



Recent Advances in Understanding Pathophysiology of Scrub Typhus

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Introduction

Scrub typhus, also known as tsutsugamushi disease, is a zoonosis that is endemic in the Asia-Pacific region and carries a significant morbidity and mortality. It belongs to the genus *Rickettsia* and its etiologic agent is now identified as *Orientia tsutsugamushi*, a gram-negative obligate intracellular bacterium (1). It has a different cell wall structure and genetic composition than that of the rickettsiae. It is maintained vertically in *Leptotrombidium* spp. mites and is transmitted by the bite of the larval stage trombiculid mite or chigger to humans which are accidental hosts.

Typhus-like illnesses are significant diagnostic challenges as patients with rickettsiosis, leptospirosis, dengue fever, dengue haemorrhagic fever, typhoid and malaria can present with similar symptoms and signs. Recent studies suggest that rickettsioses account for 20-35% of undifferentiated fevers in south-east Asian adults, with scrub typhus being the most important (2,3).

The clinical manifestation of scrub typhus is nonspecific unless an eschar and regional lymphadenopathy are present. The diagnosis is usually based on the history, clinical course of illness and serological test (3,4). Because of reports of *Orientia tsutsugamushi* strains with reduced susceptibility to antibiotics, as well as reports of interesting interactions between this bacterium and HIV, a renewed interest in this reemerging illness has emerged.

Pathophysiology

Humans acquire the disease when an infected chigger, the larval stage of trombiculid mites (*Leptotrombidium deliense* and others), bites them while feeding and inoculates *Orientia tsutsugamushi* pathogens. The bacteria multiply at the inoculation site with the formation of a papule that ulcerates and becomes necrotic, evolving into an eschar, with regional lymphadenopathy that progress to generalized lymphadenopathy within a few days. Before symptoms develop, patients are rickettsemic.

As in other rickettsial diseases, increased vascular permeability, edema, hypovolemia, and hypoperfusion of some organs such as the kidneys and perivasculitis of the small blood vessels occurs. Although the pathogenesis of scrub typhus involve immune and inflammatory mediators such as cytokines, prostaglandins, leukotrienes, and kinins,

the precise cellular tropism of *Orientia tsutsugamushi* had remains unknown till recently.

Recent Advances

On the basis of histopathologic studies conducted in the patients of scrub typhus, it has been proposed that disseminated vasculitis with perivasculitis is the hallmark of scrub typhus, and involvement of the brain and lungs are the most important factors in any fatal outcome. Vascular damage usually manifests as hemorrhagic phenomena and thromboembolic events are very rare.

The pathogenesis of the initial local host immune response at the inoculation site and the mode of early dissemination of the obligate intracellular *Orientia tsutsugamushi* were always debated. Also, the probability of myocardial damage and potentially acute and chronic cardiac insufficiency owing to the histologically evident interstitial inflammation was always looked upon. The recent discovery that *Orientia tsutsugamushi* infects principally endothelial cells in all of the organs with infected macrophages and cardiac myocytes is a substantial addition to our understanding of pathophysiology of scrub typhus (6). In another study, which focused on microscopic examination of the heart in 31 cases, it was found that six were perfectly normal, and 13 with inflammatory infiltrates showed intact heart muscle fibers (7). Twelve cases showed injury to cardiac myocytes, including several with frank focal necrosis that was rarely severe.

Another study conducted in adult Thai patients have suggested that *Orientia tsutsugamushi* induces a type 1 immune response, associated with elevation of interferon-alpha, IL-18 and IL-15 levels (8). Plasmodium falciparum malaria, dengue fever and some spotted fever rickettsiosis are associated with cytokine-induced systemic endothelial activation (9-11). During the initial inflammatory response to infections, early response cytokines (tumour necrosis factor-alpha, interleukin (IL)-1beta and IL-6) up-regulate cellular adhesion molecules (CAMs) on the surface of host leucocytes and endothelial cells (EC), which co-ordinate leucocyte transmigration across the endothelium (12). The selectins mediate initial leucocyte contact with EC, capturing cells from the bloodstream, followed by characteristic

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rolling and firm tethering to the endothelium. This requires higher-affinity leucocyte integrins (LFA-1 and Mac-1) binding to members of the immunoglobulin (Ig) superfamily, intercellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1), which are expressed on activated EC, enabling subsequent leucocyte diapedesis (13).

Based on post-mortem findings and in vitro experiments, *Orientia tsutsugamushi* can target the endothelium but in vivo data are lacking (14). *Orientia tsutsugamushi* has also been described within peripheral blood mononuclear cells of patients with scrub typhus (15). It has been hypothesized that markers of endothelial activation are raised in scrub typhus, and that measurement of both EC and leucocyte activation markers may allow us to distinguish between generalized systemic inflammatory responses or endothelial tropism of *Orientia tsutsugamushi*.

These results imply that both EC and leucocyte activation occur early in the course of scrub typhus, releasing sE-selectin and L-selectin into the systemic circulation. This may reflect direct infection of both cell types by *Orientia tsutsugamushi*. Endothelial recruitment of neutrophils and lymphocytes from the eschar would encourage localized inflammation and contribute potentially to subsequent dissemination, by localized increased vascular permeability and direct haematogenous spread, by circulation of pre-apoptotic infected EC, or by infection of lymphocytes, which could recirculate into the lymphatic system. In addition, high levels of sL-selectin could also reflect the homing potential of lymphocytes to peripheral lymph nodes and/or immune modulation through inhibition of endothelial-leucocyte attachment (16). Identifying the cellular sites of replication in the eschar, such as endothelium, leucocytes or intrinsic fibroblasts/dendritic cells, will be important in determining which of these potential routes the organism takes to disseminate from the initial inoculation site. The information they give on cellular activation and tropism of rickettsial agents suggests a role for early leucocyte and endothelial activation in the immune response and subsequent dissemination of the bacteria.

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 (17). 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 (17).

Conclusion

However, detailed studies on the pathogenesis of cardiovascular and pulmonary dysfunction in scrub typhus are thus needed to ensure early diagnosis and treatment target to reduce related mortality.

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