American Journal of Medical Case Reports, 2017, Vol. 5, No. 3, 69-76
Available online at http://pubs.sciepub.com/ajmcr/5/3/7

DOI:10.12691/ajmcr-5-3-7

A Probable Case of Scrub Typhus Meningoencephalitis – In the Era of Dual Seropositivity and Possible Emerging Doxycycline Resistance - Are Dictums Changing?

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Abstract Scrub typhus is an acute febrile illness which has varied manifestation from febrile illness to a more severe multi-organ dysfunction including CNS involvement in the form of meningitis and meningoencephalitis and in extremes cases, septic shock and death. Scrub typhus is prevalent in India and there have been reported case series from north-eastern regions of India and also from various institutes of south India. In sharp contrast, our case is a single incidence and classically showed features of lung involvement which predisposes to CNS involvement (in the form of meningitis or meningoencephalitis) later. All the published case reports/series from the subcontinent, it is unanimously stated that response is dramatic upon starting of oral doxycycline and the clinical scenario changes within 48- 72 hours. However in this anecdotal case of ours, intravenous doxycycline was started and still patient went downhill before he stabilised after 10 days of the therapy. Although doxycycline failures have been reported from Korea and the medical scientists have put forward their explanations about the questionable emerging resistance to doxycycline, still this case remains important because it is one of the first reported cases from the Indian subcontinent where the clinical features deteriorated even after starting Doxycycline ("The erstwhile gold standard antibiotic against Scrub Typhus) and that too via intravenous route. The case presents a dilemma in the minds of the clinician as to what strategy may be taken to achieve higher MIC values of Doxycycline (to overcome the emerging resistance) and also triggers the search for new antibiotic regimen which can help us to control scrub typhus early and prevent the more severe and life threatening complications of the disease.

Keywords: *scrub typhus, meningoencephalitis, doxycycline resistance, dual seropositivity, India*

Cite This Article: Soumyabrata Roy Chaudhuri, Deep Das, Hindol Dasgupta, Dipnarayan Mukherjee, and Kingshuk Bhattachacharjee, "A Probable Case of Scrub Typhus Meningoencephalitis – In the Era of Dual Seropositivity and Possible Emerging Doxycycline Resistance - Are Dictums Changing?" *American Journal of Medical Case Reports*, vol. 5, no. 3 (2017): 69-76. doi: 10.12691/ajmcr-5-3-7.

1. Introduction

Scrub typhus is an acute febrile illness caused by Orientia tsutsugamushi and it spreads via the blood and lymphatics and causes generalised vasculitis with subsequent clinical findings of fever, generalised lymphadenopathy and multi-organ dysfunction ranging from deranged liver function, pneumonitis, meningitis, meningoencephalitis, acute kidney injury leading to acute renal failure, septic shock and death [1,2,3]. Hence, early diagnosis and doxycycline therapy isthe key to successful treatment and also becomes instrumental in preventing death. The presence of eschar though pathognomonic may be found in as low as 30.76% of patients [4]. Although the infection spreads by both haematogenous and lymphatic routes [5] the target site of multiplication are the endothelial cells of the various systems [6] and both humoral and cell mediated immunity are important for combating scrub typhus [6].

Scrub typhus is seen in all terrains of the "tsutsugamushi triangle" that is bound by India, Nepal and Pakistan in the west; south-east Siberia, China, Japan and Korea in the north; and Indonesia, Malaysia, Philippines, northern Australia and the Pacific islands in the south and has Taiwan at its centre and the disease is related mainly to agricultural and outdoor activities [7,8]. The larval forms of the trombiculid mite (that has four life cycle stages-egg, larva, nymph and adult) transmit the disease to humans and other vertebrates [9]. Horizontal transmission occurs in rodents and vertical transovarian transmission occurs in mites and human infection is accidental caused by the bite of the larval forms [10].

