SEPTIC SHOCK SECONDARY TO SCRUB TYPHUS: CHARACTERISTICS AND COMPLICATIONS

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Abstract. Scrub typhus is an acute febrile illness caused by infection with *Orientia tsutsugamushi* transmitted by the bite of larval trombiculid mites (chiggers). A prospective study was conducted in septic shock patients in Maharat Hospital, Nakhon Ratchasima Province, Thailand, from 12 November 2001 to 5 January 2002. Of the 51 septic shock patients studied during the 7 week period, 18 (35.3%) were found to have evidence of scrub typhus infection; 3 patients (16.7%) died. In this study, septic shock caused by *Orientia tsutsugamushi* is the most prominent (35.3%) in endemic area of scrub typhus. Scrub typhus with septic shock patients results in organ failure: respiratory failure, DIC were predominant, followed by renal and hepatic involvement. Two deaths were due to respiratory failure and one death was as a result of combined respiratory and renal failure. Fever was the most common symptom, followed by headache, myalgia and dyspnea; lymphadenophathy and eschar are common signs. Laboratory findings revealed that almost all of the patients had a mild leukocytosis, reduced hematocrit and thrombocytopenia; SGOT, ALP, direct bilirubin (DB), total billirubin (TB), BUN, Cr were elevated; hypoalbuminemia was noted. Urinalysis showed that 88.9% of the patients had albuminuria. 77.8% of patients had abnormal chest X-rays.

INTRODUCTION

Scrub typhus remains a public health problem in the Southwest Pacific and Southeast Asia (Ralph and Jerome, 1987; Berman and Kundin, 1973; Joseph and Daniel, 1992; Singharaj and Watt, 1997). Scrub typhus, an acute febrile illness, is caused by *Orientia tsutsugamushi*, which is transmitted by the bite of larval trombiculid mites (chiggers). The organism differs from other rickettsiae by the existence of multiple strains (or serotypes): the Karp, Gilliam and Kato are the commonest in three western provinces (Kanchanaburi, Phetchaburi and Ratchaburi) in Thailand, (Chanyasanha *et al*, 1998). They have varied levels of virulence in humans and all share common antigens with *Proteus* OX-K.

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Scrub typhus can present with fever, chills, cough, headache, diarrhea, dyspnea, eschar, lymphadenopathy, macular rash or hepatosplenomegaly. The eschar is the pathonomic sign of scrub typhus. Regional lymph nodes are usually enlarged and tender. An eschar is found in about 60% of primary infections and less frequently in secondary infections (Watt and Olson, 2000). Scrub typhus can progress to severe and complicated illness (Watt and Strickman, 1994; Tsay and Chang, 1998; Ben *et al*, 1999). About 1 million cases are transmitted every year and range in severity from mild to fatal. The fatality rates ranged from 0 to 35% in the pre-antibiotic era: this might have been due to undefined rickettsial virulence factors, immune status and other host factors (Maxcy, 1946). In Thailand, in 2001 there were 4,082 cases of scrub typhus (diagnosed clinically) (Ministry of Public Health, Thailand, 2001). However, there is a large discrepancy between the seroprevalence and

the incidence of the disease due to the lack of an appropriate confirmatory test, the wide range of severity of the disease, and the poor sensitivity and specificity of diagnosis.

Septic shock is severe sepsis with hypotension despite adequate fluid resuscitation and carries a high mortality. It is most often caused by Gram-negative organisms (57% to 64%), Gram-positive organisms (35% to 40%), and occasionally by mixed infection or fungemia (Zanetti *et al*, 1999).

Nakhon Ratchasima is the second large province in Thailand located in the northeastern part of the country and is an areas of endemic scrub typhus. High prevalence rates of scrub typhus have been reported, with a morbidity rate of 16.99 cases per 100,000 population (1999): fifth of the ten leading causes of morbidity. To date there have been no published reports on the clinical findings and prevalence of scrub typhus infection in septic shock patients. Our study aims to describe the clinical findings and complication of septic shock secondary to scrub typhus.

PATIENTS AND METHODS

This prospective study was conducted at Maharat Hospital, Nakhon Ratchasima Province, Northeast Thailand, between the 12 November 2001 and the 5th January 2002. Patients older than 15 years who were admitted to the IPD and ICU and who had a three-day history of fever in Maharat Hospital and who fulfilled the inclusion criteria for septic shock (Zanetti *et al*, 1999) were enrolled; each patient gave written consent for the study. Reasons for exclusion were HIV seropositivity, pregnancy, and admission for less than 24 hours.

