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Common Infectious Etiologies of Acute Febrile Illness in a Remote Geographical Location: Could Scrub Typhus be the Most Common Cause?

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Authors' contributions

This work was carried out in collaboration between all authors. Author DD designed the study, wrote the protocol and wrote the first draft of the manuscript. Author BD managed the literature searches and data analyses of the study. Author ADR confirmed the cases by pathological investigations and wrote the final draft of the manuscript. Author TSKS supervised the whole study. All authors read and approved the final manuscript.

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ABSTRACT

Background: Disease burden of acute febrile illness due to infectious etiologies is under reported in various parts of India including Sikkim due to lack of laboratory confirmation. Undifferentiated febrile illnesses common in tropical areas of Asia are dengue, chikungunya, malaria, leptospirosis, enteric fever, chikungunya, rickettsia, Japanese encephalitis and scrub typhus.
Aims: This study was conducted to determine various infectious etiologies of acute febrile illness with their clinical presentations, complications and mortality with special emphasis to scrub typhus.
Setting and Design: This was a cross-sectional study and 205 patients including paediatric patients admitted with acute febrile illness were evaluated.
Materials and Methods: A detailed history was taken and complete physical examination was done in all patients. Basic laboratory tests were done in all cases along with confirmatory tests.
Results: In our study the most common cause of acute febrile illness was found to be scrub typhus

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74(36.1%) followed by dengue 25(12.2%), malaria10 (4.9%) and enteric fever 10 (4.9%). Sikkim is non endemic state for filariasis and visceral leishmaniasis. Interestingly in our study we found 2 cases (0.97%) of visceral leishmaniasis and 1(0.5%) case of filariasis.

Conclusions: Scrub typhus was observed to be the common cause of acute febrile illness during the study period. Lack of diagnostic facilities makes scrub typhus an under-recognised cause of acute febrile illness in several parts of India even today. Although previously reported as occasional solitary cases from this region, this study witnessed the emergence of dengue as an outbreak in this region. Prompt recognition of acute febrile illness is important for specific treatment and better outcome in patients.

Keywords: Acute febrile illness; scrub typhus.

1. INTRODUCTION

The etiologies of human febrile illness can vary region wise in India suggesting that diagnosis, treatment, and control programs need to be based on a methodical evaluation of area-specific etiologies. Knowledge of local prevalence of infections is critical in order to target clinical work up and treatment [1]. The various common causes of acute febrile illness in tropical countries have similar clinical presentation. A large number of patients present to Indian hospitals with acute febrile illness and multisystem involvement. There may be overlapping clinical presentation in various acute febrile illnesses and it is important to diagnose the specific etiology so that appropriate treatment can be initiated. Disease burden of infectious etiologies of acute febrile illness is under reported in various parts of India due to lack of laboratory confirmation. Undifferentiated febrile illnesses are common in tropical areas of Asia. Common causes include dengue, malaria, leptospirosis, enteric fever, chikungunya, rickettsia and Japanese encephalitis [2].

World Health Organization (WHO) identifies scrub typhus as a re-emerging disease in South-East Asia and the South-Western Pacific region with a case fatality rate of up to 30% in untreated cases and stresses the need for its surveillance [3]. Although there have been reports of scrub typhus from various parts of India, still the true burden of the disease is not known for such a populous country like India [4-7]. Scrub typhus could be one of the important causes of acute febrile illness with multiorgan involvement. Many of the cases remain undiagnosed and therefore not treated resulting in high mortality. Scrub typhus is grossly under-diagnosed in India due to its non specific clinical presentation, limited awareness and low index of suspicion among clinicians, and lack of diagnostic facilities. The infection manifests clinically as a non-specific febrile illness often accompanied by headache, myalgia, nausea, vomiting, diarrhoea, cough or breathlessness. Severity varies from subclinical illness to severe illness with multiple organ system involvement, which can be serious enough to be fatal, unless diagnosed early and treated [4]. Scrub typhus in humans results after the introduction of *Orientia tsutsugamushi* through the skin by the bite of a larval-stage (chigger) trombiculid mite [5]. The bite of this mite leaves a characteristic black eschar that is useful for making the clinical diagnosis [8,9]. The observation of the eschar is often missed and other signs and symptoms of the disease are not characteristic thus posing the problem of delayed diagnosis by the clinician. In view of low index of suspicion, non-specific signs and symptoms, and absence of widely available sensitive and specific diagnostic tests, these infections are notoriously difficult to diagnose [4].