Historically, scrub typhus was known in China in the 3rd century AD, however Hakuju Hashimoto in 1810,as

tsutsugamushi fever in the people living on the banks of river Shinano [11]. In 1879, Baelz and Kawakami described it as Japanese "flood fever" [12,13]. The Japanese word tsutsugamushi has two parts – tsusuga – meaning "illness" and mushi- "insect". The earliest case from the tsutsugamushi triangle was reported from Taiwan in 1915, whereas Korea now reports the highest incidence in the world [15] amongst the one million new cases identified annually [16]. India reported its first case in 1934 from the state of Himachal Pradesh [13]. During World War II, the disease was noted in the troops stationed in the Indian states of Assam and West Bengal and also during the Indo-Pak warin 1965 the disease increased in incidence. Although scrub typhus is prevalent in many parts of India but specific data is not available [17]. In recent times, there were reports of scrub typhus outbreaks in Himachal Pradesh, Sikkim and Darjeeling during 2003, 2004 and 2007.Scrub typhus data from different parts of the country especially from the large tertiary care hospitals do not provide us with a true picture of prevalence of the disease in the country and again there are not many available community based studies to give us statistically significant data regarding prevalence of the disease. With regards to therapy in scrub typhus meningoencephalitis a study from south India [18] and one from the north east Indian state of Meghalaya [4] have reported early and quick recovery with institution of oral doxycycline therapy with/without intravenous azithromycin. Both studies [4,18] reported improvement within 48 hours and stated that all neurological abnormalities resolved within 5 days of institution of doxycycline therapy. However the patient in question received intravenous doxycycline and developed neurological abnormalities beyond the third day of intravenous doxycycline therapy and it took him 14 days of doxycycline therapy along with intravenous dexamethasone for correction of neurological abnormalities and is hence being reported.

2. Case report

A 64 year old Indian male was referred to our hospital with history of five days of fever, cough and occasional headache with clinical suspicion of dengue (on background of a dengue outbreak in West Bengal). The blood picture done elsewhere showed -a borderline white cell count with a low platelet count of 50,000/cumm., a negative Widal test, a negative malaria parasite slide test (thick and thin smear) and a negative NS1antigen test for dengue. Laboratory tests on admission showed a platelet count of 1,20,000, an elevated C reactive protein (CRP) of 209.4 mg/dl with hyponatremia (sodium[Na] – 122 mEq/lit), borderline low albumin 2.9gm/dL and mildly raised bilirubin (1.4 mg/dL) Clinical examination revealed no abnormal breath sounds, barely palpable liver, mild tachycardia (105/min) and body temperature was 101.2 degrees Fahrenheit. No neurological abnormality was detected and the patient was oriented in time and space. Chest skiagram was unremarkable.

On the sixth day of fever, total count of WBC dropped to 3600/cumm from an initial 5500/cumm, platelet count dropped to 82,000/ cumm,C reactive protein (CRP) increased to 252.8mg/dL. Repeat check for Salmonella IgM and Dengue IgG and IgM were both negative and serum ferritin level was astronomically high at 6397ng/ml. On the account persisting cough, patient was reviewed by the pulmonologist who also noted the chest skiagram to be unremarkable. During the next day, the fever continued, but patient maintained oxygen saturation in room air, malaria was ruled out (slide as well as antigen was negative), Widal test was negative, ferritin remained in the same level but albumin dropped to2.1 gm/dl from 2.9gm/dl [Table 1]. On the eighth day of fever, patient became mildly dyspnoeic (required 1-2 litre of oxygen flow to maintain oxygen saturation of 95%), remained in tachycardia (heart rate -110-120/min) and dropped a bit on haemoglobin. CRP and ferritin levels further increased and repeat dengue serology was negative. Blood culture and urine cultures send on admission came out to be negative. During the ninth day, oxygen requirement increased and patient was shifted to ICCU.

Chest skiagram done in ICCU showed bibasal haziness with elevated CRP and pro-calcitonin, hyponatremia was nearly correctedbut liver parameters worsened with a drop in albumin to 2 gm/dl and International normalised ratio (INR) was 1.39. Patient was started on BIpap support with high flow oxygen support, infusion of 20% human albumin was started and antibiotic was upgraded to Meropenem and Doxycycline was added to it. Ferritin crossed the 10,000 mark and IgM tests for Scrub typhus, Legionella, Leishmania and Chikungunya were send along with repeat cultures of endotracheal suction, blood and urine. Over the next 24 hours urine output dropped and intravenous furosemide was added to maintain output, BIpap support was hiked up however the patient stopped spiking temperature. Laboratory results showed a mild drop in CR P and ferritin levels, with an increase in albumin levels. However, the platelet count plummeted to 30,000/cumm and Chikungunya IgM, anti-nuclear antibody (ANF) and anti-double stranded DNA (anti ds DNA) was negative.

