



## ARDS in Scrub Typhus

S.N. Kaore, P.Sharma, V.K. Yadav, R.Sharma, N.M. Kaore

### Introduction

Scrub typhus is a mite-borne infectious disease caused by *Orientia tsutsugamushi*. It is an acute febrile illness which generally causes non-specific symptoms and signs. The clinical manifestations of this disease range from sub-clinical disease to organ failure to fatal disease. Deaths are attributable to late presentation, delayed diagnosis, and drug resistance. Acute respiratory distress syndrome (ARDS) is a serious complication of scrub typhus. The mortality rate for the scrub typhus patients with ARDS can range up to 25% (1).

Recently with increasing trend of outdoor recreation activities, mountaineering, urbanization into rural areas, even physicians those who are not in the endemic areas may encounter the disease and should be aware of its symptoms and complications.

If there is delay in the initiation of the appropriate antimicrobial therapy patient may present with serious complications when diagnosis is delayed or patient is not treated with appropriate antibiotic, the scrub typhus can present with serious complications such as renal failure, myocarditis, septic shock, meningoencephalitis and rarely acute respiratory distress syndrome that may lead to death. The pulmonary manifestations of scrub typhus are varying grades of bronchitis and interstitial pneumonitis progressing to ARDS (1). Acute respiratory distress syndrome is defined as an acute and persistent lung inflammation with increased vascular permeability and is most often associated with sepsis syndrome, aspiration, primary pneumonia, or multiple traumas (2).

### Pathology of ARDS

The pathologic progression of ARDS reflects the sequentially occurring exudative, organizing (fibroproliferative) and fibrotic stages. There are reports of diffuse alveolar damage in the organizing stage without evidence of vasculitis (3). Pathological findings in ARDS patients on gross inspection reveal oedematous and haemorrhagic lungs. Microscopic examination revealed diffuse alveolar damage with hyaline membrane formation and interstitial pneumonitis with infiltration of inflammatory cells. Immunohistochemical stain showed *O. tsutsugamushi* antigen depositions in the endothelial cells.

It is also possible to demonstrated iNOS in the alveolar macrophages and lung tissue debris in both cases. Thus, direct endothelial cell invasion of the organism and marked iNOS expression may be involved in the pathogenesis of ARDS associated with scrub typhus (4).

### Clinical Studies with ARDS

A retrospective study in Taiwan, China reviewed the medical records of 72 patients diagnosed with scrub typhus from January 1998 to August 2006. Patients with ARDS were included in study while patients without ARDS served as controls. Mortality rate was found to be 25%. The study highlighted that significant predictors of ARDS are initial presentations of dyspnea and cough, white blood cell count, hematocrit, total bilirubin, and delayed use of appropriate antibiotics while albumin, prothrombin time, and delayed use of appropriate antibiotics are independent predictors of ARDS. Identification and keeping these relative risk factors in the mind may help clinicians to evaluate & identify clinical cases of scrub typhus with ARDS early (5).

In the same study group the biochemical parameters were studied in detail, which indicated that WBC counts of the ARDS group were significantly higher than those of the control group, which reflects the seriousness of infection in the ARDS group. Hematocrit in the ARDS group was significantly lower than that of the control group, which suggested that the ARDS group was more anemic than the control group. Although all liver enzyme levels (AST, ALT, ALP, and total bilirubin) were increased in both the ARDS and control groups, only the total bilirubin level was significantly higher in the ARDS group than in the control group. Therefore, a scrub typhus patient with severe infection, anemia and jaundice may be considered to be at high risk for developing ARDS (5).

In general, fever for more than one week was the only common manifestation in patients clinically and serologically confirmed to have scrub typhus. At times, it may present without the typical symptom of high fever, as in case of an aged patient in Japan and subsequently developed the complication of ARDS but improved dramatically on timely intervention with minocycline and supportive measures (6)

In another study, scrub typhus patients presented in

From the Peoples College of Medical Sciences Campus, PCMS, Bhanpur, Bhopal-462010 Madhya Pradesh-India.

Correspondence to : Dr S.N. Kaore, Senior MIG - C/4, PCMS Campus, PCMS, Bhanpur, Bhopal-462010 Madhya Pradesh - India



emergency with acute respiratory distress syndrome and history of fever for more than one-week duration and were positive for Weil Felix reaction. All these patients with scrub typhus and ARDS responded dramatically to doxycycline and the fever subsided after five days (7).

Interstitial pneumonia is the most frequent chest manifestation of scrub typhus. The presence of interstitial pneumonia is closely associated with morbidity and severity of disease for patients with scrub typhus. The physician should recognize the presence of interstitial pneumonia as being the important determining factor for predicting the clinical course and prognosis for patients with scrub typhus (8).