Early diagnosis and management of scrub typhus are necessary as delay in diagnosis and appropriate antibiotic administration can lead to increased mortality. As antimicrobials effective for rickettsial diseases are usually not included in empirical therapy of nonspecific febrile illnesses, treatment of rickettsial diseases is not provided unless they are suspected [10]. Several tests are available with their own advantages and limitations [11]. Among all the serological tests available Weil-Felix test is the cheapest and easily available, but this is notoriously unreliable. Indirect immune-fluorescence test, the gold standard is beyond affordability especially in poor countries and needs expertise for interpretation as the choice of cut-off values for positive diagnosis is influenced by several factors such as antibody kinetics, geography, negative seroconversion and seasonality [12,13]. IgM ELISA has been evaluated and found to be quite satisfactory in comparison to the gold standard [10]. A recent study by Gurung S, et al. reported high prevalence of scrub typhus (31%) in this

geographical area [5]. Therefore this study was conducted to identify acute febrile illness among the cohort and to determine various infectious etiologies of acute febrile illness with their clinical presentations, complications and mortality with special emphasis to scrub typhus.

2. METHODS

This cross-sectional study was conducted after due clearance from the Institutional Ethics Committee. This study included a total of 205 patients (including paediatric patients) who were admitted with acute febrile illness to a tertiary care hospital in Sikkim between May 2013 and October 2013. Detailed clinical examination including a careful search for eschar was made in all patients which was an important finding in case scrub typhus.

Demographic details and clinical course were recorded for all patients. A detailed history including signs, symptoms, geographical and social background was taken and complete physical examination was done in all patients to specifically look for presence of eschar, rash and lymphadenopathy as scrub typhus was reported to be an emerging disease in that region.

Acute febrile illness was defined as at least 2 consecutive days of fever ≥ 38℃. Consecutive febrile episodes separated by a symptom free (i.e fever free) interval of more than 14 days were regarded as separate episode and not included in this study [2]. Patients presented with fever but later diagnosed as confirmed cases of tuberculosis were not included in this study. Basic laboratory tests were done in all cases (complete blood count, peripheral smear, urine analysis, Haemoglobin estimation, ESR). Additional investigations including blood culture, urine culture, sputum culture, chest X-ray, Widal test, rapid card test for malarial antigen and dengue IgM, IgG and NS1 (non structural protein 1) were performed to establish the cause of fever. Only culture proven cases of enteric fever were included in the study. Serology positive but culture negative cases were considered as clinically diagnosed typhoid and were excluded from the study. Culture proven cases of UTI (Urinary Tract Infection), RTI (Respiratory Tract Infection), septic arthritis and acute gastroenteritis were included in our study. One case of meningitis was confirmed by isolation of *Streptococcus pneumoniae* from CSF. Culture negative but clinically suspected cases were not included in this study. Malaria was confirmed on the basis of positive slide test or positive antigen. Two cases of visceral leishmaniasis was confirmed by presence of L D bodies (Leishman Donovan) in bone marrow smear stained by Leishman stain. One case of filariasis was confirmed by presence of microfilaria in FNAC (Fine Needle Aspiration Cytology) smear stained by Leishman and Giemsa. Clinically suspected cases of scrub typhus were confirmed by positive IgM antibody against *O. tsutsugamushi* in their serum. Presence of eschar was considered as a characteristic finding in case of scrub typhus along with other clinical symptoms [8,9].

IgM antibody for Scrub typhus was detected by Scrub typhus DetectTM IgM ELISA System (InBios International, Inc) according to manufacturer's instructions. An optical density (OD) >0.5 was considered positive [14]. In most of the studies in India IgM ELISA for scrub typhus is done for confirmation of the cases of scrub typhus due to lack of diagnostic facility and resources for other specific immunological test like IFA (Indircet Immunofluorescence) and molecular test like PCR (Polymerase chain reaction) [10,15,16]. A study by Bithu R *et al* emphasised the importance of ELISA technique as a rapid and more accurate diagnostic tool than Weil-Felix test as it has better specificity because of use of standardised r56 recombinant antigen which is a 56-kDa major outer membrane protein of *Orientia tsutsugamushi.* In their study they also mentioned that ELISA can be carried out timely for early diagnosis of scrub typhus in patients with acute febrile illness in developing country like India [17]. Weil Felix test was not done in our study due to lack of sensitivity and specificity [15].