The next day, which was the third day after starting intravenous doxycycline 100 mg twice daily as hourly infusion bore good news that Scrub typhus IgM resulted positive with a confounding report of Leptospira IgM also being positive. In order to confirm the diagnosis, we send blood for DNA PCR for Leptospira as facilities for Scrub Typhus PCRwas not available in our laboratory or even in the reference laboratory to which it outsourced samples. Clinically the patient became stuporous and was confused and disoriented. Platelets increased marginally, bilirubin increased but INR remained 1.35. Urine output improved but there was rise of urea and creatinine, ferritin values reduced remarkably to 6395 ng/ml and also CRP values decreased to 71.6mg/dL. Neurology review was requested and the attending Neurologist ordered a MRI (Magnetic resonance imaging)of the brain and a CSF (cerebrospinal fluid) study after improvement of platelet count. MRI of brain revealed features of pachymeningitis (Figure 1a and Figure 1b) and dexamethasone was added to the regime. Meanwhile repeat cultures were all negative and hence Meropenem was stopped while azithromycin was started intravenously.

The critical condition of the patient continued over the next 48 hours. However the lab parameters gradually

improved with only exception of urea, which showed a slightly upward trend. Confusional state and disorientation still persisted but the bipap support was scaled down. On the sixth morning after the start of intravenous Doxycycline, dose was escalated to 200 mg twice daily over a period of two hours, the platelet counts rose to 80,000/cu mm, patient was put onto high flow oxygen support without the BiPAP support, albumin stood at a healthy figure of 3.5 gm/dl.CSF study was done which revealed - 12 nucleated cells /cmm all of whom were lymphocytes, sugar – 98mg/dl, protein- 63.6 mg/dl (above the reference range of 15-45) and ADA- MTB was 8.63U/L (normal upto 9U/L). This excluded tubercular meningitis and reconfirmed the diagnosis of Scrub typhus meningoencephalitis. A couple of days later patient was shifted out of intensive care unit as his sensorium improved and oxygen demand came down. DNA PCR for Leptospira came out to be negative. In the ward he was gradually weaned off oxygen and nasogastric tube was also taken out as patient was feeding orally. His sensorium gradually improved and he was ambulated and discharged after 14 days of intravenous doxycycline therapy without any residual neurodeficit. (Important laboratory values are computed in Table 1 attached below).

