Section: Tropical Medicine

Original Research Article

ATYPICAL PRESENTATION OF A TROPICAL DISEASE IN A SERVICE HOSPITAL IN WESTERN RAJASTHAN

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ABSTRACT

Scrub typhus is a mite borne disease caused by Orientiatsutsugamushi. Central nervous system (CNS) involvement is a known complication of scrub typhus which range from mild meningitis to frank meninigoencephalitis. Eschar helps in early diagnosis but in majority it remains absent. Thus a high degree of clinical suspicion and a positive rapid, diagnostic test remains an important point in the management of scrub typhus as the timely initiation of specific therapy results in complete recovery and fewer complications. Most of the cases respond well to the oral doxycycline.

Keywords: Scrub typhus, meningitis, tropical infection, doxycycline

INTRODUCTION

CASE SUMMARY

CASE 01 – 28 yrs old serving soldier, with no known comorbidities, presented with complaints of fever, severe headache and multiple episodes of vomiting. On examination terminal neck rigidity present. Patient was admitted in ICU in suspicion of Acute meningitis and was evaluated for the same. Patient was started on injectable broad spectrum antibacterial and antiviral agents. On evaluation, CSF analysis s/o viral etiology (appearance clear, predominantly lymphocytes, proteins slightly raised), no growth in CSF or blood culture after 48 hrs, MRI Brain reveals empty sella, prominent CSF sleeve around optic nerves and relatively narrow frontal horns of lateral ventricle possibility of Idiopathic Intracranial Hypertension. Patient continued to deteriorate, became unresponsive and disoriented. GCS fall from 15 to 10. On furthur examination, there was an ulcer present at the base of right hemiscrotum.

On further evaluation, CSF sample sent for RT-PCR to rule out HSV1 or HSV2 infection, IgM antibody positive for O. tsutsugamushi. Patient was started on oral doxycycline and was managed symptomatically. Individual responded well to treatment and discharged in a stable condition.

CASE 02 – 25 yrs old serving soldier, with no known comorbidities, transferred in from pokharan as a case of fever with altered sensorium with pancytopenia (inv). Admitted with c/o mild to moderate grade, intermittent type fever for past 10 days, epistaxis x 02 episodes and altred sensorium since one day. Also gave h/o generalized headache and bodyache. Patient was on leave and went home to mewad, haryana 1 month back. Had blood in stools during leave. Pt showed in civil and was given some treatement after which the bleeding resolved. On evaluation patient was thrombocytopenic with platelet count 16000/mm3 and Hb 9.9 g%. Patient was taken to ICU and was given 6 units of RDP(AB+VE) in v/o thrombocytopenia and epistaxis.He had features suggestive of meningism.His NCCT brain was normal and CSF study was showing lymphocytic pleocytosis and mildly elevated proteins and normal sugars. His CEMRI was normal.Patient was empirically started on oral as well as injectable broad spectrum antibiotics. On further evaluation, PBS s/o pancytopenia with no toxic granules, Bedside USG s/o Hepato splenomegaly with minimal ascitis and bilateral pleural effusion, ELISA IgM positive for brucella and scrub typhus, Weil Felix test positive

for proteus Ag OXK. Patient was started on doxycycline once the report came positive for scrub typhus and later rifampicin was also added in view of brucellosis. Pt responded well to treatment and was discharged.

CASE 03 – 42 yrs old serving soldier, with no known comorbidities, transferred in from pokharan, admitted with h/o mild to moderate grade fever and altered sensorium for past 02 days and multiple episodes of vomiting. On examination, patient was conscious, not oriented to time, place and person, delayed verbal response, was febrile and neck rigidity present. Patient was admitted to ICU, sent for urgent NCCT Brain and LP was done under aseptic precautions. Patient was then empirically started on injectable broad spectrum antibacterial and antiviral agents. NCCT Brain revealed small ill-definedhypodensity involving deep white matter of Lt parietal lobe? Focal cerebral edema?Cerebritis, CSF analysis s/o viral etiology (appearance clear, lymphocyte predominant, proteins raised, sugar normal), no growth. On further evaluation, CEMRI Brain - normal study and Weil Felix test positive for proteus OX K Ag. Patient was then started on oral doxycycline of 14-day course and has responded well to treatment.

CASE 04 – 23 yrs old serving soldier, with no known comorbidities, transferred in from jaisalmser, admitted with h/o moderate to high grade fever for past 04 days and altered sensorium for past 01 day. Associated with h/o headache, photophobia and irrelevant talk. Patient came back from leave 20 days back from Jharkhand. On examination, patient was conscious, not oriented to time, place and person, GCS 13/15 (E4V4M5), was febrile (T 101.4F), neck stiffness present. Pt was admitted in ICU and LP was done under aseptic precautions and was empirically started on broad spectrum injectable antibacterial and antiviral agent in v/o acute meningitis. On evaluation, CEMRI Brain s/o mild meningitis, CSF analysis s/o viral etiology (appearance mild turbid, lymphocyte predominant, proteins raised, sugar normal), Urine RE/ME s/o UTI (WBCs 4-6/hpf, protein detected), USG Abd reveals mild hepatomegaly and IgM for scrub typhus came positive. Patient was started on doxycycline for 14 days. Patient has responded well to treatment, his GCS improved and was discharged later.

