Scrub Typhus: Chest Radiographic and Clinical Findings in 130 Thai Patients

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Objective: *To describe chest radiographic findings and their clinical correlation in patients with scrub typhus diagnosed in Thailand and to determine abnormalities that assist in the diagnosis of scrub typhus.*
Material and Method: *Between July 2001 and December 2002, 130 patients with scrub typhus admitted to three hospitals in the northeastern Thailand were studied. Data of clinical presentations and chest radiographic findings, reviewed by two radiologists who were unaware of the final diagnosis, were analyzed.*
Results: *There were 33 women, 97 men; age range, 11-92 years; median age, 45 years old. Pulmonary symptoms occurred in 61.5% of the patients and eschar was found in 33.1%. Hepatic dysfunction occurred in 58.5% and cardiovascular dysfunction in 33%. Pulmonary involvement was the major presentation in 41.5%. Acute respiratory distress syndrome developed in 7 patients. Overall 5 patients died. The initial radiography showed abnormalities in 64.6% of the patients. Common radiographic abnormalities included bilateral reticular opacities (48.5%), cardiomegaly (28.5%), congestive heart failure (18.5%), air space nodules (13.1%), and pleural effusion (10.8%). Significant association between chest radiographic abnormalities and hepatic and cardiovascular dysfunction were documented.*
Conclusion: *Chest radiography should be included in the initial evaluation of patients with suspected scrub typhus. Bilateral reticular infiltration, with or without cardiomegaly or congestive heart failure, was the most frequent radiographic finding of scrub typhus.*

Keywords: *Scrub typhus, Chest radiography, Acute febrile illness*

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Scrub typhus is an acute febrile illness caused by *Orientia (Rickettsia) tsutsugamushi*. It is an important consideration in the differential diagnosis of acute febrile illness in eastern Asia and the western Pacific region, from Korea to Australia and from Japan to India and Pakistan[1,2]. Cases of scrub typhus acquired in Asia have been increasingly reported in Europe and America[2,3]. *O. tsutsugamushi* is transmitted to humans by the bite of a larval-stage trombiculid mite or chigger[1]. The incubation period is 5-10 days[1]. The clinical manifestation of scrub typhus is nonspecific unless an eschar and regional lymphadenopathy are present in a person who is exposed in an endemic area. The diagnosis is usually based on the history, clinical course of illness and serological test[1,2].

Pulmonary manifestations of scrub typhus occurred between 20-72% of patients[1,4-6]. A cough with or without infiltrates on the chest radiograph is one of the common presentations of scrub typhus, and acute respiratory distress syndrome occurs as a serious complication[5,7-10]. Myocardial involvement has been reported as a rare but life-threatening compli-

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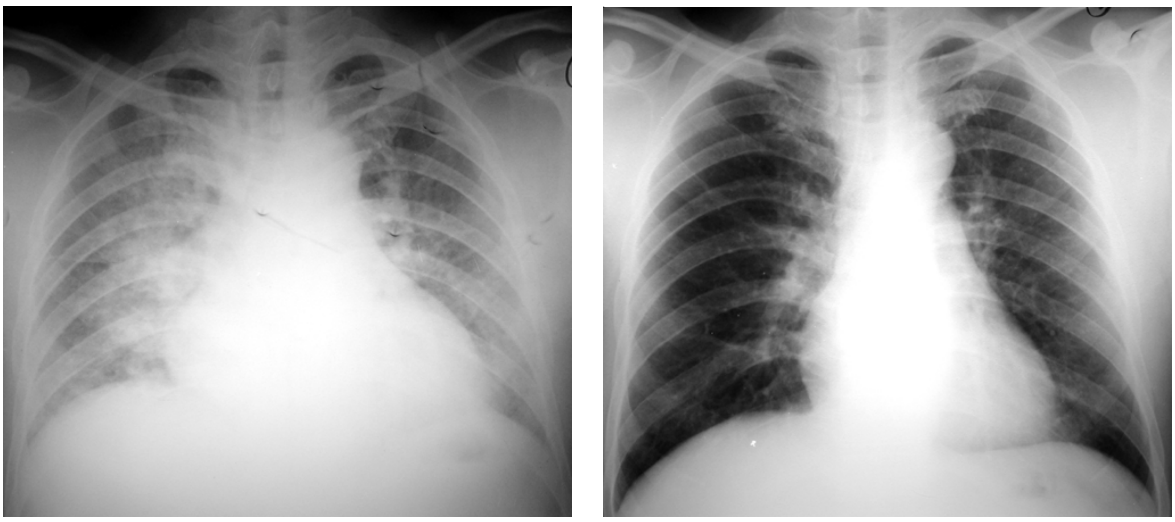
cation in scrub typhus[11,12]. The authors report here the results of the present study on chest radiographic findings of scrub typhus and their clinical correlation in 130 Thai patients.

