

## Scrub Typhus and Lung: Suspect Early and Treat Promptly

“Scrub typhus is probably one of the most under-diagnosed and under-reported febrile illnesses requiring hospitalisation in the region (South-East Asia)”.<sup>1</sup> This statement by World Health Organization portrays the ignorance for a disease which is easily treatable but leads to high fatality rate, if not diagnosed and treated accordingly. Where documented, scrub typhus can account for up to 20% of acute undifferentiated febrile hospitalisations in rural areas.<sup>2</sup> Scrub typhus is endemic to a large area of the Asia-Pacific rim, extending from Afghanistan to China, Korea, the islands of the South-Western Pacific and Northern Australia.<sup>3</sup> In India also there are reports from various regions including Himalayas, Rajasthan and South India, either as retrospective case studies or outbreak investigations with high incidence of complications and mortality.<sup>4,5</sup>

Scrub typhus is an acute febrile illness caused by *Orientia tsutsugamushi* and transmitted by the bite of larval trombiculid mites. It presents with the formation of eschar at the inoculation site followed by fever, headache, myalgia, generalised lymphadenopathy, cough, gastrointestinal symptoms, transient hearing loss and rash. In few cases, disease further progresses in the form of acute respiratory distress, meningo-encephalitis, gastrointestinal bleeding, acute renal failure, hypotensive shock and coagulopathy.<sup>6,7</sup>

Out of these, pulmonary manifestations of scrub typhus are usually perplexing for the clinicians due to its non-specific clinical presentation causing delay in the diagnosis that leads to high incidence of complications and mortality.<sup>4</sup> Though accurate diagnosis supported by precise diagnostic modalities along with appropriate therapy is desirable to combat the pulmonary complications, importance of early clinical suspicion in acute febrile illness can not be denied. A detailed knowledge of clinical and radiological presentations of scrub typhus could be beneficial in this regard.

Basic pathological process described in pulmonary involvement is interstitial pneumonia with or without vasculitis. Moreover, interstitial pneumonia is believed to be an important prognostic factor for predicting the clinical course as presence of interstitial pneumonia is related with more severe clinical presentation, prolonged hospitalisation and higher mortality.<sup>8</sup> Acute respiratory distress syndrome (ARDS) is another serious manifestation of pulmonary involvement which may affect up to 19.2% of the patients with high mortality of 33% in these cases.<sup>5,9</sup>

Incidence of chest radiographic abnormalities in patients with scrub typhus is variable and conventional radiological findings include bilateral diffuse areas of reticulonodular opacity, hilar lymph node enlargement and septal thickening implying

interstitial involvement. Airspace consolidation, if present, affects lower zones of both the lungs. Characteristic high-resolution computed tomography (HRCT) manifestations of scrub typhus include interlobular septal thickening, axial interstitial thickening, ground-glass opacity, and centrilobular nodules; however consolidation and large nodules are relatively less common.<sup>10,11</sup>

Though haematological dissemination of *Orientia tsutsugamushi* is postulated through involvement of vascular endothelial cells and macrophages, it has a predominant macrophage rather than endothelial tropism in the lung as demonstrated in experimental studies. In murine model of scrub typhus, three types of infiltrates are described: perivascular BALT (Bronchus associated lymphoid tissue), parenchymal nodules and pleuritic lesions with different pathogenetic mechanisms. While BALT and pleuritic infiltrates could contribute to early bacterial degradation, solitary infected cells in the parenchymal nodules may have escaped immuno-surveillance.<sup>12</sup> These pulmonary lesions recapitulate essential features of pulmonary involvement in human scrub typhus. Sub-pleural, interlobular septal thickening and peribronchial infiltrates closely resemble the BALT and pleuritic infiltrates in murine lungs. Similarly, pulmonary inflammation occurs rather late, being usually progressive during the first week after the onset of symptoms.<sup>13</sup> Endothelial infection has been reported to be a hallmark of lethal human infection.<sup>14</sup>

The mainstay of the diagnosis remains serology and indirect immunofluorescence assay (IFA) is the gold standard. All serological tests have inherent limitations as diagnosis is retrospective, and therefore, cannot guide initial treatment. Higher background antibody levels in endemic population might further complicate the scenario. Polymerase chain reaction (PCR) assay is valuable as it can detect *Orientia* DNA (deoxy-ribonucleic acid) before appearance of the antibody response. However, the high resource costs and requirement of technical expertise limits the scope in endemic areas.<sup>15</sup> Therefore, point of care testing including both pathogen and antibody based tests will be more advantageous to overcome the hurdles in diagnostics of scrub typhus.

Initiation of antibiotics at the earliest is the mainstay of therapy to impede the complications and to reduce the mortality. Doxycycline is the antibiotic of choice and should be commonly used, although resistance has been documented in some parts. In cases of doxycycline resistance, rifampicin is usually effective. Azithromycin is the recommended drug for pregnant females and children. Additionally, efficacy of azithromycin therapy is comparable to doxycycline therapy in cases of complicated scrub typhus.<sup>16</sup>

Though the disease in initial stages can be treated with antibiotics; it is very difficult to treat advanced life-threatening cases that may require intensive care. Therefore, a strong clinical suspicion as well as acquaintance with various clinical and radiological manifestations of scrub typhus could be life saving.

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