields. Hepatosplenomegaly was present. There were no signs of meningeal irritation and also no neurodeficit. His SPO_2 and PO_2 were low. He soon required mechanical ventilation. Blood Pressure couldnot be maintained without inotropic support (noradrenaline). We started him with broad spectrum antibiotic (piperacillin + tazobactum) and other supportive management. Review of investigations showed normal leukocyte count, mildly deranged Liver function tests, reduced sr. albumin (1.9g/dl) normal renal function tests. Chest X ray showed bilateral haziness (rt>lt) s/o ARDS (Image I). Workup for common viral & tropical illnesses including malaria, dengue, leptospira & blood culture was negative. Patient did not show any improvement after few hours of therapy. Diagnostic dilemma increased our worries. We reviewed clinical history and investigations carefully and decided to workup for other possible causes of such condition. Hence we asked lab. to do Weil-Felix test and started doxycycline 100mg twice daily. Patient showed marked clinical and radiological improvement within 24 hours of therapy. Fever subsided in 24 hours, chest X ray got better (Image II). He was soon weaned off and inotrops were stopped. He was shifted out of ICU and subsequently discharged. Meanwhile lab. Informed us that his titers for ricketssial disease were positive (OXK titer 1:160). Other specific tests were not easily available and were not considered cost effective at this point. The following points helped us to make a final diagnosis of Ricketssial Disease (scrub typhus): potential occupational exposure to anthropods, typical clinical features, negative workup for other viral and tropical diseases, serological tests suggestive of rickettsiosis and rapid defervescence after doxycycline therapy.

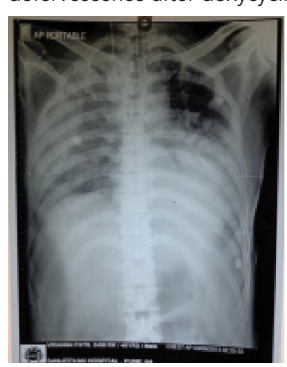
Image I

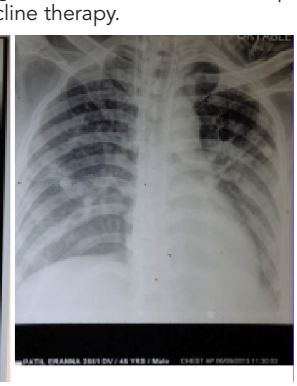
Image II

Discussion:
Ricketssioses can be divided into the following biogroups:

TABLE I : BIOGROUPS OF RICKETTSIACEAE[2,3]

Biogroup	Disease	Vector	Host	Organism
Spotted fever	Rocky Mountain spotted fever (RMSF)	Tick	Dogs rodents,	R. rickettsii
	Rickettsialpox	Mite	mice	R. akari
	Indian tick typhus / Boutonneuse fever/ Mediterranean spotted fever (MSF)	Tick	dogs, rodents	R. conorii
Typhus	Epidemic louse borne typhus	Louse	Human	R. Prowazekii
	Brill-Zinsser disease	Louse	Human	R. Prowazekii
	Endemic/Murine flea borne typhus	Flea	Rats	R. typhi
Scrub typhus	Scrub typhus	Chigger	Rodents	O. tsutsugamushi
Miscellaneous	Ehrlichioses and Anaplasmosis	Tick	deer,dog, rodent	Ehrlichia, Anaplasma
	TIBOLA*	tick	wild boar	R. slovaca
	DEBONEL**	Tick	wild boar	R. slovaca

Volume : 3 | Issue : 12 | Dec 2013 | ISSN - 2249-555X

*TIBOLA- tick borne lymphadenopathy,

**DEBONEL-dermacentor borne necrosis-eschar lymphadenopathy

Rickettsial infections are prevalent throughout the world. Rickettsial disease in India has been documented from Jammu and Kashmir, Himachal Pradesh, Uttaranchal, Rajasthan, Assam, West Bengal, Maharashtra, Kerala and Tamil Nadu.[1,3] Males appear to be at higher risk for infection with tick-borne rickettsioses. This is likely because of greater recreational or occupational exposures to tick habitats. Two thirds of patients with RMSF are aged 15 years or younger. Rickettsialpox, boutonneuse fever, epidemic and endemic typhus, and Tsutsugamushi disease affect all ages. Q fever is more prevalent between age 30-70 years.

Pathophysiology
They are obligate intracellular gram-negative coccobacillary forms that multiply within eukaryotic cells.[2,4] Rickettsiae take on a characteristic red color when stained by the Giemsa or Gimenez stain. *Rickettsia* parasitize the endothelial cells of the small venous, arterial, and capillary vessels leading to vasculitic process. This process may cause thrombosis, and the deposition of leukocytes, macrophages, platelets may result in loss of intravascular colloid with subsequent hypovolemia and decreased tissue perfusion. Loss of electrolytes is common. The consequent of cell-to-cell spread of rickettsiae maculo-papular rash develops. The vascular injury and subsequent host lympho-histiocytic response correspond to distribution of rickettsiae and systemic features. Platelets are consumed locally.

