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Pulmonary Manifestations of Scrub Typhus: Wisdom May Prevail Obstacles

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Abstract

Scrub typhus is a bacterial infection caused by Orientia tsutsugamushi. The disease is prevalent in a very large geographical area and usually presents with undifferentiated febrile illness. Pulmonary manifestations impart further challenge for clinician due to nonspecific clinical presentation, lack of sensitive and specific diagnostic tests and high incidence of complications and mortality, if not treated timely. Proper elucidation of underlying pathogenetic mechanisms and immune response is essential to understand the sequence of events, clinical implications, prognostic factors and prospects for vaccine development for this potentially fatal infection.

Keywords: Scrub typhus; Pulmonary; Pathogenesis

Introduction

Scrub typhus, also known as tsutsugamushi disease is a bacterial infection transmitted by larval trombiculid mites [1]. Causative organism is *Orientia tsutsugamushi,* an obligatory intracellular bacterium which leads to formation of eschar at the inoculation site and followed by fever, headache, myalgia, generalized lymphadenopathy, cough, gastrointestinal symptoms, transient hearing loss, and rash. Further progression of disease may manifest as acute respiratory distress, meningoencephalitis, gastrointestinal bleeding, acute renal failure, hypotensive shock, and coagulopathy [2,3].

Referring to scrub typhus, which leads to severe though easily treatable disease if diagnosed correctly, the World Health Organization (WHO) stated, "Scrub typhus is probably one of the most underdiagnosed and underreported febrile illnesses requiring hospitalization in the region [4]". This statement denotes the overall neglected status of the disease despite its distribution in a large geographic area, rising incidence in previously unrecognized areas and fatality of the disease. Approximately, one million cases of scrub typhus are reported to occur every year with an estimated 10% case fatality rate resulting in even more deaths than dengue [5]. In areas where disease is documented, scrub typhus can account for up to 20% of acute undifferentiated febrile hospitalizations in rural areas [6]. Even this data is depicted as underestimation because, given the variety of strains and the short-lived humoral immunity, seroepidemiological studies must fail to capture all previous cases [7]. It 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 [8]. In India also, there are reports from various regions including Himalayas [9,10], Rajasthan [11] and South India [12] either as retrospective case studies or outbreak investigations with high incidence of complications and mortality from the disease [10,11].

Lung is one of the preferential organs for the bacterium and clinical manifestations of the pulmonary spread might be non-specific and overlooked if not scrutinized intensely leading to fatality. Therefore, detailed discussion about pulmonary manifestations with particular stress on its pathogenesis is essential to improve the overall outcome of the disease.

Clinical Manifestations and Prognostic Determinants of Pulmonary Involvement

Pulmonary involvement has been well reported and basic pathologic process in pulmonary involvement of scrub typhus is interstitial pneumonia with or without vasculitis [13]. Up to 58.4% of the patients may portray pulmonary involvement in the form of symptoms like cough and dyspnoea [11]. An important and serious manifestation of the scrub typhus is acute respiratory distress syndrome (ARDS) which affects approximately 11.1% of the patients with high mortality of 25% in these cases [14]. One of the recent study from India illustrates 19.2% incidence of ARDS with higher mortality (33%) [11].

Our partially published data also demonstrated pulmonary involvement in 31.2% of the patients with cough, dyspnoea and chest pain being the dominant symptoms and restrictive venilatory defect as commonest spirometry pattern [15].

Interstitial pneumonia is considered as important determining factor for predicting the clinical course and prognosis by some authors as presence of interstitial pneumonia is related with more severe clinical presentation, prolonged hospitalization and higher mortality compared to the patients who did not develop this complication [16]. The outcome is determined by multiple factors including age of the patient and genetic factors but the virulence of infecting strain of *O. tsutsugamushi* is believed to be the most important one. Indeed, bacterial proliferation (as opposed to immunopathology) and the time of antibiotic control of the infection are very important predictors of lethality [17,18]. Thus, the delayed treatment leads to complications such as adult respiratory distress syndrome, disseminated intravascular coagulation, acute renal failure, meningoencephalitis and gastrointestinal tract bleeding [17,19].

Radiological Manifestations

Incidence of chest radiographic abnormalities in patients with scrub typhus varies from 59% to 72%. Most common radiological findings reported in the literature include bilateral diffuse areas of reticulonodular opacity, hilar lymph node enlargement, and septal lines implying interstitial involvement. Airspace consolidation is relatively uncommon and affects lower zones of both lungs [13,16]. Song et al.

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[16] in a study of 101 patients reported interstial pneumonia (51.4%) as most common radiological finding followed by pleural effusion (42.6%), cardiomegaly (37.6%), pulmonary alveolar edema (20.8%), hilar adenopathy (13.8%) and focal atelectasis (11.8%) [16].

Similar to chest radiography, computed tomography (CT) findings also reflect cellular infiltration, edema, and hemorrhage caused by vasculitis or may be illustrative of interstitial edema secondary to cardiac involvement. Characteristic high-resolution computed tomography (HRCT) manifestations of scrub typhus include interlobular septal thickening, axial interstitial thickening, ground-glass opacity, though centrilobular nodules with consolidation and large nodules are relatively less common [13]. In our partially published study, abnormal chest radiograph was reported in 22% of the cases and HRCT findings demonstrated mediastinal lymphadenopathy (47.37%), pleural effusion (42.11%), ground glass opacity (21%) and consolidation (21%) [15].

