

Acute Respiratory Distress Syndrome Associated with Scrub Typhus: Diffuse Alveolar Damage without Pulmonary Vasculitis

Pathologic findings of scrub typhus have been characterized by vasculitis of the microvasculature of the involved organ resulting from a direct invasion by *Orientia tsutsugamushi*. We experienced a case of acute respiratory distress syndrome (ARDS) associated with scrub typhus. The case was proven by eschar and high titer of serum IgM antibody (positive at 1:1280). Open lung biopsy showed diffuse alveolar damage (DAD) in the organizing stage without evidence of vasculitis. Immunofluorescent antibody staining and polymerase chain reaction for *O. tsutsugamushi* failed to demonstrate the organism in the lung tissue. The patient expired due to progressive respiratory failure despite doxycycline therapy. Immunologic mechanism, without direct invasion of the organism, may participate in the pathogenesis of ARDS associated with scrub typhus.

Key Words: Scrub Typhus; Respiratory Distress Syndrome; Adult

Jae Seuk Park, Young Koo Jee, Kye Young Lee,
Keun Youl Kim, Na Hye Myong*, Pil Weon Seo†

Department of Internal Medicine, Pathology* and
Chest Surgery†, College of Medicine, Dankook
University, Cheonan, Korea

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Address for correspondence

Jae Seuk Park, M.D.

Department of Internal Medicine, College of
Medicine, Dankook University, 29 Anseo-dong,
Cheonan 330-715, Korea

Tel: +82.417-550-3055, Fax: +82.417-550-3256

E-mail: jspark@anseo.dankook.ac.kr

INTRODUCTION

Scrub typhus is a zoonotic disease caused by *Orientia tsutsugamushi* transmitted by chigger, and is widely distributed in the Asia-Pacific area (1). The pathologic findings are characterized by vasculitis of small vessels of the involved organs caused by a direct invasion of the organism.

The pulmonary involvement of scrub typhus usually shows the pattern of mild interstitial pneumonia and severe pulmonary involvement like acute respiratory distress syndrome (ARDS) have been rarely seen since the introduction of specific antibiotic therapy. Recently, a few cases of ARDS associated with scrub typhus have been reported without description of pathologic findings (2, 3). We experienced a case of ARDS associated with scrub typhus. The patient died of progressive respiratory failure despite adequate antibiotic therapy, and open lung biopsy showed diffuse alveolar damage (DAD) without evidence of vasculitis. The trials for direct demonstration of the organism in the lung specimen failed. This case report suggests that immunologic mechanism may also participate in the pathogenesis of ARDS associated with scrub typhus.

CASE REPORT

A 72-year-old woman was admitted with progressive

dyspnea, which developed 2 days prior to admission. She lived in the rural area of Korea, which is the endemic area of scrub typhus. She had a few days of febrile sense and generalized myalgia, which developed 12 days prior to admission. On admission, vital signs were blood pressure 110/70 mm Hg, oral temperature 36.6°C, heart rate 96/min and respiratory rate 26/min. A 1 cm-sized black-crusted shallow ulcer (eschar) was found on the anterior chest wall and fine crackles were heard on both lower lung fields of the patient.

Laboratory data revealed white blood cell count of 14,000/ μ L, with 49% neutrophils and 31% lymphocytes. Erythrocyte sedimentation rate (14 mm/hr) and C-reactive protein (0.89 mg/dL) were mildly elevated. While the patient was on supplemental oxygen of 6 L/min with nasal prong, arterial blood gas study revealed pH 7.43, PCO₂ 48 mm Hg and PO₂ 62 mm Hg. Chest radiograph showed bibasilar interstitial infiltrations (Fig. 1). The patient was unable to cooperate for the pulmonary function study. Serologic test for Hantaan virus (Korea Ab) and *Leptospira* antibody were negative but serologic test for *O. tsutsugamushi* (indirect hemagglutination test) antibody (IgM) was positive at 1:1,280 dilution (reference value was negative at 1:160). Despite oral doxycycline (100 mg q 12 hr) therapy from admission, dyspnea was aggravated and chest radiograph finding progressed to diffuse bilateral infiltrations. Mechanical ventilatory support was started on the fifth day of admission. Repeated sputum examination showed normal throat flora and no



Fig. 1. Chest radiograph on admission shows bibasilar interstitial infiltration.



Fig. 2. High-resolution computed tomography of lung checked on eighth day of admission shows diffuse inhomogeneous airspace consolidation.

acid fast bacilli or fungus were found. Blood cultures showed no bacterial growth. Rheumatoid factor and anti-double stranded DNA antibody were negative, but fluorescent anti-nuclear antibody was weakly positive with speckled pattern. High resolution CT, checked on the eighth day of admission, showed diffuse inhomogeneous airspace consolidations (Fig. 2). Open lung biopsy was done on the seventh day of mechanical ventilation because hypoxemia aggravated despite ventilatory support (PaO₂



Fig. 3. Chest radiograph checked on the sixth day of mechanical ventilation shows diffuse bilateral pulmonary infiltration.