Complications and outcome were also recorded for all patients.

SIRS (Systemic Inflammatory Response Syndrome) was defined as 2 or more of the following variables:

1. Fever >38℃ or < 36℃
2. Heart rate >90 beats per minute
3. Respiratory rate >20 breaths per minute or PaCO2 <32 mm Hg
4. Abnormal white blood cell count (>12,000/ mm3)

Multi organ dysfunction syndrome (MODS) was also defined as a state of physiological derangements in which organ function is not

capable of maintaining homeostasis [18]. Acute respiratory distress syndrome (ARDS) was defined as PaO2/FiO2≤ 300 mm Hg [19]. Hyperbilirubinaemia was defined as serum total bilirubin > 1.2 mg/dL; elevated serum glutamate oxaloacetate aminotransferase (SGOT) as > 40 U/L; elevated serum glutamate pyruvate aminotransferase (SGPT) as > 40 U/L and elevated serum alkaline phophatase (ALP) >130 U/L [20]. Acute Kidney Injury (AKI) was defined and staged according to Kidney Disease: Improving Global Outcomes (KDIGO) definitions [21]. Raised creatinine was considered when serum creatinine was >1.6 mg/l [17].

Statistical analysis was done by SPSS version 16.0(IBM Corp., Armonk NY)

3. RESULTS

Among 205 patients with acute febrile illness 116 were male (56%) and 89(43%) were female. Age and sex distributions of patients are shown in Table 1. Most commonly affected age group was from 21 years to 40 years.

Different etiological patterns of acute febrile illness are demonstrated in Table 2.

Among 205 febrile patients a total of 74 (36.1%) were diagnosed as cases of scrub typhus followed by dengue 25 (12.2%).

Age specific disease categories are demonstrated in Table 3. Most common age group affected by scrub typhus and dengue was 21-40 years. Prevalence of scrub typhus and dengue in that age group were 33.8% and 56% respectively.

Although visceral leishmaniasis and filariasis are not common in this region we observed 2 (0.98%) cases of visceral leishmaniasis (Fig. 1) and 1 (0.5%) case of filariasis (Fig. 2).

Mean duration of fever for scrub typhus observed was 5.36 days and for other causes of febrile illness was 5.26 days (Table 4).

Table 1. Age and sex wise distribution of febrile patients

Age group	Male	Female	Total
0-20	18(15.5%)	11(12.4%)	29(14.1%)
21-40	47(40.5%)	40(44.9%)	87(42.7%)
41-60	25(21.6%)	16(18.0%)	41(20.0%)
61-70	18(15.5%)	15(16.9%)	33(16.1%)
71-80	8(6.9%)	7(7.9%)	15(7.3%)
Total	116(100%)	89(100%)	205(100.0%)

Table 2. Etiological pattern of febrile patients

Diagnosis	No of patients (Male)	No of patients (Female)	Total
Dengue	18(15.5%)	7(7.9%)	25(12.2%)
Scrub typhus	42(36.2%)	32(36.0%)	74(36.1%)
Enteric fever	6(5.2%)	4(4.5%)	10(4.9%)
UTI	10(8.6%)	12(13.5%)	22(10.7%)
RTI	14(12.1%)	9(10.1%)	23(11.2%)
Hepatitis A	6(5.2%)	5(5.6%)	11(5.4%)
Leishmaniasis	1(0.86%)	1(0.86)	2(0.98%)
Pneumococcal meningitis	0(0)%	1(1.1%)	1(0.5%)
Malaria	5(4.3%)	5(5.6%)	10(4.9%)
Filariasis	1(0.9%)	0(0%)	1(0.5%)
No definitive diagnosis	3(2.6%)	9(10.1%)	12(5.9%)
Septic arthritis	0(0%)	2(2.2%)	2(1%)
Acute gastro enteritis	8(6.9%)	4(3.4%)	12(5.8%)
Total	116(100%)	89(100%)	205(100%)