CASE 05 – 43 yrs old man, with no known comorbidities, transferred in from jaisalmser, admitted with h/o moderate to high grade fever for past 03 days and altered sensorium for past 01 day. Associated with h/o headache, photophobia and irrelevant talk. Patient came back from leave 16days back from Delhi. On examination, patient was conscious, not oriented to time, place and person, GCS 14/15 (E4V5M5), was febrile (T 101.4F), neck stiffness present. Pt was admitted in ICU and LP was done under aseptic precautions and was empirically started on broad spectrum injectable antibacterial and antiviral agent in v/o acute meningitis. On evaluation, CEMRI Brain s/o meningitis, CSF analysis s/o viral etiology (appearance mild turbid, lymphocyte predominant, proteins raised, sugar normal), Urine RE/ME s/o UTI (WBCs 5-6/hpf, protein detected), USG Abd reveals mild hepatomegaly and IgM for scrub typhus came positive. Patient was started on doxycycline for 14 days. Patient has responded well to treatment, his GCS improved and was discharged later.

DISCUSSION

This report highlights an uncommon presentation of a common tropical infection seen in western rajasthan where a diagnosis was established with high index of clinical suspicion,searching for common clinical signs like an Eschar,antibody testing with rapid diagnostic kits &neuroimaging.Acute febrile illness with CNS symptom requires timely diagnosis and treatment to prevent mortality and sequelae. Subsequent investigations were done to rule out other common diseases or conditions that could mimick this clinical scenario.In India, scrub typhus has been reported in at least 16 states(Jammu & Kashmir, Himachal Pradesh, Rajasthan, Haryana,Maharashtra, Karnataka, Andhra Pradesh, Kerala, Tamil Nadu,Pondicherry, West Bengal, Sikkim, Uttaranchal, Assam, Arunachal Pradesh, and Nagaland). Although most studies from Tamil Nadu are from one institute, documentation has been done in at least 15 districts. The differential diagnoses of scrub typhus in our setting include enteric fever, dengue, leptospirosis and malaria all of which had been ruled out in our patients. Clinical diagnosis is often made/confirmed by the presence of an eschar and clinical improvement following doxycycline therapy. Eschars are seen in 7 to 80% of patients, with a higher percentage seen in children. Japan and Korea have a higher reportage of eschars when compared to Taiwan and Thailand. Identification of eschars in the Indian population is difficult due to dark skin with incidence ranging from 4% to 46%.

Absence of an eschar was a risk factor for mortality. Hepatomegaly and pneumonitis were the commonest manifestations in one study. In our setting hepatomegaly and hepatic dysfunction were seen in 41.8% and 24.6% of subjects respectively while CXR abnormalities were observed in 20(30.8%) patients.Unusual manifestations include ARDS, myocarditis, pancreatitis, hemophagocytic syndrome, disseminated intravascular coagulation (DIC) and meningoencephalitis. Myocarditis, pleural effusion and gastrointestinal (GI) hemorrhage are more common with winter scrub typhus.Hypoalbuminemia can be seen in one-fourth to three fourths of patients of scrub typhus. Perivasculitis, endothelial damage predisposes to capillary leak and hypoalbuminemia. Scrub typhus

involves both the central and peripheral nervous system. Tsutsugamushi is the rickettsia with the most meningeal involvement but central nervous system(CNS) involvement is higher in epidemic typhus than that of scrub typhus. CNS complications include infarction, cerebellitis, hemorrhages, encephalitis, demyelination, subdural hematoma, typhus nodules and meningitis causing altered sensorium, agitation, motor weakness, seizures, neck stiffness, cranial nerve deficits(CND). Low platelets and DIC contribute towards haemorrhage. Microglial nodules suggested cortical invasion. The involved cranial nerves are the optic, abducens, facial and cochlear nerves. Peripheral nervous system involvement reported are mononeuritis multiplex, brachial plexus neuropathy, polyneuropathy, myelitis and Guillain-Barre syndrome (GBS).Cranial nerve deficits are seen in ,25% of patients with the sixth being most commonly involved. Unilateral or bilateral abducens palsies occur with or without meningitis and facial palsies ensue singly or in association with GBS. Facial nerve palsy has also been described with R. typhi and R. conorii infections.There is a ,19% incidence of ear symptoms in scrub typhus that includes sensorineural hearing loss, otalgia and tinnitus. Direct central nervous system invasion and involvement of the cochlear division or a secondary immune mediated effect in the vasovasorum of the cochlear nerve has been hypothesised.