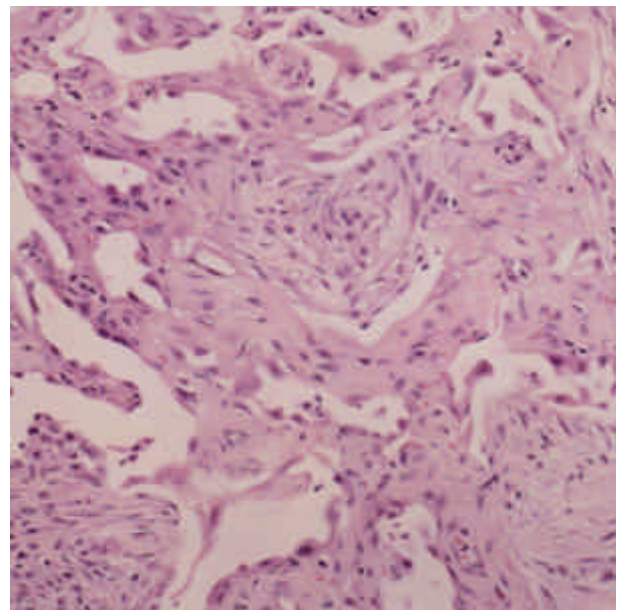


Fig. 4. Open lung biopsy shows diffuse interstitial widening with abundant fibroblast proliferation compatible with organizing phase of diffuse alveolar damage (H&E, ×200).

54.2 mm Hg with fraction of inspired oxygen of 0.5) and chest radiograph showed diffuse bilateral infiltration (Fig. 3). The pathologic finding showed diffuse interstitial widening containing abundant fibroblast proliferation compatible to the organizing stage of DAD, but the evidence of vasculitis was not found (Fig. 4). Immunofluorescent antibody staining and PCR technique for *O. tsutsugamushi* failed to demonstrate the organism in the lung tissue (4, 5). After open lung biopsy, pulmonary

infiltrations and arterial hypoxemia progressed despite full ventilatory support and medical therapy. She died of respiratory failure on the fifteenth day of admission.

DISCUSSION

Scrub typhus is an acute febrile infectious disease caused by *O. tsutsugamushi*. With the introduction of appropriate antibiotics like doxycycline, serious complications like ARDS or disseminated intravascular coagulation are rarely seen (6, 7).

It is generally known that the main pathologic findings in scrub typhus are systemic vasculitis and perivasculitis, which are caused by proliferation of *O. tsutsugamushi* in endothelial cells of microvascular system and such microangiopathies may involve the heart, lungs, brain and kidneys (8).

But, recently, the immune system has been proposed as having a possible role in the pulmonary manifestations of scrub typhus. Chan et al. (9) reported a case of scrub typhus presenting as chronic interstitial pneumonitis on open lung biopsy. In addition, pathologic study of mice infected with *O. tsutsugamushi* R19 strain showed non-specific interstitial inflammation without vasculitis (10). Lee et al. (11) performed transbronchial lung biopsies in patients with scrub typhus who showed interstitial pneumonia pattern on chest radiograph. The pathologic findings showed interstitial edema with mononuclear cell infiltration, mainly lymphocytes, without any evidence of vasculitis or perivasculitis. Immunofluorescent study using monoclonal antibody against *O. tsutsugamushi* and electron microscopic examination failed to demonstrate rickettsial organism in the lung tissue of the study, suggesting that not only vasculitis due to direct invasion of rickettsial organism but also immunologic mechanism may participate in the pathogenesis of pulmonary involvement of scrub typhus.

In this case, dyspnea and pulmonary infiltrations on chest radiograph were aggravated despite doxycycline therapy and open lung biopsy showed diffuse interstitial widening, containing abundant fibroblast proliferation compatible with organizing stage of DAD (Fig. 4). There was no evidence of vasculitis in the lung tissue. Moreover, we could not demonstrate organisms in the lung tissue with immunofluorescent antibody staining and PCR technique.

ARDS is caused by direct or indirect lung injury. The pathologic progression of ARDS reflects the sequentially occurring exudative, organizing (fibroproliferative) and fibrotic stages, regardless of the specific etiology (12). A subset of ARDS patients, defined as acute interstitial pneumonia, had a prior illness similar to a viral upper respiratory infection (13). These findings suggest that

immunologic response of the lung to a single past injury such as viral infection might participate in the pathogenesis of ARDS (13). In our case, immunologic response of the lung to previous *O. tsutsugamushi* infection might have operated in the pathogenesis of ARDS.

To our knowledge, this is the first pathologically proven ARDS case report associated with scrub typhus.

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