UTI-Urinary Tract Infection, RTI-Respiratory Tract Infection

Table 3. Age specific disease categories

Age (years)/ dignosis	Dengue	Scrub typhus	Enteric fever	UTI	RTI	Hepatitis A	Leishmanisis	Pneumococcal meningitis	Malaria	Filariasis	No definitive diagnosis	Septic arthritis	Acute gastroenteritis
0-20	0(0%)	5(6.8%)	5(50%)	2(9.1%)	4(17.4%)	3(27.3%)	1(50%)	0(0%)	3(30%)	0(0%)	0(0%)	2(100%)	4(33.3%)
21-40	14(56%)	25(33.8%)	5(50%)	12(54.5%)	2(8.7%)	8(72.7%)	1(50%)	1(100%)	4(40%)	1(1%)	8(66.7%)	0(0%)	6(50%)
41-60	10(40%)	24(32.4%)	0(0%)	6(27.3%)	0(0%)	0(0%)	0(0%)	0(0%)	1(1%)	0(0%)	0(0%)	0(0%)	0(0%)
61-70	1(4%)	20(27%)	0(0%)	2(9.1%)	3(13%)	0(0%)	0(0%)	0(0%)	1(1%)	0(0%)	4(33.3%)	0(0%)	2(16.7%)
71-80	0(0%)	0(0%)	0(0%)	0(0%)	14(60.9%)	0(0%)	0(0%)	0(0%)	1 (1%)	0(0%)	0(0%)	0(0%)	0(0%)
Total	25(100%)	74(100%)	10(100%)	22(100%)	23(23%)	11(100%)	2(100%)	1(100%)	10(100%)	1(1%)	12(100%)	2(100%)	12(100%)

UTI-Urinary Tract Infection, RTI-Respiratory Tract Infection

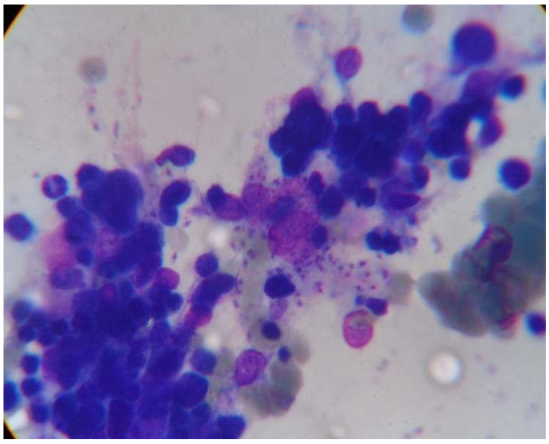

Fig. 1. Bone marrow smear showing both intracellular and extracellular LD bodies (Leishman, 1000x)

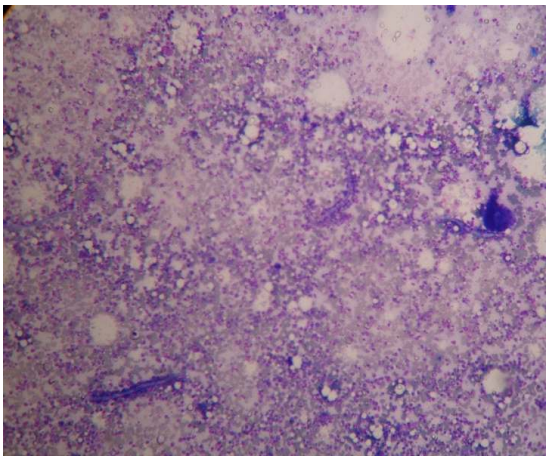

Fig. 2. Cytology of inguinal node showing presence of microfilariae (Leishman and Giemsa, 400x)

Signs and symptoms of patients of acute febrile illness are mentioned in Table 5 and disease wise complications of different causes of acute febrile illness are mentioned in Table 6. Eschar which is an important finding in case of scrub typhus was found in 44 (59.4%) cases of scrub typhus (Fig. 3).

Table 4. Mean duration of fever

Duration of fever	Scrub typhus (n=74)	Others (n=131)
Mean	5.36	5.25
SD	2.9	3.5

Fig. 3. Oval shaped eschar below axilla

Disease wise complications are depicted in Table 6.