Material and Method

The present study was part of a prospective clinical study of patients with acute febrile illness, conducted in three hospitals in northeastern Thailand; Maharat Nakhon Rachasima Hospital, Nakhon Rachasima Province; Loei Hospital, Loei Province, and Banmai Chaiyapod Hospital, Bureerum Province. The patients were admitted to these hospitals from July 2001 to December 2002. The study protocol was approved by the Ethical Review Subcommittee of the Ministry of Public Health Thailand. Written inform consent was obtained from all the patients before entering the study.

After admission to the study, a detailed history and results of physical examination were recorded on standard forms. Baseline investigations included a full blood cell and platelet count, blood culture for aerobic bacteria and leptospires, plasma glucose, serum urea, creatinine, liver function test, electrolytes concentration, urine analysis and chest radiography. At least two serum specimens were taken, one on admission and another during an outpatient follow-up visit 2-4 weeks after discharge from the hospital. Sera were stored at -20^{0}C until tested. Acute and convalescent sera were tested by the microscopic agglutination test (MAT) and indirect immunofluorescent antibody test (IFAT) for leptospirosis antibody as previously described[13]. Scrub typhus and murine typhus were diagnosed by a microimmunofluorescence assay employing a combination of 3 *O. tsutsugamushi* strains (Karp, Gilliam and Kato) and *R. typhi* as antigen. The diagnosis of scrub typhus was confirmed by either a four-fold or greater rise of total anti-rickettsial immunoglobulins and specific IgG or IgM titer to at least 1:200 in IFAT in paired sera; or a single titer or stable IFA titer of 1:400 or greater[14,15]. Murine typhus and leptospirosis were excluded in all patients in the present study by negative antibody titer against *R. typhi* and *L interrogans.*

Patients with confirmed scrub typhus were classified into different subgroups. Cardiovascular dysfunction was defined as the presence of hypotension (systolic blood pressure of < 90 mmHg) which required dopamine infusion, or the presence of clinical manifestation of congestive heart failure or symptomatic arrhythmia such as atrial fibrillation. Hepatic dysfunction was defined as either a rise in total bilirubin to ≥50 mol/L (normal range 5.1- 17 mol/L), or aminotransferase levels either aspartate (AST) or alanine (ALT) to ≥120 U/L (normal range 0- 40 U/L), or alkaline phosphatase to ≥350 U/L (normal range 39-117 U/L). Renal dysfunction was defined as either oliguria (a urine output < 0.5 ml/kg/hr for at least one hour or <400 ml in 24 hours) or azotemia (serum creatinine of ≥ 266 mol/L). Multiorgan dysfunction was defined by the presence of three or more vital organ systems dys-



a **b**

Fig. 1 Chest radiographs: a) initial film showed cardiomegaly with congestive heart failure pattern b) early follow-up film, findings were resolved

Fig. 2 Chest radiograph showed cardiomegaly, bilateral reticular infiltration predominantly at lower lobes and bilateral pleural effusion

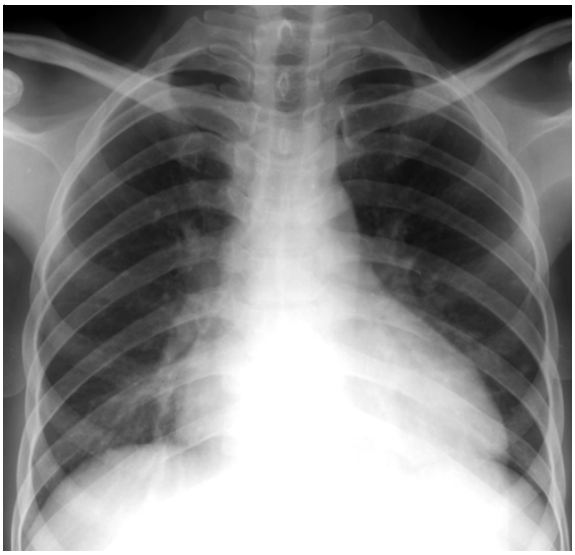


Fig 4. Chest radiograph showed cardiomegaly with bilateral reticular infiltration

Fig. 3 Chest radiograph revealed bilateral reticular infiltration

function. Thrombocytopenia was defined as a platelet count of less than 100, 000/ cu.mm.

