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ORIGINAL ARTICLE

Associated factors and clinical implications of serum aminotransferase elevation in scrub typhus

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Background/Purpose: Timely diagnosis and prompt treatment can reduce the complications of scrub typhus. It is thus important to find easy laboratory tests to help in the diagnosis, especially in patients without eschar at initial presentation. Because serum aminotransferase elevation is common in scrub typhus, its associated factors and clinical implications need further investigations.
Methods: We conducted a retrospective study in Kinmen, Taiwan, to collect clinically suspected scrub typhus patients notified to Taiwan Centers for Disease Control for confirmation during 2005–2010. Scrub typhus was diagnosed and *Orientia tsutsugamushi* was genotyped by serological or molecular assays. The laboratory data and clinical information were recorded for analysis.
Results: Overall, 344 suspected scrub typhus patients were reported to Taiwan Centers for Disease Control and 288 of them were certified scrub typhus. Scrub typhus patients had significantly more thrombocytopenia, serum aminotransferase elevation (76% vs. 54%, $p = 0.001$), higher frequency of fever, eschar, and lymphadenopathy, compared with nontyphus patients. Hepatic dysfunction in scrub typhus was associated with older age, longer fever duration, and

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absence of lymphadenopathy, but seemed to be unrelated to the rickettsial genotypes. Multivariate analysis showed that serum aminotransferase elevation (odds ratio: 3.75; $p = 0.003$; 95% confidence interval: 1.56—9.01) independently predicted scrub typhus. Furthermore, in suspected scrub typhus patients without eschar, 92% of true typhus patients had serum aminotransferase elevation compared with the nontyphus ones (odds ratio: 6.47; $p = 0.028$, 95% confidence interval: 1.23—34.11).

Conclusion: Hepatic dysfunction in scrub typhus patients is associated with older age, longer fever duration, and absence of lymphadenopathy. Serum aminotransferase elevation can aid in the diagnosis of scrub typhus, especially in suspected patients without eschar.

Introduction

Scrub typhus is a zoonotic disease caused by *Orientia tsutsugamushi*, which is transmitted vertically in the life cycle of mites (especially *Leptotrombidium* species); rodents are common animal hosts of scrub typhus. Humans contract scrub typhus after being bitten by mites in the trombiculid larval stage (chiggers) during recreational activities or agricultural works.[1] Scrub typhus prevails in eastern and southern Asia, the Western Pacific islands, and eastern Australia.[2] Taiwan is located within this region; the eastern parts of this country and its offshore islands have been reported to be endemic for scrub typhus.[3,4] Scrub typhus has been listed as a notifiable infectious disease in Taiwan since 1955; therefore, all clinically suspected patients of scrub typhus should be reported to the Taiwan Centers for Disease Control (CDC) for registration and confirmation.

After an incubation period of 9—12 days, the clinical features including eschar, fever, headache, skin rash, lymphadenopathy, myalgia, arthralgia, malaise, and cough start to occur.[5] The initial presentations of scrub typhus are nonspecific, and the more specific signs (e.g., eschar and skin rash) develop several days after fever. Despite being a pathognomonic sign of scrub typhus, however, eschar could not be found in a portion of patients, making the diagnosis challenging.[6] The definite diagnosis relies largely on serological or molecular assays on paired sera collected 2 weeks apart.[1] Therefore, a correct diagnosis of scrub typhus may be delayed, occasionally leading to severe complications such as acute respiratory distress, acute renal failure, interstitial pneumonitis, encephalitis, and even death.[7] It is important to find inexpensive and quick laboratory tests to aid in the diagnosis, especially in endemic areas with constrained medical resources.

Of particular note, hepatic dysfunction has been occasionally reported in 77—96% of patients with scrub typhus in some studies with small case numbers.[7,8] Although serum aminotransferase elevation was shown to serve as a distinguishing parameter for scrub typhus associated with acute hepatitis A,[9] the associated factors and clinical implications of hepatic dysfunction for scrub typhus remains largely unclear.

Kinmen island (24°44′N and 118°33′E) is an offshore island of Taiwan, located between Taiwan and southern China. The climate is subtropical, and the rainy season is between April and September, with average temperatures of 19—28°C. Kinmen is reported to be highly endemic for scrub typhus with a bimodal summer—autumn distribution.[4] Taking advantage of this fact, with a large cohort of scrub typhus patients in Kinmen, this study aimed to evaluate the associated factors and clinical implications of serum aminotransferase elevation in scrub typhus, especially in patients without eschar.

Methods

Patients

We retrospectively included all clinically suspected cases of scrub typhus notified to Taiwan CDC by Kinmen Hospital, Kinmen, Taiwan between January 1, 2005 and December 31, 2010. The clinical information, laboratory data, and relevant medical history of these patients were reviewed from the medical records. Serum aminotransferase elevation was defined as either elevated aspartate aminotransferase level ($>$ 40 U/L) or elevated alanine aminotransferase level ($>$ 65 U/L) at the initial clinical visit with the suspicion of scrub typhus. Leukopenia was defined as a white blood cell count of $<$ 4000/μL and thrombocytopenia as a platelet count of $<$ 120k/μL. This study was performed in accordance with the principles of the Declaration of Helsinki and had been approved by the Institutional Review Board of the National Taiwan University Hospital (200904057R), Taipei, Taiwan.

Serological and molecular diagnosis of scrub typhus

As the standard procedure of Taiwan CDC, serum and whole blood were collected in the acute and convalescent phases (within 7 days and 14 days after symptoms onset, respectively) from each patient, and were sent to the laboratory of Taiwan CDC for serological or molecular assays. The indirect immunofluorescence antibody assay with antigens of major strains of *O. tsutsugamushi* (Karp, Kato, Kawasaki, and Gilliam strains) was used. Scrub typhus was diagnosed as an initial immunoglobulin M titer of $>$1:80 or a greater than four-fold rise of immunoglobulin G titer in paired serum.[1] In addition, a positive polymerase chain reaction of