

Role of Scrub Typhus in Hepatic Dysfunction: Focus on Acute Hepatitis in Differentiating it from other Causes

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Abstract

Elevated liver enzymes are frequently observed but overlooked during scrub typhus. Moreover, acute hepatitis associated with scrub typhus has rarely been described in the literature. Herein, a case with scrub typhus manifested with acute hepatitis was reported and review of relevant literature was performed. Although abrupt fever, headache and rash (including eschar and maculopapular rash) are considered to be the potential indicators for scrub typhus, elevated hepatic transaminases with various degrees even acute hepatitis could be another striking feature in scrub typhus that physicians need to know in an endemic area.

Keywords: Acute hepatitis; Scrub typhus

Case Report

It has been estimated that almost 1 million individuals proven of scrub typhus throughout a widespread area in eastern Asia and the western Pacific region [1]. Scrub typhus is curable; however, it is still a potential life-threatening disease with the mortality rate reaching 30% if unrecognized or left untreated [2]. Although it has been found that the hepatitis-scrub typhus relation is present in the literature few studies have emphasized this association. Many studies have reported the prevalence of elevated liver transaminases (up to 90%) in patients with scrub typhus that is far more 60% addressed in the textbook [3-11]. Most of the reports about hepatic dysfunction in scrub typhus were mild to moderate elevation of hepatic transaminases. Acute hepatitis associated with high liver enzymes levels in scrub typhus has rarely been described in the literature. The possibility of scrub typhus should be kept in mind when patients present with fever and varying degrees of hepatic dysfunction, even acute hepatitis, particularly if skin lesions (including eschar and maculopapular rash) exist, along with a history of exposure in an endemic area.

Since recently a previously healthy 36-year-old female presented to the emergency room (ER) with a 7-day history of intermittent high fever, rigors, dizziness and flu-like symptoms despite receiving treatment at outpatient department for several times on July 22nd, 2010. She noted non-pruritic skin rash over face and bilateral upper limbs since 3 days ago. She had history of travel to Lanyu (Orchid Island), an island in the Pacific Ocean to the southern-east of Taiwan, two weeks ago. On admission, she presented acute ill looking with marked prostration. Significant physical examinations were as follows: a temperature of 39.5°C, blood pressure of 112/74 mmHg, respiratory rate of 20/min and heart rate of 109/min; maculo-papular skin rashes found over upper and lower limbs; not icteric; an eschar-like ulcerative wound about 0.5 cm x 1.0 cm in size over right lower abdomen. Laboratory investigations revealed a white blood cell count of $7.2 \times 10^9/L$, with neutrophil count of 65%, lymphocyte count of 22%, monocyte count of 6% and band form of 4%; platelet count, $134 \times 10^3/\mu L$; hemoglobin, 12.6 g/dL; hematocrit, 36.7%. Results of liver function test were as follows: aspartate transaminase (AST) 419 IU/L and alanine transaminase (ALT) 997 IU/L; LDH, 896 IU/L; alkaline phosphatase (ALP) 778 IU/L; total bilirubin 1.34 mg/dL; serum albumin, 3.3 g/dL. C-reactive protein revealed 9.41 mg/dL (range, 0-0.5 mg/dL). Her chest radiograph was clear. Abdominal ultrasound revealed normal study. An intensive workup for acute hepatitis, including viral hepatitis, mycoplasma infection, syphilis, scrub typhus and leptospirosis were performed. Blood

cultures were obtained before treatment. Initial antimicrobial therapy consisted of intravenous moxifloxacin (400 mg daily) and oral doxycycline (100 mg twice per day). Twelve hours after admission, she developed a spiking fever up to 40°C accompanied with generalized skin rashes. These skin rashes diminished after resolving fever. She became afebrile on the 2nd hospitalization. In the subsequent days, her clinical picture and liver function tests continued to improve. On the 4th day of admission, the report for scrub typhus was positive by polymerase chain reaction (PCR) assay to *Orientia tsutsugamushi* from blood from Taiwan CDC. Hence the diagnosis of scrub typhus was made. The studies for hepatitis A, hepatitis B, hepatitis C, hepatitis E, syphilis, cytomegalovirus, Epstein-Barr virus and human immunodeficiency virus were negative. The initial Weil-Felix slide agglutination (proteus OX-K) showed negative result. Serology for leptospira was negative. She was discharged with stable condition on the 7th day of admission and continued to receive oral doxycycline as maintenance therapy. Scrub typhus was further confirmed by immunofluorescence antibody studies (IgM 1:160; IgG 1:640) 2 weeks later. A following Weil-Felix slide agglutination (proteus OX-K) showed positive (1:640) 10 days apart from the first test, consistent with the diagnosis of scrub typhus by the fourfold rise in proteus OX-K titer. On follow-up, ALT/AST levels declined gradually and they returned to normal levels within 1 month. She remained well without sequelae in the subsequent follow-up.