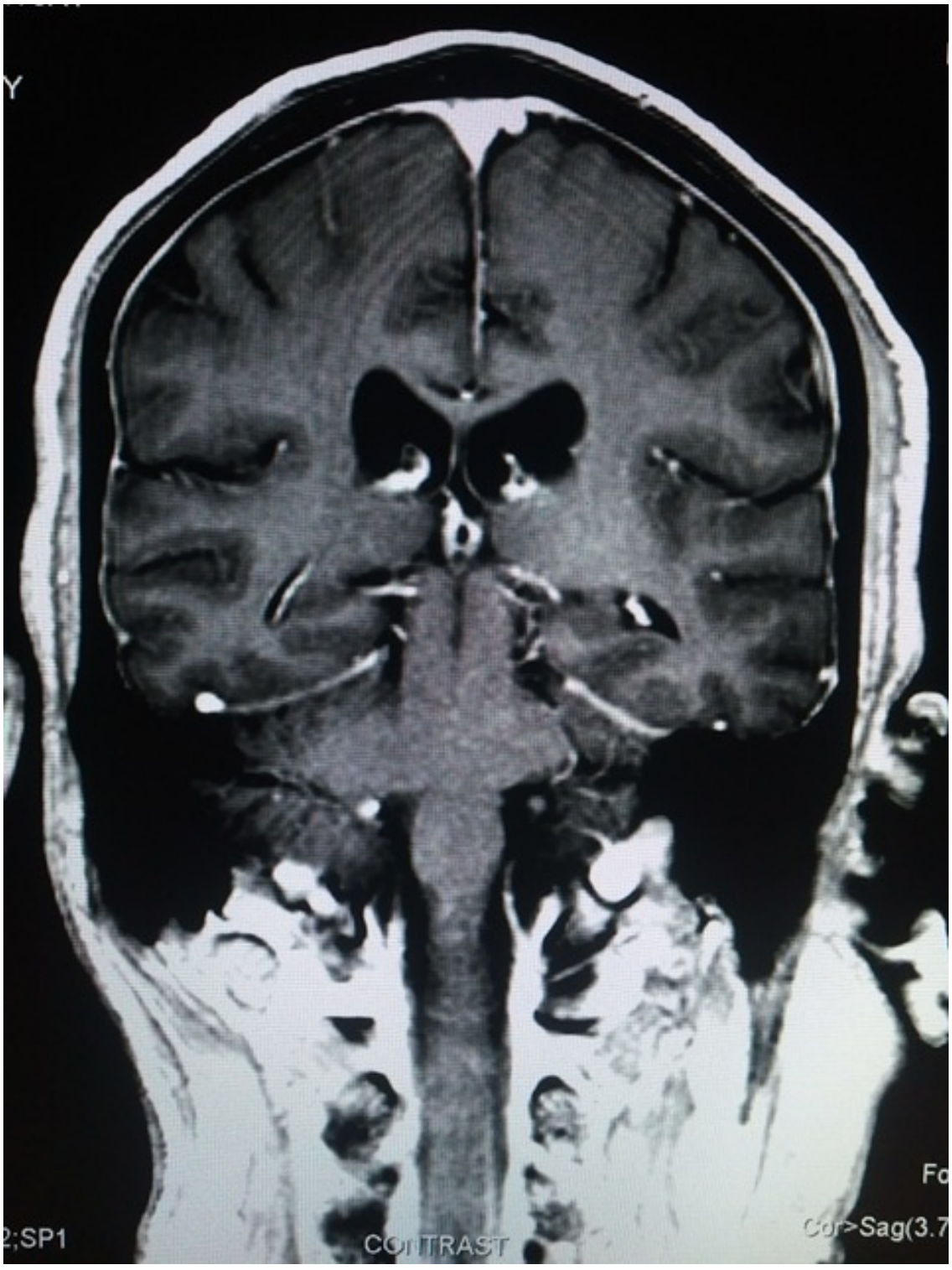

Figure 1a. MRI of brain revealed features of pachymeningitis

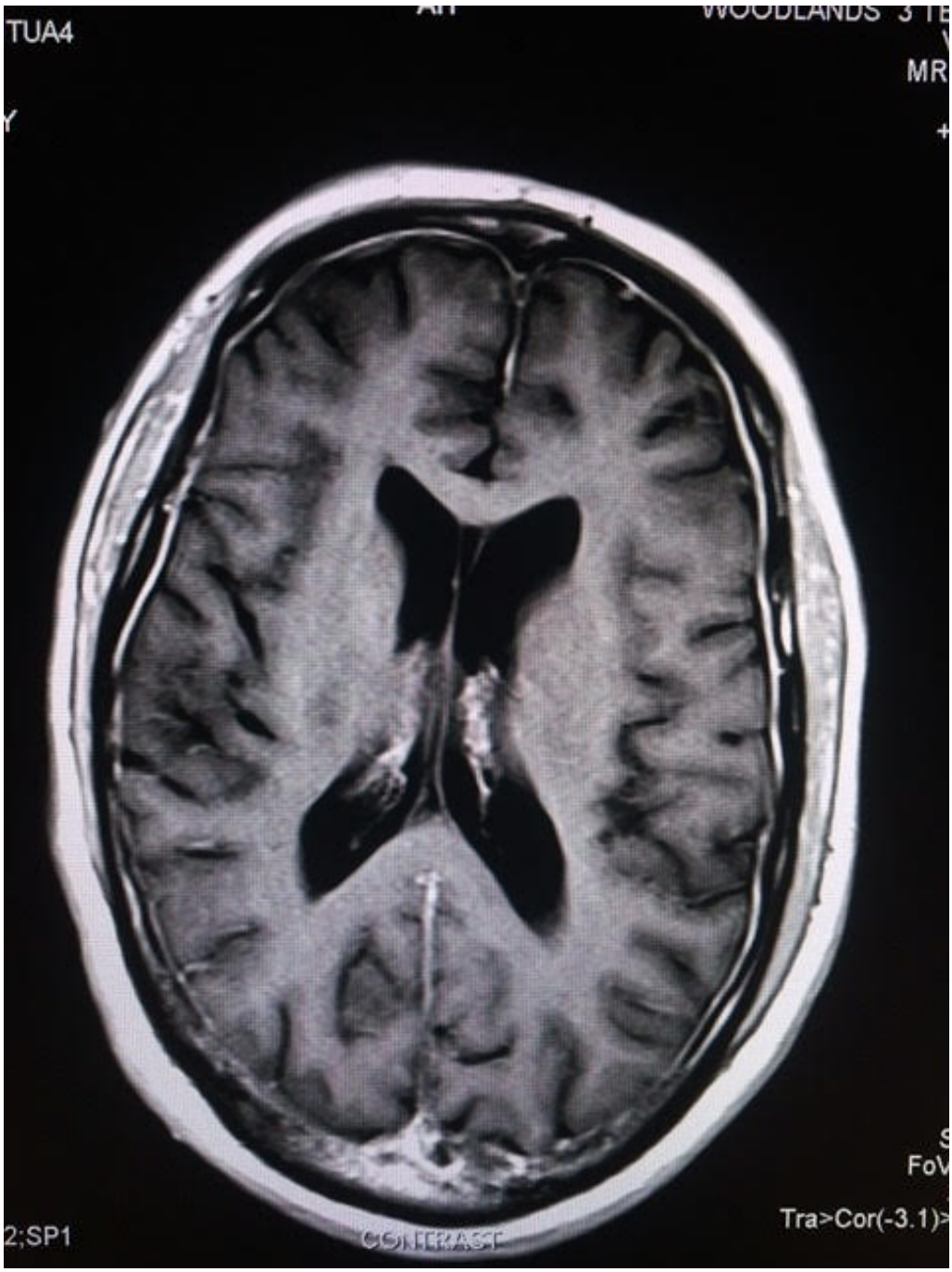

Figure 1b. MRI of brain revealed features of pachymeningitis

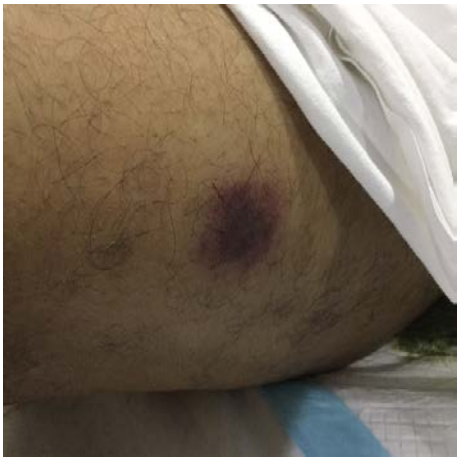

Figure 2. A small eschar was also noted in the upper aspect of left thigh

Table 1.

		DAY-1	DAY-2	DAY-3	DAY-4	DAY-5	DAY-6	DAY-7
SL NO	TEST NAME							
1	HB% (gm/dl)	14.5		14.3	13.7	13.9		
2	TC (/cumm)	5500	3600	4200	5300	6700	5700	4900
3	PLATELET COUNT (LAKH)	1.2	0.82	0.8	1	0.9	0.3	0.4
4	NEUTROPHIL (%)	86						
5	ALBUMIN (gm/dl)	29		2.1		2	2.4	3.2
6	BILIRUBIN (mg/dl)	1.4		1.8		3.3(3)		3.8 (3.4)
7	AST (U/L)	135		182		258		
8	ALT (U/L)	80		85		88		
9	CRP (mg/l)	209.4	252.3		286	283.3	260.9	71.6
10	UREA (mg/dl)	23			32.85			100.77
11	CREATININE (mg/dl)	1.1			0.99			1.54
12	Na+ (meq/dl)	122		126		130		143
13	K+ (meq/dl)	3.4		3.9		4.1		3.8
14	FERRITIN (ng/ml)		6397	6540	7769	10648	10227	6395