Two radiologists who were unaware of the final diagnosis assessed chest radiographs. They reviewed the chest radiographs independently and reached a decision on the final interpretation by consensus. The radiographic interpretations were assessed for the presence of reticular infiltration, air space nodules, parenchymal consolidation, cavity formation, atelectasis, cardiomegaly, cardiomegaly with radiographic evidence of pulmonary congestion (congestive heart failure), hilar adenopathy and pleural effusion. The radiographic findings were classified into pulmonary involvement (reticular infiltration, air space nodules, parenchymal consolidation, atelectasis), cardiovascular involvement (cardiomegaly or congestive heart failure), and mixed pulmonary and cardiovascular involvement. The review of follow-up studies, performed within 7 days (early follow-up) and more than 7 days (late follow-up) after admission was also analyzed.

Statistical analysis

Descriptive analyses, such as percentage and means, were calculated at the appropriate place. The association between abnormal chest radiographs and clinical parameters such as pulmonary symptoms, hepatic or cardiovascular dysfunction, and thrombocytopenia was calculated by Chi-square. The association was considered significant when $p < 0.05$.

Results

Of 150 patients with laboratory confirmed scrub typhus, 130 patients with adequate clinical information and a least a chest radiography were included in the present study. The diagnosis of scrub typhus was made by a four-fold rising of specific antibody

against *R. tsutsugamushi* in 82 patients (63.1%), a single antibody titer of higher than 1:800 and 1:400 in 31 patients (23.8%), and 17 patients (13.1%) respectively. Demographic data and clinical manifestations on admission are summarized in Table 1. Pulmonary symptoms (cough and/ or dyspnea) were reported in 80 patients (61.5%). Hemoptysis occurred in 3 patients. The physical signs included hepatomegaly (16.9%), eschar (33.1%), and maculopapular rash (9.7%). Cervical, inguinal and post auricular lymphadenopathy were demonstrated in 27.6%, 12.4% and 9.2% of patients, respectively. Thrombocytopenia was found in 27 patients (22.9%). Twelve patients developed progressive multiorgan dysfunctions and required mechanical ventilation support. Acute respiratory distress syndrome occurred in 7 patients. Overall 5 patients died in the present study, three of which presented with multiorgan dysfunction on admission.

The initial radiography showed abnormalities in 84 patients (64.6%). The most common abnormal finding was the presence of bilateral reticular infiltration (63 patients, 48.5%). Other abnormalities included cardiomegaly (37 patients, 28.5%), congestive heart failure (24 patients, 18.5%), pleural effusion in 14 (10.8%) patients, air space nodules in 17 (13.1%) patients, hilar adenopathy in 2 (1.5%) patients, atelec-tasis and parenchymal consolidation in one each (0.8%). One third of the patients (34.7%) had mixed pulmonary and cardiovascular involvement. Details of chest abnormalities in these patients are summarized in Table 2.

The rate of chest radiograph abnormalities was similar between patients who presented with or without pulmonary symptoms. Mixed cardiovascular and pulmonary abnormalities shown by chest radiograph were significantly more common in patients with cardiovascular or hepatic dysfunction than those without. Renal dysfunction and thrombocytopenia were not associated with chest radiograph abnormalities. The distributions of chest radiograph abnormality in these subgroups are shown in Table 3.

Table1. Demographic and clinical presentations on admission of 130 patients

Characteristics	Number (%)
Male : female ratio	9.7:3.3
Median (range) age, years	45 (11-92)
Median (range) duration of fever, day	7 (2-14)
Clinical presentations on admission	
- Acute flu-like syndrome	26 (20)
- Hepatic dysfunction	76 (58.5)
- Pulmonary involvement	54 (41.5)
- Cardiovascular dysfunction	43 (33.1)
- Renal dysfunction	27 (20.8)
- Multiorgan dysfunction	25 (19.2)
- Aseptic meningitis	2 (1.5)

Table 2. Abnormal chest radiographic findings in scrub typhus (n = 84)

Findings	N (%)
Pulmonary involvement	23 (27.4%)
- reticular infiltration	18
- reticular infiltration plus air space nodules	3
- reticular infiltration plus other patterns	2
Cardiovascular involvement	16 (19.0%)
- cardiomegaly	4
- congestive heart failure	12
Mixed pulmonary and cardiovascular involvement	45 (53.6%)
- reticular infiltration and cardiomegaly	25
- reticular infiltration and congestive heart failure	6
- reticular infiltration, plus air space nodules and cardiomegaly/congestive heart failure	11
- cardiomegaly or congestive heart failure plus air space nodules	3