Acute hepatitis by definition means the clinical evidence in which an acute inflammation of the liver marked by hepatocyte degeneration and necrosis less than six months. The spectrum of clinical presentation in acute hepatitis may range from completely asymptomatic infection to fulminant liver failure. In terms of liver involvement, the prevalence of hepatitis in patients with scrub typhus has been reported with the range from 58.5% to 95% in recent review articles (Table 1) [4-11],

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Author (reference)	Years	No. of case	Country	AST		ALT	
				Means±SD (range)	abnormality (%)	Means±SD (range)	abnormality (%)
Berman [15]	1973	87	South Vietnam	NA	47.1	NA	NA
Yang [4]	1995	45	Taiwan	222.9±198.3 (42— 862)	74.5	220.3±195.6 (51— 732)	74.5
Ogawa [5]	2002	462	Japan	NA	87	NA	77
Park [14]	2003	22	Korea	92.5±11.7 (34— 255)	NA	93.2±17.3 (18— 345)	NA
Hu [7]	2005	30	Taiwan	148(median) (14— 461)	89.3	120(median) (24— 538)	91.7
Charoensak [10]	2006	130	Thailand	NA	58.5	NA	58.5
Wie [11]	2008	212	Korea	93±86	93.4	86±84	93.4
Huang [12]	2009	28	Taiwan	NA	100	NA	91.3
Kim [8]	2010	89	Korea (severe)*	100.9±77.3	88.8	75.0±74.4	94.4
		119	Korea (non-severe)	104.1±86.8	90.8	91.2±86.5	89.1
Lee [9]	2010	84	Korea (Group I)**	121.60±85.95	NA	107.35±168.92	NA
		162	Korea (Group II)	106.87±99.44	NA	97.15±103.94	NA

Note: AST: aspartate transaminase; ALT; alanine transaminase; SD, standard deviation; NA: none analysis.

*severe cases indicate patients with complications, including pneumonia, renal failure, meningoencephalitis, myocarditis, GI bleeding, shock, or death.

**Group I indicates patients with albumin < 3.0 mg/dL; Group II indicates patients with albumin ≥3.0mg/dL.

Table 1: Hepatic dysfunction from various studies in the published literature.

that is far more 60% addressed in the textbook [3]. The relationship between hepatitis and scrub typhus appears to be obvious, suggesting scrub typhus increases the risk for hepatitis.

In addition, there were some hints found in addition to the higher prevalence of hepatitis in scrub typhus in view of the survey in these published literatures. First, most of the reports described the abnormal liver enzymes in scrub typhus were mild to moderate elevation of transaminases (AST or ALT < 5 times upper limit of normal value). The magnitude of elevated levels of liver transaminases in scrub typhus is currently unknown and few studies have addressed this issue in the literature. This presented case had unusual high liver transaminases levels (ALT 997 IU/dL; AST 419 IU/dL) with the manifestation of acute hepatitis. Apart from the elevated liver transaminases, other liver parameters including ALP and LDH also revealed high levels abnormality in this patient. Acute hepatitis is known much more common in hepatocyte injury and necrosis related to drugs, toxins, ischemia and viral hepatitis and it has rarely been described in scrub typhus in the literature. However, there were 6 patients presented as acute hepatitis reported in Taiwan in 1995 [4]. Meanwhile, high levels of hepatic transaminases in scrub typhus had been found in other studies [7,9,12]. Furthermore, a recent study conducted by Deepak et al. [13] in India, 2 patients proven of scrub typhus manifested as acute hepatic failure [13]. Accordingly, scrub typhus may manifest as acute hepatitis during its clinical course. However, acute hepatitis in scrub typhus does not to be recognized well by clinicians. It is difficult to differentiate between scrub typhus hepatitis and other causes of acute hepatitis (e.g. viral hepatitis), but a correct diagnosis is critical since treatment is very different. Scrub typhus usually responds well to appropriate antimicrobial therapy with rapid defervescence in several days if early diagnosis was made. Second, there is no constant difference in the elevation between ALT and AST in patients with scrub typhus hepatitis. In view of the fact that most of the studies (except one study conducted by Park et al. [14] in this survey had shown the higher levels in AST than ALT (Table 1), which is unusual because ALT is more specific than AST in damage of hepatocytes in hepatitis from various causes. This phenomenon could not be well explained and need further studies to elucidate it in the future. Third, there was no significant difference in the magnitude of AST/ALT levels between severe cases and non-severe cases in scrub typhus hepatitis. One report conducted by Kim et al. [8] in 2010 had supported this finding. This result probably indicates that the magnitude of hepatic transaminases levels is not correlated to the severity

of scrub typhus. However, more large-scale, prospective cohort studies are needed to provide evidence that the association between them.

The importance of a wide spectrum of hepatic dysfunction in patients with scrub typhus, especially acute hepatitis, is emphasized here in hope of early diagnosis and treatment and preventing fatal complications of scrub typhus in an endemic area.

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