History and physical examination were recorded using a case record form (daily); follow-up was daily until discharge, death or transfer. The laboratory tests included: CBC (RBC, Hct, Hb, WBC, differential count, platelet count), BUN, creatinine, SGOT, SGPT, alkaline phosphatase (ALP), total bilirubin (TB), direct bilirubin(DB) and electrolytes; hemoculture x 3 specimens, thick and thin films for malaria parasites; Widal test; urine examination and culture, stool examination and culture, sputum for AFB, Gram stain and culture. Chest X-rays were performed if the patient had a cardiovascular problem, abnormal arterial blood gases, or a leptospirosis titer. Blood samples for serology for IFA (gold standard test for scrub typhus; WHO, 1999) were taken on day 0 and day 7 and sent for testing at the Arm Forces Research Institute of Medical Science (AFRIMS): IgM titer ≥1: 400 or IgG titer ≥1: 1,600 was reported as positive for scrub typhus. The clinical outcome of scrub typhus was categorized into 4 groups: 1) Single organ failure and recovery; 2) Multi-organ failure and recovery; 3) Single organ failure and death; 4) Multi-organ failure and death. All patients fulfilling the inclusion criteria received broad-spectrum antibiotics for sepsis and vasopressin was started as soon as possible (within the first 24 hours).

Statistical analysis was conducted using EPI INFO (version 6) and Microsoft Excel-4 for Windows. The test for distribution was the Kolmogorov-Smirnov office test. Means of normal continuous variables were compared by Student's *t* test. The chi-squared or, when appropriate, Fisher's Exact test was used for the comparison of categorical values. Statistical significance was set at $p < 0.05$.

RESULTS

Fifty-one patients with septic shock were studied, eighteen cases (35.3 %) had evidence of scrub typhus infection and 33 cases (64.7%) were infected with other organisms, as shown in Table 1. The characteristics of the patients with septic shock are given in Table 2, mean age was 56 ± 13.8 (25-76) years. Male and female were equally infected. All the scrub typhus patients came from Nakhon Ratchasima Province. People who worked outdoors (farmers, gardeners, manual worker) accounted for most of the cases 16/18 (88.9%). The mean number of days of illness before admission was 4.9 (±2.14).

Table 1
Percentage of septic shock: scrub typhus and other causes.

Disease	No. of cases (n = 51)	%
Scrub typhus	18[a]	35.3
Other causes	33	64.7
Leptospirosis	8	15.7
Typhoid or paratyphoid fever	2	3.9
Melioidosis + leptospirosis	1	2.0
Septic shock with Gram-ve bacteria	8	15.7
Septic shock with Gram+ve bacteria	7	13.7
Liver abscess	1	2.0
Unknown	6	11.8
Total	51	100.0

[a]1 case of mixed infection with *E. coli*.

Table 2
Demographic characteristics of patients with septic shock and scrub typhus.

Characteristic	Number of patients n=18 (%)
Age groups (years)	
15-29	1 (5.6%)
30-44	3 (16.7%)
45-59	7 (38.9%)
≥60	7 (38.9%)
Sex	
Male	9 (50.0%)
Female	9 (50.0%)
Occupation	
Farmer, gardener, worker	16 (88.9%)
Housewife, student	2 (11.1%)

Table 3
Clinical manifestations of septic shock with scrub typhus.

Clinical feature	Number of patients n=18 (%)
Fever	18 (100)
Headache	14 (77.8)
Myalgia	14 (77.8)
Dyspnea	11 (61.1)
Eschar	11 (61.1)
Lymphadenopathy	5 (27.8)
Cough	5 (27.8)
Mild jaundice	5 (27.8)
Confusion	4 (22.2)
Nausea	3 (16.7)
Abdominal pain	3 (16.7)
Diarrhea	3 (16.7)
Conjunctivitis	2 (11.1)
Chills	2 (11.1)
Vomiting	2 (11.1)

Clinical and laboratory features

Fever was seen in all the patients, headache and myalgia in 77.8%, dyspnea and eschar in 61.1%, and other features as shown in Table 3. Almost all of the patients had low hemoglobin, with a mean hemoglobin of 11.2 ± 1.9 g/dl; leukocytosis was mild and hematocrit was low. Twelve cases in the scrub typhus group were thrombocytopenic: 6 cases had platelet counts of less than 50,000 cells/mm^3. SGOT, ALP, DB, TB, BUN, Cr were elevated and globulin and albumin were reduced. About 88.9% of the patients had albulminuria and 77.8% of patients had abnormal chest X-rays, including pleural effusions (5.6%).

