POSSIBLE SCRUB TYPHUS COINFECTIONS IN THAI AGRICULTURAL WORKERS HOSPITALIZED WITH LEPTOSPIROSIS

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Abstract. Possible coinfections with Orientia tsutsugamushi, the causative agent of scrub typhus, were prospectively evaluated in rice farmers hospitalized with leptospirosis in Northeast Thailand. Of 22 adults with leptospirosis diagnosed by the microscopic agglutination test, 9 also had serologic evidence of scrub typhus. Of 9 individuals with possible coinfections, 5 had signs or symptoms typical of scrub typhus and atypical of leptospirosis. Patients who appeared to have mixed infections had significantly higher median platelet counts and significantly lower median serum bilirubin and creatinine concentrations (P < 0.05, Mann-Whitney U test) than did individuals with leptospirosis alone. One patient with serologic evidence of scrub typhus and leptospirosis was treated only with penicillin, to which scrub typhus is not sensitive. Respiratory distress worsened during therapy, and the patient died of respiratory failure. Physicians should consider the possibility of scrub typhus infection in leptospirosis patients who respond poorly to treatment or who have atypical disease manifestations.

INTRODUCTION

Leptospirosis and scrub typhus are common infections in Thailand and have been associated with rice farming.1,2 Rice farmers could become infected with leptospirosis and Orientia tsutsugamushi, the causative agent of scrub typhus. Mixed infections have not been reported, however, perhaps because diagnostic tests for these 2 diseases are not readily available in rural Thailand.

A 46-year-old male Thai rice farmer presented to the hospital in Nakhon Ratchasima, northeastern Thailand, with typical features of Weil’s disease, the severe form of leptospirosis. A cigarette burn–like lesion characteristic of a scrub typhus eschar was noted on physical examination. Serodiagnostic tests supported the clinical suspicion that the patient had acute leptospirosis and probably also was infected with O. tsutsugamushi. This finding led us to evaluate prospectively possible scrub typhus coinfections in patients hospitalized with leptospirosis.

MATERIALS AND METHODS

Patients. Informed consent from patients was obtained, and human experimentation guidelines of the U.S. Army Medical Research and Materiel Command and Nakhorn Ratchasima Maharaj Hospital were followed in the conduct of clinical research. The study was conducted during the rainy season months of October and November 1997, at Maharaj Hospital, Nakhorn Ratchasima, a tertiary care referral hospital in Northeast Thailand. Hospitalized patients ≥18 years old in whom leptospirosis was thought likely by history, physical examination, and admission laboratory test results were evaluated. Leptospirosis was suspected if there was a history of contact with water and severe myalgia or muscle tenderness. Jaundice, conjunctival suffusion, or increased serum creatinine concentration also raised the suspicion of leptospirosis.3

Serology. Serodiagnostic testing for leptospirosis was performed at the Royal Tropical Institute, World Health Organization collaborating Center for Reference and Research on Leptospirosis, Amsterdam, the Netherlands. Acute and convalescent sera from suspected cases were tested by the microscopic agglutination test, the gold standard serodiagnostic assay for leptospirosis.4 A panel of 20 strains representative for Thailand was used as antigen.5 The serogroups (serovars) included were Australis (bangkok, bratislava), Autumnalis (rachmati, new), Ballum (ballum), Bataviae (bataviae), Canicola (canicola), Celledoni (celledoni), Cynopteri (cynopteri), Djasiman (djasiman), Fainei (hurstbridge), Grippotyphosa (grippotyphosa), Icterohaemorrhagiae (copenhageni, icterohaemorrhagiae), Javanica (poi), Louisiana (saigon), Pomona (pomona), Pyrogenes (pyrogenes), Sejroe (hardjo, sejroe), and Semaranga (patoc). Leptospirosis was diagnosed if there was a 4-fold rise in titer against any 1 serovar or any single titer was ≥1:320.6 O. tsutsugamushi infection was diagnosed using a dot blot immunoassay of proven sensitivity and specificity.7 The cutoff titer for this test is set high such that a positive test result indicates active disease rather than residual antibody from past infection. A positive dot blot immunoassay correlates with IgG titers of ≥1:1,600 or IgM titers of ≥1:400, or both.