15	OTHER 'S		IgG & IgM DENGUE AND TYPHOID IgM NEGATIVE	MALARIA AND WIDAL NEGATIVE	BLOOD CULTURE &URINE culture negative	CHEST XRAY BIBASAL HAZINESS	SCRUB TYPHUS IgM and leptospira IgM POSITIVE	CHIKUNGUNYA IgM, ANF, anti dsDNA negative
		DAY-8	DAY-9	DAY-10	DAY-11	DAY-13	DAY-15	DAY-17
SL NO	TEST NAME							
1	HB% (gm/dl)	11.5			11.2	12.5	12.8	13
2	TC (/cumm)	5200			3600	4000	4200	4800
3	PLATELET COUNT (LAKH)	0.45	0.5	0.8	1	1.1	1.2	1.5
4	NEUTROPHIL (%)				75	68		62
5	ALBUMIN (gm/dl)	3	3.3	3.5		3.4		3.5
6	BILIRUBIN (mg/dl)					2.8(1.6)		1.6
7	AST (U/L)					192		84
8	ALT (U/L)					119		56
9	CRP (mg/l)		54.5		29.1	20.4		16
10	UREA (mg/dl)	106.75	109.09		76.9	58.3		42
11	CREATININE (mg/dl)	1.28	1.13		0.79	0.74		0.76
12	Na+ (meq/dl)	149	158	159	157	152	146	140
13	K+ (meq/dl)	4.3		4.4	4.7	4.2	4.1	4.2
14	FERRITIN (ng/ml)					1877		720
15	OTHER 'S		REPEAT BLOOD, URINE, ET CULTURES NEGATIVE	CSF STUDY-ADA NEGATIVE 12CELLS ALL LYMPHOCYTES		DNAPCR FOR LEPTOSPIRA NEGATIVE		