Outcome and complications

Of the 18 cases of scrub typhus with septic shock, 12 recovered, 3 were transfered to the surgical ward (*cellulitis*) or to private hospitals without follow-up (at the request of the family); 3 patients died. More than 80% of patients were treated with multiple antibiotics. Fifteen cases were followed-up: all had organ failure (renal failure, respiratory failure, liver involvement or DIC); respiratory failure and DIC were prominent.

In comparison between complication and outcome of scrub typhus patients (Table 4), one organ or multi-organ failure in scrub typhus can be improve. However, there were three deaths in our study: two caused by respiratory failure, and one by respiratory and renal failure.

Table 4
Comparison of the complications and outcome of patients who recovered and those who died.

Organ failure	Patient improved		Patient died	
	Single organ	Multi-organ	Single organ	Multi-organ
Renal	1	0	0	0
Respiratory	3	0	2	0
DIC	4	0	0	0
Renal and DIC	0	1	0	0
Respiratory and liver involved	0	0	0	1
Renal, liver involved and DIC	0	1	0	0
Respiratory, liver involved and DIC	0	1	0	0
Renal, respiratory, liver involved and DIC	0	1	0	0
Total	8	4	2	1

DISCUSSION

Of the 110 patients with sepsis admitted to the medical ward, 53 were diagnosed as fulfilling the criteria for septic shock (1 case was due to malaria and another was due to carcinoma of the bladder). Fifty-one cases of septic shock were therefore included in the 7-weeks study. Eighteen cases had evidence of scrub typhus infection (35.3%), including 1 case of mixed infection with *E. coli* (hemoculture positive). Almost all the patients had been transferred from district hospitals and had been treated with antibiotics before admission.

Although, this study was not carried out during the peak season for scrub typhus, which is from June to October (Ministry of Public Health, Thailand, 1999-2001), our data, which was collected at the end of peak period, still showed a high incidence rate of scrub typhus in septic shock patients. It may be that there are particularly virulent or resistant strains that lead to septic shock (Watt *et al,* 1996). This is first study to report on scrub typhus with septic shock in Thailand; the findings are different from those of other studies that compared scrub typhus and sepsis (Myint Kyi, 1998), FUO, and acute febrile illness (Ministry of Public Health, 1999; Watt *et al,* 2000; Lelarassamee, 2001).

The prevalence of bacteremia was lower than scrub typhus in our study. This may have been because about 80% of the patients had been transferred from district hospitals and had already received board spectrum antibiotics that treated the bacterial infections but had no anti-rickettsial action.

Most of the patients with scrub typhus and septic shock were older than 45; almost all of the patients came from Nakhon Ratchasima, where scrub typhus is known to be endemic (Ministry of Public Health, 1999). The at-risk age group, as reported by Ministry of Public Health, in 1999, is >35 years. Chanyasanha *et al* (1998), who surveyed the western provinces of Thailand, found the highest prevalence in those aged 45-49 years. Males and females were equally affected, which were similar to the studies in Thailand by Chayasanha *et al* (1998) and Ministry of Public Health (1999). However, a predominance in males was reported by the Ministry of Public Health in 1993 and by Chinprasatsak *et al* in 2001.

The at-risk groups of patients were farmers, gardeners and workers. Their risk is directly related to the nature of their work: they are exposed to infection in the rice fields and grasslands where the vector-rodent cycle takes place. This underlines the importance of an accurate history in clinical diagnosis (Ministry

of Public Health, Thailand in 1993-1999; Watt *et al*, 1996). The time needed for *O. tsutsugamushi* infection to progress to septic shock may be longer than that associatecd with bacterial infections; this may be due to the degree of virulence of the organism (Song *et al*, 1995).

Previous studies describing the clinical features of scrub typhus found that in septic patients fever was the most common presenting symptom; this was followed by headache, myagia, dyspnea, and lymphadenopathy. Most of scrub typhus patients had high fever associated with severe frontal and temporal headache, a very common finding (Myint Kyi, 1998; Choi *et al*, 2000).