Table 7 shows the laboratory parameter in these patients. Leukocytosis was observed in 30 (40.5%) cases of scrub typhus and 58(44.2%) cases of acute febrile illness due to other causes.

Table 5. Sign and symptoms of febrile patients due to scrub typhus and other causes

Parameter	Scrub typhus(n=74)	Others(n=131)
Symptoms		
Myalgia	39(52.7%)	74(56.5%)
Headache	55(74.3%)	90(68.7%)
Cough	44(59.5%)	73(55.7%)
Diarrhoea	8(10.8%)	19(14.5%)
Nausea/ Vomitting	46(62.2%)	75(57.3%)
Rash	11(14.9%)	15(11.4%)
Eschar	44(59.4%)	0(0%)
Signs		
Lymphadenopathy	3(4.1%)	11(8.4%)
Hepatomegaly	9(12.2%)	27(20.6%)
Splenomegaly	19(25.7%)	43(32.8%)

Table 6. Disease wise complications

Complication	ARDS	Renal failure	SIRS	MODS	CNS involvement	Hepatitis
Dengue (n=25)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	2(8%)
Scrub typhus (n=74)	57(77.0%)	43(58.1%)	65(87.8%)	27(36.5%)	22(29.7%)	45(60.8%)
Enteric fever (n=10)	0(0%)	0(0%)	10(100%)	0(0%)	0(0%)	8(80%)
UTI (n=22)	0(0%)	3(13.6%)	14(63.3%)	0(0%)	0(0%)	0(0%)
RTI (n=23)	23(100%)	0(0%)	15(65.2%)	6(26%)	0(0%)	0(0%)
Hepatitis A (n=11)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	11(100%)
Leishmaniasis (n=2)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	1(50%)
Pneumococcal meningitis (n=1)	1(100%)	1(100%)	1(100%)	1(100%)	1(100%)	0(0%)
Malaria (n=10)	3(30%)	4(40%)	0(0%)	4(40%)	3(30%)	4(40%)
Filariasis (n=1)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
Septic arthritis (n=2)	0(0%)	0(0%)	2(100%)	0(0%)	0(0%)	0(0%)
Acute gastroenteritis (n=12)	0(0%)	0(0%)	6(50%)	0(0%)	0(0%)	0(0%)
No definitive diagnosis (n=12)	3(25%)	3(25%)	6(50%)	3(25%)	1(8.3%)	6(50%)

ARDS-Acute respiratory distress syndrome, SIRS: Systemic Inflammatory Response syndrome, MODS-Multiple organ dysfunction syndrome

Table 7. Laboratory parameter in patients

Laboratory parameters	Scrub typhus(n=74)	Others(n=131)
Anaemia (<9 g/dl)	24(32.4%)	44(33%)
Thrombocytopenia (<100000 cells/µl)	2(2.7%)	10(7.6%)
Leucopenia (<4000 cells/µl)	13(17.6%)	24(18.3%)
Leukocytosis (>11000 cells/µ)	30(40.5%)	94(71.7%)
Hyperbilirubinaemia	47(63.5%)	58(44.2%)
Total bilirubin (>1.2 mg/dl)		
Raised SGOT (>40 U/L)	49(66.2%)	52(39.6%)
Raised SGPT (>40 U/L)	52(70%)	54(41.22%)
Raised ALP (>130 U/L)	41(55.4%)	60(45.8%)
Raised creatinine (1.6 mg/l)	48(64.8%)	16(12%)

SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, ALP: Alkaline phosphatase

It was also observed that mortality was higher 13.51% among the febrile patients due to scrub typhus. Mortality rate observed among the febrile patients due to other causes of acute febrile illness was 7.6% (Table 8).