RESULTS

Of the 22 adults infected with leptospirosis, 19 were men (Table 1). All patients were agricultural workers, and 20 of 22 (91%) worked in rice fields. Every patient reported contact with flooded streets or rice fields during the month before admission to the hospital. Compared with patients with leptospirosis only, patients with serologic evidence of scrub typhus in addition had significantly (Mann-Whitney U test) higher median platelet counts (96,000 and 183,000, P = 0.049), significantly lower median serum bilirubin concentrations (12.4 and 3.3 mg/dl, P = 0.002), and significantly lower median serum creatinine concentrations (5.4 and 1.3 mg/dl, P = 0.018).

Scrub typhus coinfection was suspected serologically in 9 patients, but coinfection could not be documented definitively because O. tsutsugamushi was not isolated from patient samples. Of these 9 patients, 4 had a 4-fold rise in leptospirosis antibody titer and 5 had a reciprocal titer >320 in a single sample. In the 13 individuals with leptospirosis only, 7 patients had a 4-fold rise in leptospirosis antibody titer, and 6 had a reciprocal titer >320 in a single sample. Of the 9 dually infected patients, 5 had signs or symptoms typical of scrub
typhus and atypical of leptospirosis. Three patients had eschars, which are pathognomonic when seen by a physician experienced in scrub typhus diagnosis. One patient had a rash typical of scrub typhus, and 1 of these individuals gave a history of hearing loss coincident with the onset of fever. This is an uncommon but specific symptom of scrub typhus (G. Watt, unpublished data) and has not been reported with leptospirosis.

One patient with an apparent double infection was begun on penicillin for presumed leptospirosis but deteriorated during treatment and developed respiratory distress. Scrub typhus was suspected, and a change in antibiotics from penicillin to intravenous chloramphenicol was followed by clinical recovery. Another similar patient with serologic evidence of scrub typhus succumbed to respiratory failure. This patient received high-dose intravenous penicillin G (3.2 million U every 4 hours) but was not given antibiotics active against *O. tsutsugamushi* because clinical and laboratory findings did not suggest scrub typhus.

### DISCUSSION

To our knowledge, this is the first published report suggesting that coinfection with leptospirosis and scrub typhus is not rare; 41% of agricultural workers with acute leptospirosis had serologic evidence of *O. tsutsugamushi* infection. Of the patients, 91% were rice farmers, an occupational group known to be at high risk for scrub typhus and leptospirosis in Thailand.\(^1\)\(^,\)\(^8\) Causative agents were not obtained, and the possibility that patients had 2 distinct, yet temporally close infections cannot be excluded with certainty. The serologic evidence of dual infection was supported by physical findings and results from routine hematology and biochemistry. Of the 9 patients with serologic evidence of dual infections, 5 had signs atypical of leptospirosis alone and suggestive of active, acute scrub typhus.

Scrub typhus and leptospirosis are common, serious infections that can be fatal if not treated. One of the patients in this series presented with leptospirosis and was treated appropriately with high-dose intravenous penicillin. Her condition deteriorated rapidly, however, and she died with adult respiratory distress syndrome, the most common cause of death from *O. tsutsugamushi* infection.\(^9\) Perhaps a fatal outcome could have been avoided had antibiotics active against scrub typhus been administered.

A mixed infection should be considered in patients with either leptospirosis or scrub typhus who are responding poorly to treatment. Even if diagnosed, however, a severe, combined infection with leptospirosis and scrub typhus is difficult to treat. Intravenous penicillin is the treatment of choice for severe leptospirosis,\(^10\) but *O. tsutsugamushi* is not susceptible to this antibiotic.\(^1\) Patients in rural Asia with severe scrub typhus generally are treated with intravenous chloramphenicol, which would not be expected to be effective against leptospirosis. Clinicians probably would opt to treat severe, dual infections with penicillin combined with either chloramphenicol or doxycycline even though this violates the interdiction against combining a bactericidal with a bacteriostatic antibiotic. Mild cases of either disease generally respond well to oral doxycycline.\(^11\)\(^,\)\(^12\)

It is difficult to make physicians aware of leptospirosis/scrub typhus coinfections. The clinical manifestations of these 2 diseases can be nonspecific, and fever, headache, myalgia, and conjunctival suffusion occur in both. Rapid diagnostic tests exist but are not generally available in geographic areas where the diseases are common. Mixed infections should be kept in mind in trials of new diagnostic tests and in febrile travelers returning from endemic areas. Leptospirosis is found worldwide, whereas scrub typhus occurs only in Asia, the South Pacific, and northern Australia. Leptospirosis and scrub typhus occur in travelers returning from endemic areas, and both have been associated with ecotourism.\(^11\)\(^,\)\(^13\)

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