3. Discussion

In scrub typhus, incubation period ranges from 6-20 days [19], chills and fever occur by the third – fourth day of bite and whereas rash and lymphadenopathy occur by the end of first week [20]. Serious complications arise in the second week of illness and comprises of pneumonitis, pleural effusion, oedema, acute kidney injury (AKI), acute respiratory distress syndrome (ARDS) and meningitis with meningoencephalitis. Scrub typhus involves both the central and peripheral nervous system. Tsusugamushi is the rickettsia with the most meningeal involvement [21] but the incidence of CNS involvement is higher with endemic typhus than with scrub typhus [22]. Although the CNS is affected in a small minority of the cases in scrub typhus (2-5%) [23], the name typhus is derived from the word 'Typhos" which means "stupor".

Rickettsia directly invades the CSF and rickettsial DNA has been isolated from CSF of scrub typhus patients using nested PCR (polymerase chain reaction) by Pai and his colleagues [24]. O. Tsutsugamushi appears to enter the CNS via the infected monocytesduring the phase of meningeal inflammation or by invading the endothelium through the luminal membrane. The organism is then released, via the basal membrane into the perivascular space [24] and usually causes leptomeningeal infiltration [25]. It has been reported that that mild pleocytosis with lymphocyte predominance and protein levels >45mg/ dl is present in CSF in 48 % of cases with scrub typhus meningitis [24]. These features are however non specific, and may be found in viral meningoencephalitis, leptospirosis and tubercular meningitis(TBM) also and hence need to be excluded before stamping the patient as a case of scrub typhus meningitis.

Specific tests for scrub typhus include indirect immunofluorescence test (IFA), immunoperoxidase test (IPT) and complement fixation test (CFT) [26]. IFA is the standard test for diagnosis but lack of fluorescent microscope makes the test difficult to be performed except in a handful of medical facilities. In most of the centres, the diagnosis of acute scrub typhus is usually confirmed by immunoglobulin M (IgM) enzyme linked immunosorbent assay (ELISA) and/ or the pathognomonic presence of eschar with PCR confirmation where feasible. However the identification of eschar is difficult in Indian population due to dark skin with incidence ranging from 4% to 46% [27,28]. IgM ELISA for detection of scrub typhus is not totally without fallacy as is shown by Gupta et al [29] who conclude that in endemic areas the possibility of serological dual infection is on the cards due to high chances of serological cross reactivity and in such cases molecular confirmation must be sought for.