Table 8. Disease wise mortality

Diagnosis	Total	Mortality
Dengue	25	0
Scrub typhus	74	10(13.51%)
Enteric fever	10	0
UTI	22	0
RTI	23	4(17.4%)
Hepatitis A	11	0
Leishmaniasis	2	0
Pneumococcal meningitis	1	1(100%)
Malaria	10	1(10%)
Filariasis	1	0
No definitive diagnosis	12	4(33%)
Septic arthritis	2	0
Acute gastro enteritis	12	0
Total	205	20(9.7%)

UTI-Urinary Tract Infection, RTI-Respiratory Tract Infection

4. DISCUSSION

To the best our knowledge this is the first study from North East Himalayan region with a focus on acute febrile illness. Only few scattered cases of dengue were previously reported from Sikkim. In this study when evaluating patients of acute febrile illness dengue was found to be the second most common cause of acute febrile illness. Singh R et al., [22] evaluated 1141 patients of acute febrile illness and observed dengue (71.2%) as the most common cause of acute febrile illness followed by malaria (12.8%), typhoid (8.1%) and scrub typhus (6%). Mixed infection was also noted (1.9%).

In our study the most common cause of acute febrile illness was found to be scrub typhus 74(36.1%) followed by dengue 25(12.2%), malaria10 (4.9%) and enteric fever (4.9%). In this geographical area Gurung S et al. [5], tested 204 patients with fever of unknown origin of which 63 were confirmed positive (30.8%) for scrub typhus. In our study of among 205 febrile patients a total of 74(36.1%) were diagnosed as cases of scrub typhus. In a study from Karnataka, 100 patients of acute febrile illness were diagnosed with: scrub typhus (33%), dengue (25%), enteric fever (14%), malaria (8%) [23]. In another study by Chrispal A et al. [24] reported high prevalence of scrub typhus (47.5%) amongst adult hospitalized patients of acute febrile illness followed by malaria (17.1%), enteric fever (8.0%) and dengue (7.0%).

Sikkim is non endemic state for visceral leishmaniasis and filariasis. Few case reports were reported from this region [25,26]. Interestingly in our study we found 2 cases (0.97%) of visceral leishmaniasis and 1(0.5%) case of filariasis.

In scrub typhus usually an eschar of approximately 5-20 mm in diameter is formed at the site bitten by trombiculid mites, this may be considered the most important clinical finding for diagnosis of scrub typhus.[27] In our study we observed 44 (59.4%) cases of scrub typhus had eschar (Fig. 3). Contrary to this, two recent studies reported no single patient of scrub typhus with eschar [10,28].

In this study duration of fever was taken as a part of the history and mortality was high in the group diagnosed after 5 days of fever. Among the causes of acute febrile illness, scrub typhus could be the most common cause as we observed in this study. Among the patients of scrub typhus 65 (87.8%) cases presented with SIRS and among the patients of acute febrile illness due to other causes 54(41.2%) cases presented with SIRS. In a study by Singh S P et al., the most common organ dysfunction was hepatitis followed by ARDS, shock and circulatory collapse and acute renal failure [29]. In our study also, the most common complication among patients of scrub typhus was respiratory failure (77%) followed by hepatitis (60.8%).

The study by Kumar V, et al., mentioned renal abnormalities in almost 82% of all patients with evidence of AKI (Acute Kidney Injury) in 53%. In our study AKI was observed in 58.1% of patients of scrub typhus [20].

The present study reports 13.51% mortality due to scrub typhus. Study by Bithu et al., reported 9.7% mortality due to scrub typhus [17]. In our study 34 cases of acute febrile illness due to other causes had hepatitis (24.6%) and 30 cases (22.9%) had ARDS.

Since this study was conducted in a tertiary care hospital in Sikkim, the referral bias may overestimate the rates of complications.

The similarity in symptoms between these infections may complicate the diagnosis of acute fever. The clinician should look for other causes

of fever especially if atypical presentations arouse suspicion of other possible etiologies.

5. CONCLUSION

In our study scrub typhus has emerged as the most common cause of acute febrile illness in this remote geographical region, Sikkim. Lack of diagnostic facilities makes scrub typhus an under-recognised cause of acute febrile illness in several parts of India even today. Therefore an early diagnosis followed by timely and adequate treatment with antibiotics like doxycycline, azithromycin etc. can prevent serious complications of scrub typhus which are usually associated with high mortality. It is also important to mention here that although Sikkim is considered non endemic for dengue fever, yet, in our study dengue has emerged as an important cause of febrile illness.

Therefore, this study emphasizes on the fact that an appropriate and early diagnosis of the infectious etiologies of acute febrile illnesses is always important for timely intervention, appropriate treatment and better patient care.

CONSENT

All authors declare that 'written informed consent' was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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