The most significant finding in this study was the presence of an eschar, which was seen in more than 60% of the patients. Previous surveys showed similar incidence of eschar in scrub typhus cases; an eschar forms at the bite site in about 60% of primary infections and in less than 50% of secondary infections (Watt and Olson, 2000). We believe that most of our patients were suffering from a primary infection. Eschar is a pathogromonic feature of scrub typhus: it was not found in the patients whose shock was caused by other infections ($p<0.05$).

Lymphadenopathy was present in 27.8% of the scrub typhus cases. *O. tsutsugamushi* replicates in the cytoplasm of the vascular endothelium, causing lymphangitis (Silverman and Bond, 1984). Regional lymph node enlargement at the site of eschar drainage is common in scrub typhus (Berman and Kundin, 1973; Fang *et al*, 1975); generalized lymphadenopathy develops later. This has been the most characteristic physical finding for diagnostic of acute febrile illness (Berman and Kundin, 1973; Saah, 2000).

Myint Kyi (1998) found that SGOT levels were higher in scrub typhus with sepsis than in sepsis by other causes. However, Berman and Kundin (1973) reported that the SGOT levels of 41 patients during the febrile phase of the illness showed great variability, with no discernible correlation between the SGOT value and the presence of rash, the duration of fever, or hepatomegaly; the mechanism remains unclear. Most the patients had a leukocytosis mild, and hematocrit and albumin values were low, in keeping with the reports Fang *et al* (1975) and Kim *et al* (2000). Thrombocytopenia was predominant in our patients, consistent with the findings of Kim *et al* (2000). Around 77.8% of our scrub typhus patients had abnormal chest X-rays, as found by Choi *et al* (2000): almost all the patients had diffuse bilateral reticulonodular opacities with lower lung predominance. The underlying pathology may be that scrub typhus causes a multi-organ vasculitis, secondary to direct endothelial injury by *O. tsutsugamushi* (Silverman and Bond, 1984) or it may be that an immunological reaction in the lung occurs in response to the infective organism (Yotsukura *et al*, 1991); it is possible that the organism causes direct injury. Cough, tachypnea, and infiltration on chest radiography are the most common findings in scrub typhus; tachypnea sometimes progresses to dyspnea or cyanosis (Chaykul *et al*, 1988; Silpapojakul *et al*, 1991).

Respiratory failure and DIC were prominent: 3 patients died as the result of respiratory failure similar to the reports of Saah (2000) and Sayen *et al* (1946). Our 3 fatalities were in females older than 51 years with jaundice. One died due to electrolyte imbalance with low globulin, one had underlying problems, including hypertension, alcohol and tobacco use, and pleural effusion, and one had complicated symptoms with severe diarrhea and confusion. Pai *et al* (1997) and Berman and Kundin (1973) suggested that *O. tsutsugamushi* invades the CSF and causes a mononuclear meningitis; patients with scrub typhus have presented with mild to moderate neurological manifestations (Berman and Kundin, 1973; Lin and Lo, 1988).

It is worth noting that the outcome of the disease may be influenced by the size of the inoculum. Previous studies have reported that short incubation periods and the degree of severity of the illness are proportional to the

size of the inoculum (Walker, 1996). In fatal scrub typhus cases in this study the patients probably received a large amount of inoculum. The virulence of the strain as well as old age of the patient might also probably contribute the death with lower level immunity or delay of treatment, mixed infection with other organism, infection of resistance strain. However, the mechanism of severity and the cause of death due to the heart failure and circulatory collapse or pneumonia are unclear (Saah, 2000).

Deaths are attributable to a variety of factors, including late presentation and delayed diagnosis. The severity of scrub typhus does not appear to be increased in patients infected HIV (Watt and Walker, 1999). Recently, drug resistance of scrub typhus (drug of choice, tetracyline for scrub typhus) was reported in Northern Thailand (Watt *et al*, 1996), but has not been proven in Northeast Thailand.

Previous studies have shown that scrub typhus can progress to severe, complicated disease: Tsay and Chang (1998) detailed a case of septic shock in Taiwan and Kim *et al* (2000) found that four of eighty-nine patients with septic shock had scrub typhus. However, determinants of severity have not been clearly identified. Possibilities include infection by different strains that vary in their degree of virulence, host factors, differences in nutritional status, access to medical care, and concomitant infection (Singharaj and Watt, 1997; Watt and Olson, 2000). When a primary focus of infection is complicated by systemic sepsis or septic shock, emphasis should be given to the parenteral administration of high doses of appropriate antibiotics in order to cure both scrub typhus and other common causes of sepsis, especially areas endemic for scrub typhus.

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