Clinical Manifestations:
Early signs and symptoms of these infections are nonspecific and mimic benign viral illnesses, making diagnosis more difficult. Clinical presentation may mimic other common infections in the tropics.[1-4] Incubation period of various rickettsial infections varies between 2-21 days. Fever of undetermined origin is the most frequent presentation of rickettsial disease. Fever is usually abrupt onset, high grade, sometimes with chills, occasionally with morning remissions. Severe frontal headache and generalized myalgia especially in muscles of the lumber region, thigh and calf is seen in variable proportion of cases. Though rash is considered as hallmark of rickettsial disease, it is neither seen at presentation nor in all the patients. [1,4] Rash usually becomes apparent after 3-5 days of onset of symptoms. Initially rash is in the form of pink, blanching, discrete macules which subsequently becomes maculopapular, petechial or hemorrhagic. The rash of typhus group rickettsioses is quite atypical, initially appearing on trunk, spreading centrifugally and usually sparing palms and soles. A necrotic eschar at the inoculating site is seen in variable proportion of Indian tick typhus, scrub typhus and rickettsialpox cases and is associated with regional lymphadenopathy. Generalized lymphadenopathy and hepatosplenomegaly are seen in majority of scrub typhus patients. ***Systemic features:*** Clinical features referable to various systems are sometimes seen in rickettsial infections.[3-5] Gastrointestinal symptoms including nausea, vomiting, abdominal pain and diarrhea are seen with varying frequency. Constipation is seen particularly in epidemic typhus. Respiratory symptoms include cough and distress are sometimes seen. Neurological manifestations like dizziness, drowsiness, disorientation, tinnitus, photophobia, delirium, meningismus, and visual disturbances; are seen more commonly with typhus group rickettsioses. The word 'typhus' refers to cloudy state of consciousness. Periorbital edema, conjunctival hyperemia, epistaxis, acute reversible hearing loss and arthralgia are sometimes reported.

SEVERE MANIFESTATIONS AND COMPLICATIONS
Rocky Mountain spotted fever (RMSF): Complications are uncommon, Acute complications include bronchopneumonia and congestive heart failure. Neurological sequele and gangrene may be seen in long term. Rickettsialpox is usually a self-limited disease with no complications. Boutonneuse fever occasionally may follow a malignant and rapidly fatal course. **Louse-borne (epidemic) typhus and Murine Typhus**: Complications are uncommon but include gangrene, parotitis, otitis, myopericarditis, pneumonia, and pleurisy. **Scrub Typhus:** The complications of scrub typhus usually develop after the first week of illness. Jaundice, renal failure, pneumonitis, ARDS, septic shock, myocarditis and meningoencephalitis are known with this disease. **Q fever:** Complications include chronic Q fever, endocarditis, myocarditis, meningoencephalitis, glomerulonephritis, and SIADH

Differential Diagnoses:
Dengue, Leptospirosis, Malaria, Measles, Meningococcal Infections, Rubella, Streptococcal Infection , Syphilis, Toxic Shock Syndrome, Vasculitis.

Laboratory Findings:
Thrombocytopenia, hypoalbuminemia, hyponatremia and normal to low leucocyte count are certain clues to early diagnosis.[1,3,4,5] Hepatic transaminase values are frequently elevated. Blood urea is elevated due to prerenal mechanisms. **The Weil Felix (WF)** : Commonly used test, easily available .Test is based on the detection of antibodies to various proteus species, which contains antigens with cross reacting epitopes to antigens from members of the genus Rickettsia. Even though the WF agglutination test is not very sensitive, when positive, it is a rather specific test.[1,3,7-10] Enzyme linked Immunosorbent Assay (ELISA), Indirect immunoflorescence test (IFA), PCR although considered more specific[6-8] but are not easily available.

DIAGNOSIS :
Following five factors taken together should help in diagnosis, which can then be confirmed with serology. ***Compatible clinical presentations, Tick bite or tick exposure, Epidemiological data, Suggestive laboratory features, and Rapid defervescence with appropriate antibiotics***[3]

Treatment: Adequate antibiotic therapy initiated early in the first week of illness is highly effective. Fever usually subsides within 24-72 hours after starting antibiotic therapy. If fever fails to subside with the use of a suitable antibiotic, the diagnosis of rickettsial disease should be reconsidered. Treatment may be terminated 2-3 days after the patient is afebrile and at least 10 days of therapy has been given. Doxycycline is the drug of choice.[2,4,5] Other drugs are chloramphenicol, fluroqunolones & rifampin. Murine (endemic or flea-borne) typhus: A single dose of doxycycline is the treatment of choice. Thrombocytopenia, hypoalbuminemia, hypotension, and coagulation defects require supportive management.

Prognosis:
Rocky Mountain spotted fever (RMSF): Fatalities are mainly caused by delay in diagnosis and treatment. The overall mortality rate currently is 5-7%.[1,5] Rickettsialpox is usually self-limited. **Louse-borne (epidemic) typhus:** Mortality may be uncommon in children younger than 12 years, but rates rise to as high as 60-70% in individuals older than 50 years. Murine typhus although considered a mild illness, at times may prove fatal. **Scrub Typhus:** Fatalities are rare with use of antibiotics. **Q fever:** The mortality rate is less than 1%.

Volume : 3 | Issue : 12 | Dec 2013 | ISSN - 2249-555X

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