Otalgia occurs in the first week, while sensorineural hearing loss and tinnitus occur during the second week. Cochlear and retrocochlear damage has been proven histopathologically with demyelination and patchy neuritis having been noted in the 7th and 8th cranial nerves. Lymphocytic infiltrate of the organ of Corti and the coclear nerve have been described. Hearing loss has been reported in R. conorii. The rickettsia directly invades the CSF and has been grown from CSF. Nested PCR study revealed rickettsial DNA in CSF in patients with scrub meningitis. A prospective study of Thai children revealed that scrub typhus was the second most common cause of aseptic meningitis next to Japanese encephalitis. Meninoencephalitis is an autopsy finding in all fatal cases. Involvement is generally due to leptomeningeal infiltration. Histiocytes, lymphocytes and plasma cell infiltration of the meninges and perivascular spaces have been described. Meningeal signs were seen in 14% of patients with scrub typhus in a study conducted in Assam and Burma way back in 1946. In a study by Pai et al., on 25 patients with CNS involvement, only half of them had CSF lymphocytosis and only a third had elevated protein; O. tsutsugamushi DNA was isolated in six CSF samples. TBM remains the closest differential in our setting. India is one among the five countries that have the highest prevalence of TBM with an estimated mortality of 1.5/100,000 population.

Staining for acid fast bacilli(AFB) in CSF has low sensitivity and CSF culture for AFB takes up to 8 weeks and are positive only in 50–75% of cases. Hence other markers are necessary. Adenosine deaminase(ADA) increases the post-test probability of TBM. Hence ADA levels may be helpful in differentiating scrub meningitis from tuberculous meningitis but more studies are necessary in that direction.Prospective studies with cryptococcal antigen testing and PCR based kits like Xpert MTB/RIF (which were not performed in our patients due to unavailability) is needed in scrub meningitis to rule out other differential diagnoses. Scrub typhus meningitis can also be differentiated from TBM by the shorter period taken towards normalization. Rifampicin is also used to treat severe scrub typhus and presence of lymphocytic CSF in a given patient, with improvement following antituberculous therapy (ATT) may mask the diagnosis of scrub typhus. Doxycycline remains the drug of choice, but azithromycin is used in pregnant patients and those with renal failure. In some instances, progressive neurological damage has occurred despite treatment with doxycycline either due to resistance, immune-mediated injury or due to drug interaction with oral antacids. Doxycycline is bacteriostatic to O. tsutsugamushi and does not cross the blood brain barrier beyond 15–30%. Recovery in meningoencephalitis is brisk with appropriate therapy. All neurological abnormalities in our case series recovered well with Doxycycline. Specific tests for scrub typhus include indirect immunofluorescence test (IFA), immunoperoxidase test (IPT) and complement fixation test (CFT). IFA is the standard test for diagnosis, but lack of fluorescent microscopes makes it difficult for most hospitals. IgM ELISA, based on the detection of 56 Da antigen is a dot blot test which has high specificity (,90%) and sensitivity (,90%) when compared to IFA and IPT. Scrub IgM was positive in all our patients.

On the other hand, a serological diagnosis may prevent prolonged treatment with ATT for suspected TBM. Also, a correct diagnosis could pre-empt a label of tuberculosis. Leptospiral serology (IgM), malarial antigen testing, Widal, dengue IgM, IgG, Ns1 and blood culture was performed in all patients.Pre antibiotic era mortality was 60% and 30% in a 2006 series from Vellore but with prompt diagnosis and therapy, the mortality now is very low. There were no deaths arising from scrub typhus during the duration of our study, partly contributed by earlier institution of doxycycline in patients with fever and multisystem involvement. Empirical treatment of fevers with chloramphenicol and tetracyclines and insect eradication measures could have led the disease to insignificance after initial reports in India in the 1930s. But currently with increasing awareness, facilities for diagnosis, more literature is being published from India.[7]

CONCLUSION

Scrub typhus meningitis is a milder complication compared to respiratory or gastrointestinal problems even if it is associated with altered sensorium or cranial nerve deficits and generally resolves completely with doxycycline therapy. Also keeping in this diagnosis in mind it is always better to rule out this disease based on high index of clinical suspicion and can be treated with cheaply available antibiotics and can save the patient from developing further neurological sequlae and also won't have serious financial implications to the individual and instituition.Due to the presence of lymphocytic pleocytosis with increased CSF protein, TBM is a close differential diagnosis. This may result in rifampicin based ATT masking the diagnosis of scrub typhus and sometimes results in patients continuing long term therapy for TBM. Since India is endemic for both TB and scrub typhus, awareness of simple-to treat scrub typhus with access to specific tests like scrub IgM and CSF ADA may go a long way in avoiding unwarranted treatment in patients.

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