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 are the most frequent radiographic finding of scrub typhus. The pulmonary manifestations of scrub typhus include interstitial pneumonia, interstitial edema, and hemorrhage caused by vasculitis. Interstitial pneumonia (IP) frequently occurs in patients with scrub typhus and is closely associated with severity of the disease. The recognition of the presence of Interstitial Pneumonia is an important determining factor for predicting the clinical course and prognosis for patients with scrub typhus.

Bilateral diffuse areas of reticulonodular opacity and septal lines are the most common findings (1, 2). Airspace consolidation is relatively uncommon and generally appears in the lower zone of both lungs (1, 2). Unilateral or bilateral hilar enlargement and pleural effusion are common radiographic features, found in 25%-27% and 12%-43% of patients, respectively (1, 2).

Ground-glass opacity, interlobular septal thickening and pleural effusions are common findings at thin-section CT, whereas bronchial wall thickening, centrilobular nodules and axial interstitial thickening are less common.

HRCT of lower lung zones shows interlobular septal thickening, bronchial wall thickening, diffuse ground glass opacities in the dependent lung zones, increased vascular diameter may also be present.

Doxycycline would be an appropriate initial antimicrobial treatment in patients who develop cardiovascular involvement shown by chest radiography as been depicted in a study and azithromycin & rifampicin in resistant cases (9,10). Meticulous respiratory supportive care must then be provided. Treatment of the hypoxemia seen in ARDS usually requires tracheal intubation and positive-pressure mechanical ventilation.

The public health importance of this disease is underestimated due to difficulties in clinical diagnosis and lack of laboratory methods in many geographical areas. Scrub typhus is known to occur all over India and therefore

physicians should be aware of this potentially serious but easily treatable disease. This strategy, if meticulously followed, by all practitioners will surely help to bring down the occurrences of ARDS associated with scrub typhus.

### Conclusion

Scrub typhus is a mite-borne infectious disease caused by *Orientia tsutsugamushi*. Acute respiratory distress syndrome (ARDS) is a serious complication of scrub typhus. The mortality rate for the scrub typhus patients with ARDS can range upto 25%. Initial presentations of dyspnea and cough, white blood cell count, hematocrit, total bilirubin, and delayed used of appropriate antibiotics are significant risk factors of ARDS. Identification of these relative risk factors with timely and aggressive treatment of this fatal complication may help clinicians to reduce related mortality associated with Scrub Typhus

### References

1. Chayakul P, Panich V, Silpapojakul K. Scrub typhus pneumonitis: an entity which is frequently missed. *Q J Med* 1998; 68:595-602.
2. Bernard GR, Artigas A, Brigham KL, *et al*. The American-European consensus conference on ARDS: Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; 149: 818-24.
3. Park JS, Jee YK, Lee KY, *et al*. Acute respiratory distress syndrome associated with scrub typhus: diffuse alveolar damage without pulmonary vasculitis. *J Korean Med Sci* 2000; 15: 343-45.
4. Hsu YH, Chen HI. Pulmonary pathology in patients associated with scrub typhus. *Pathology* 2008; 40 (3):268-71.
5. Wang CC, Liu SF, Liu JW, Chung YH, Su MC, Lin MC. Acute respiratory distress syndrome in scrub typhus. *Am J Trop Med Hyg.* 2007 Jun;76(6):1148-52.
6. Ichimura K, Uchida Y, Arai K, *et al*. Afebrile scrub typhus (tsutsugamushi disease) with acute respiratory distress syndrome. *Intern Med* 2002;41(8):667-70.
7. Pandey D, Sharma B, Chauhan V, Mokta J, Verma BS, Thakur S. ARDS complicating scrub typhus in Sub-Himalayan region. *J Assoc Physicians India* 2006; 54:812-13.
8. Sun WS, Ki TK, Young MK, *et al*. Clinical Role of Interstitial Pneumonia in Patients with Scrub Typhus:A Possible Marker of Disease Severity. *J Korean Med Sci* 2004; 19: 668-73.
9. Aphinya C, Orasa C, Chaunpit S, *et al*. Scrub Typhus: Chest Radiographic and Clinical Findings in 130 Thai Patients. *J Med Assoc Thai* 2006; 89 (5): 600-07.
10. Kim YS, Yun HJ, Shim SK, *et al*. A comparative trial of a single dose of azithromycin versus doxycycline for the treatment of mild scrub typhus. *Clin Infect Dis* 2004 1;39(9):1329-35.