IgM ELISA has extensively been used for diagnosis of scrub typhus and leptospirosis in low resource settings. IgM antibodies for scrub typhus appear as early as 4 days after fever and stays for more than 120 days. The sensitivity and specificity of the commercial IgM ELISA kit used for scrub typhus has shown to be around 85.3 % and 95.5% respectively in a previous study. IgM antibody in leptospirosis begins as early as first week of illness and may take months or years to decrease. The sensitivity and specificity of the kit used for leptospirosis has shown to be 52.3% and 66.4% respectively. The possibility of cross reactivity has been a major issue with ELISA. So, a patient diagnosed with leptospirosis on the basis of IgM ELISA may turn out to be falsely positive with antibodies against scrub typhus cross reacting with antigen for leptospirosis and vice versa. In any case, even if the clinical features are pointing more towards one of the two diseases, sending the samples for testing of both diseases makes good sense. Several cross reactions of leptospirosis has been reported with Dengue, Hepatitis E, Enteric fever etc. in the past. With samples in our study showing serological positivity to as many as five infections, there is a strong chance that the serological dual positivity is because of cross reactivity. To check, whether the issues faced with ELISA could be resolved by using the reference standard for diagnosis of scrub typhus i.e., IFA, all patients with serological dual reactions were subjected to IgM IFA. All the ten patients were also positive for IgM IFA and no definite correlation with the end point titres could be drawn. Therefore, IFA did not give any advantage over IgM ELISA in the evaluation of serological dual positives. In a recent publication, Lim et al. questioned the accuracy of a serological gold standard for diagnosis of scrub typhus. Most of the previous reports of co-infection have used IgM ELISA. Whether these reported cases are actually co- infection or cross reactivity of antibodies is a point of contention. In a study conducted in Thailand, of the 82 patients with serological dual infection, only 5 had PCR assay positive for both scrub typhus and leptospirosis. In our study, of the 10 patients with dual infection, only 1 was positive for both by PCR assays. This indicates that there might be gross over reporting of dual infections in many studies.

In this particular patient, false positive leptospira IgM was excluded by PCR for Leptospira however due to lack of facilities molecular confirmation could not be done for scrub typhus. Although late to appear the eschar served as an adjunct to clinch the diagnosis.

A vast majority of reports of scrub typhus meningitis comes from Korea, Taiwan and India [18]. The Indian studies [4,18], usually report that dramatic improvement occurred within 2-5days of starting doxycycline (it may be presumed that doxycycline in these studies was administered orally as intravenous preparation was not available during those times). The patient in question however developed major complications in the form of pneumonitis and meningoencephalitis even after starting of intravenous doxycycline therapy which possibly improved after doxycycline dose escalation and thus warrants a deeper insight into a possible emerging resistant strain or a strain with a susceptibility at a higher minimum inhibitory concentration (MIC). Kim et al from Chosun University of Korea [30], however report that despite early initiation of appropriate antimicrobial therapy some of the patients still suffered from meningitis or meningoencephalitis during the doxycycline. In this study, they also identified via multivariate analysis, a risk factor for the development of meningitis or meningoencephalitis was pneumonitis (OR-7.7, $p<0.001$, CI-2.7-21.7). There may be three possible reasons for the failure of doxycycline therapy (a) because the drug is bacteriostatic and not bactericidal (b) the drug does not cross the blood brain barrier effectively and thus the concentration of drug achieved in the CSF is poor & (c) emerging resistance to the drug.

The drug levels of doxycycline achieved in the CSF is only 15-30% of that achieved in the blood stream [31,32,33]. Another study [34] looked at doxycycline 100mg bid versus Doxycycline 200 mg bid orally and reported that only 25%of patients in the 100mg BID group achieved drug levels in CSF above mean inhibitory concentrations for Borrelia burgdorferi whereas 75% did so in the 200mg bid group. The same authors also reported that mean inhibitory concentration of Rifampicin in the CSF against O.tsutsugamushi was more easily achieved (however in the case discussed it was not tried due to the already deranged liver profile, which will most likely be a common scenario in such patients). Further systematic studies of drug concentrations achieved in the CSF are required to determine whether increasing dose of doxycycline or using parenteral Doxycycline will be more effective for treatment of scrub typhus or use of rifampicin will usher a new era of management.

4. Conclusion

Scrub typhus meningitis and meningoencephalitisis reported in large numbers from India and must be distinguished from tubercular or viral meningitis which incidentally are also common entities. In case of dual seropositivity with IgM ELISA studies,molecular tests must be performed to establish the diagnosis. The clinician must be aware that meningitis and meningoencephalitis can occur even after institution of doxycycline therapy and the presence of pneumonitis in a patient of scrub typhus is a single most important risk factor for the development of meningitis or meningoencephalitis. Whether increase in the dose of Doxycycline, use of parenteral Doxycycline or use of Rifampicin will hold the key to successful management of the dreaded complication is a question for future studies to determine.

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