Table 3. The associations between clinical presentations and chest radiograph abnormalities

	Normal	Pattern of Abnormal Chest radiograph n (%)			p-value**
		Pulmonary	Cardiovascular	Mixed	
Pulmonary symptoms		n = 23	n = 16	n = 45	
Yes	26 (32.5)	12 (15.0)	12 (15.0)	30 (37.5)	0.38
No	20 (40.0)	11 (22.0)	4 (8.0)	15 (30.0)	
Hepatic dysfunction		n = 24	n = 15	n = 48	
Yes	20 (25.6)	16 (20.5)	7 (9)	36 (44.9)	0.003
No	31 (52.0)	8 (12.0)	8 (16.0)	12 (20.0)	
CVS dysfunction*		n = 23	n = 16	n = 48	
Yes	2 (2.3)	2 (4.7)	10 (23.3)	33 (69.8)	<0.001
No	45 (51.7)	21 (24.1)	6 (6.9)	15 (17.2)	
Renal dysfunction		n = 23	n = 16	n = 45	
Yes	5 (18.5)	6 (22.2)	3 (11.1)	13 (48.1)	0.17
No	41 (39.8)	17 (16.5)	13 (12.6)	32 (31.1)	
Thrombocytopenia		n = 20	n = 15	n = 43	
Yes	11 (40.7)	4 (14.8)	5 (18.5)	7 (25.9)	0.44
No	29 (31.9)	16 (17.6)	10 (11.0)	36 (39.6)	

* Cardiovascular dysfunction
** By Chi-square

Second and third chest radiographs were taken in 42 and 15 patients respectively. Two patients developed abnormal chest radiographs in the second chest radiograph study (cardiomegaly and mixed bilateral reticular infiltration and cardiomegaly in one each). Although most of the abnormal findings were improved, only 6 (16.7%) of them were resolved in the second chest radiograph. Six out of 15 chest radiograph abnormalities were completely resolved on the third chest radiograph. Overall 12 out of 51 chest radiograph abnormalities resolved before the patients were discharged from the hospital.

Discussion

The pathophysiology associated with scrub typhus is poorly understood. However, endothelial cell injury, resulting in various vital organ dysfunctions, is a prominent feature of the illness[16]. *O. tsutsugamushi* were found in cytoplasm of capillary endothelial cells in various organs such as lung, kidney, and cardiac myocytes in autopsy cases[17]. Hepatic dysfunction, with or without jaundice, was the most common organ dysfunction found in the present report. Pulmonary involvement was found in approximately half and cardiovascular dysfunction was found in about one-third of the cases. Chest radiographic abnormalities were common in both groups of patients presented with or without pulmonary symptoms. Findings from the present study showed that myocarditis and pericarditis were more common than previously documented. The correlation between chest radiographic abnormalities and cardiovascular dysfunction and hepatic dysfunction were also documented in the present study. These findings appear to correspond with the pathological findings of widespread vasculitis and perivasculitis in severe scrub typhus[17].

There are some reports of pleuropulmonary complication of scrub typhus in Thailand[5,6,7,18]. Pleuropulmonary abnormalities found in the present study varied from interstitial pneumonitis to the presence of air space nodules and pleural effusion. Reticulonodular opacities, septal lines, and hilar enlargement were frequent chest radiographic abnormalities found in previous reports[4,19,20]. In a study by Choi et al[4], the most frequent pulmonary abnormality was bilateral reticulonodular opacities (40%) which was similar to the present study. However, parenchymal consolidation and hilar adenopathy were found less than 2% in

the present study. Another previous study from north Thailand[6] found abnormal chest radiographs in 21.7% of patients, with various patterns of pulmonary infiltration, but the details of pulmonary consolidation and hilar adenopathy were not mentioned. This explanation of these differences was unclear. Cardiomegaly, unrelated to scrub typhus in the opinion of the authors, was reported in 13-23% in those reports. Cardiomegaly with or without congestive heart failure was very common in the present study. These abnormalities are rarely found in patients with other acute bacterial infections, except in leptospirosis[21]. The age of patients who developed congestive heart failure varied between 11 to 92 years old. Although cardiovascular dysfunction or myocarditis, caused by scrub typhus was the most likely explanation for congestive heart failure found in the present study, preexisting heart diseases such as coronary heart disease, rheumatic heart disease could not be excluded in patients without baseline chest films. Additionally, interpretation of cardiac size on follow-up chest films with different positioning may be difficult in patients who had a slightly changed finding.