Cellular Tropism is the Key to Dissemination and Pathogenesis

Diverse cellular tropism has been proposed to explain the variable manifestation of the disease. Preferential cells in the initial phase are dendritic cells and monocytes/macrophages leading to interaction of bacterium with local immune system at inoculation site [20]. Development of regional lymphadenopathy suggests lymphogenous spread [21]. Subsequently, hematogenously disseminated infection is postulated due to key involvement of endothelial cells and macrophages, both of which release soluble cell-specific adhesion molecules [22]. Although, the exact mechanism of vascular damage caused by *O. tsutsugamushi* infection remains poorly understood, the primary event might be the destruction of endothelial cells lining small blood vessels and the accompanying inflammatory responses [23,24].

In an experimental study, using scrub typhus murine model, Keller et al. demonstrated highest bacterial loads in the lung, though reason of this organ specific tropism remains unclear and found a predominant macrophage rather than endothelial localization. They further tried to elaborate pathogenetic mechanism through demonstration of histopathological findings and demonstrated that cellular infiltrates were typically found in peribronchial areas, in the parenchyma and in the visceral pleura. Peribronchial lesions showed orientation towards the adjacent arterial blood vessels, the characteristic localization of inducible bronchus-associated lymphatic tissue (BALT). Lesions in the alveoli had a nodular appearance and visceral pleura was focally invaded by inflammatory infiltrates. BALTs and pleural lesions contained mainly degraded, extracellular bacterial antigen possibly as a consequence of exocytosis of bacterial remnants. In contrast, parenchymal nodules contained infected cells with large numbers of intracellular bacteria. Thus, they concluded that BALT and pleuritic infiltrates could contribute to early bacterial degradation, while solitary infected cells in the parenchyma may have escaped immunosurveillance during the initial phase of infection. Importantly, no bacteria were found in CD31-positive endothelial cells despite a close spatial relationship in this study [25].

Need of Newer Techniques for Rapid and Accurate Diagnosis

Early and rapid diagnosis is crucial to halt the course of the disease. Therefore, scrub typhus should be always considered as a differential diagnosis in a patient from endemic region with acute febrile illness. Weil Felix test still serves as a useful and cheapest available tool for the laboratory diagnosis of rickettsial diseases. Weil-Felix test has shown reasonably high specificity but a low sensitivity for the diagnosis of scrub typhus and therefore, this test should be used only as a first line of testing in rudimentary hospital laboratories [26]. The current gold standard reference diagnostic method—the indirect immunofluorescence assay (IFA)—is imperfect, retrospective and requires a level of technical expertise and equipment thereby limiting its utility in rural areas. Advantage of Polymerase chain reaction assay lies in detection of Orientia DNA before appearance of antibody response. It also has diagnostic advantage over serology in endemic areas with high background levels of antibody in the population. However, the high resource costs and training requirement make them impractical in many endemic areas [27]. Considering the drawbacks of these techniques individually, it has been recommended that point of care testing should be developed including both pathogen and antibody based tests.

Efficacy of Antibiotics

To prevent mortality and secondary complications, initiation of antibiotics at the earliest is mainstay of therapy. Presumptive antibiotic therapy is usually prescribed to febrile individuals in endemic areas. Among the antibiotics, Doxycycline has a proven efficacy and commonly used, although resistance has been documented in parts of northern Thailand. Rifampicin is effective for doxycycline resistant cases and in areas where poor response to standard anti-rickettsial drugs is documented. Macrolides are also equally efficacious and have less adverse effects, but these are expensive. Azithromycin is the recommended drug in pregnancy and for children. Moreover, recent data suggest that outcomes of azithromycin therapy are comparable to those of doxycycline therapy in patients with complicated scrub typhus [28]. Except for this study; most of the clinical evidences as well as recommendations regarding drug therapy are concerned with cases of scrub typhus with mild to moderate severity. Therefore, to prove the efficacy of different antibiotics in the treatment of severe, life-threatening scrub typhus, further studies are desired [29].

Future Prospects of Vaccine Development

Because of significant antigenic variations among strains of *O. tsusugumashi* and limited cross protective immunity against heterologous infection, earlier attempts for vaccine development have been unsuccessful. Most recent approaches have been focused upon antigenic determinants ignoring cellular immunity, which is critical for intracellular organelle. Deficiency of comprehensive knowledge of common antigenic determinants and lack of small animal models to recapitulate systemic endothelial infection are further hurdles.

To overcome these barriers, more detailed understanding of immunopathogenesis of disease along with application of technology advancement is essential. Proposal for development of an effective and safe vaccine for scrub typhus include a new approach with a strong focus on T-cell mediated immunity, empirical testing of the immunogenicity of proteins encoded by conserved genes and assessment of protection in relevant animal models that truly mimic human scrub typhus [30].

Conclusions

Pulmonary manifestations of scrub typhus are uncommon and can be fatal, particularly in the form of adult respiratory distress syndrome. Though antibiotic therapy may prove beneficial in initial phase; advanced cases pose a considerable challenge for the treating physician. Therefore, early diagnosis is warranted to attain favourable outcomes. Further, detailed understanding of underlying pathogenesis and immunity is essential for developing effective vaccines against scrub typhus.

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