The overall mortality was low in the present study, a slow resolution of the chest radiographic abnormalities was noted. Detailed studies on the pathogenesis of cardiovascular and pulmonary dysfunction in scrub typhus are needed.

Scrub typhus was reported to cause 10 to 19% of cases of acute undifferentiated fever in Thailand and Malaysia[22,23]. According to Thai public health statistics fewer than 100 cases per year of scrub typhus were reported before 1983, and between 750 and 900 cases per year were reported from 1988 to 1991 (Ministry of Public Health, Nondhaburi, Thailand, unpublished data). Recent publications and results of the present study indicate that scrub typhus continues to be underreported in this country[6]. Lack of widely available specific serological tests to confirm the diagnosis is a major reason for underreporting. Eschars, clinical indicators for scrubs typhus, occurred in only 30-50% of patients. Although mild scrub typhus could be a self-limited disease, accurate diagnosis and proper treatment are important in shortening the duration of fever and in preventing potentially lethal complications such as renal failure, pneumonitis and ARDS. Chest radiography should be included in the initial evaluation of patients with suspected scrub typhus. Doxycycline would be an appropriate initial antimicrobial treatment in patients who developed cardiovascular involvement shown by chest radiography, as described in the presented study. Azithromycin could be considered as an alternative treatment where doxycycline-resistant scrub typhus is suspected[24].

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ลักษณะทางภาพรังสีทรวงอกและอาการทางคลินิกของโรค scrub typhus ในคนไทย 130 คน

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วัตถุประสงค์: *เพื่อศึกษาลักษณะทางภาพรังสีทรวงอกและอาการทางคลินิกของโรค scrub typhus ในประเทศไทย และหาลักษณะทางภาพรังสีที่ช่วยในการวินิจฉัยโรค*

วัสดุและวิธีการ: *ศึกษาผู้ป่วยที่เข้ารับการรักษาและได้รับการวินิจฉัยว่าเป็นโรค scrub typhus ที่รับไว้รักษาใน 3 โรงพยาบาลในภาคตะวันออกเฉียงเหนือของประเทศไทย ช่วงเวลาที่ทำการศึกษาระหว่างเดือนกรกฎาคม พ.ศ. 2544 และเดือนธันวาคม พ.ศ. 2545 ทำการวิเคราะห์ข้อมูลทางคลินิกและการแปลผลภาพรังสีทรวงอกโดยรังสีแพทย์ 2 คน ซึ่งไม่ทราบข้อมูลทางคลินิกและการวินิจฉัยโรค*

ผลการศึกษา: *ผู้ป่วยที่ทำการศึกษาเป็นเพศหญิง 33 คนและเพศชาย 97 คน มีอายุเฉลี่ย 45 ปี (11-92 ปี) พบว่ามีอาการทางปอดร้อยละ 61.5, มี eschar ร้อยละ 33.1, พบความผิดปกติของตับร้อยละ 58.5 และความผิดปกติของระบบหัวใจและหลอดเลือดร้อยละ 33 ผู้ป่วยส่วนใหญ่มาด้วยความผิดปกติของปอด ร้อยละ 41.5 ในการศึกษานี้พบผู้เสียชีวิตจำนวน 5 คน ลักษณะทางภาพรังสีทรวงอกเบื้องต้นมีความผิดปกติร้อยละ 64.6 ลักษณะผิดปกติที่พบได้บ่อยคือ ลายตาข่ายที่ปอดทั้งสองข้าง (ร้อยละ 48.5), หัวใจโต (ร้อยละ 28.5), ภาวะหัวใจวายเลือดคั่ง (ร้อยละ 18.5), air space nodules (ร้อยละ 13.1) และพบน้ำในช่องเยื่อหุ้มปอด (ร้อยละ 10.8) ในการศึกษานี้พบมีความสัมพันธ์อย่างมีนัยสำคัญทางสถิติระหว่างความผิดปกติทางภาพรังสีทรวงอก กับ ความผิดปกติของตับและความผิดปกติของระบบหัวใจและหลอดเลือด*

สรุป: *ควรทำการถ่ายภาพรังสีทรวงอกในผู้ป่วยที่สงสัยโรค scrub typhus ทุกราย ลักษณะทางภาพรังสีที่พบได้บ่อยที่สุดคือ ลายตาข่ายที่ปอดทั้งสองข้าง โดยที่อาจจะมีหัวใจโต หรือ ภาวะหัวใจวายเลือดคั่งร่วมด้วยหรือไม่ก็ได้*