



Bacteriology

Activation of the coagulation cascade in patients with scrub typhus



Hee-Jeong Lee, Chi-Young Park, Sang-Gon Park, Na-Ra Yoon, Dong-Min Kim*, Choon-Hae Chung

Department of Internal Medicine, Chosun University Hospital, Gwangju 501-717, Republic of Korea

ARTICLE INFO

Article history:

Received 10 January 2017
 Received in revised form 10 June 2017
 Accepted 12 June 2017
 Available online 19 June 2017

Keywords:

Scrub typhus
 Disseminated intravascular coagulation
Orientia tsutsugamushi

ABSTRACT

This retrospective study aimed to evaluate the levels of coagulation factors and presence of disseminated intravascular coagulation (DIC) in patients with scrub typhus. We included patients confirmed to have scrub typhus at the Chosun University Hospital between September 2004 and December 2009. The DIC scores were evaluated in 365 patients and 36 healthy controls. The median concentrations of fibrinogen, D-dimer, and fibrin/fibrinogen degradation products (FDP) were compared between patients and healthy controls ($p < 0.001$ for all tests). Patients with scrub typhus had longer prothrombin time and lower platelet counts than the controls. Major bleeding was observed in 18/365 patients with scrub typhus. Fifty-one (14.0%) patients presented with severe complications of scrub typhus. Overt DIC and thrombocytopenia ($<100,000$ platelets/ mm^3) were observed more frequently in patients with bleeding and severe illness. Furthermore, median platelet counts were low in both groups. Approximately 2.7% ($n = 10$) and 16.4% ($n = 60$) patients with scrub typhus had overt DIC, as defined by the International Society on Thrombosis and Hemostasis DIC score (DIC1) and the DIC-scoring template with a fibrinogen/C-reactive protein-ratio (DIC2), respectively. Three (16.7%) and 10 (55.6%) patients with bleeding had overt DIC, as defined by the DIC1 and DIC2, respectively. Seven (13.7%) and 26 (51%) patients with severe illness had overt DIC, as defined by DIC1 and DIC2, respectively. In conclusion, activation of the coagulation system is an important feature of scrub typhus and is correlated with severe disease, including bleeding. This is the first study to report a relationship between DIC and scrub typhus.

© 2017 Elsevier Inc. All rights reserved.

1. Introduction

Scrub typhus is an acute febrile illness caused by the intracellular bacterium *Orientia tsutsugamushi*, which is widely endemic in Asia and the western Pacific regions (Tamura et al., 1995). Scrub typhus leads to generalized vasculitis, which may cause multiple-organ dysfunction syndrome (Ogawa et al., 2002). The clinical manifestation and complications of scrub typhus vary among patients. Most symptoms of scrub typhus are mild, but severe complications such as interstitial pneumonia, acute respiratory distress syndrome (ARDS), acute renal failure, acute hepatic failure, meningoencephalitis, gastrointestinal bleeding, myocarditis, pericarditis, multiple organ failure, and disseminated intravascular coagulation (DIC) have been reported (Chang et al., 2000; Cracco et al., 2000; Levine, 1946; Silpapojakul et al., 1991; Tsay and Chang, 1998; Wang et al., 2007). Many abnormal laboratory findings and risk factors for severe scrub typhus have been reported in recent studies on the clinical characteristics of patients with scrub typhus (Hu et al., 2005; Ogawa et al., 2002; Varghese et al., 2006; Zhang et al., 2014). However, there have been very few studies on DIC in patients with scrub typhus. Clinically significant bleeding (i.e., gastrointestinal bleeding) is a manifestation of scrub typhus, and other types of bleeding

are sometimes observed in patients with scrub typhus. Therefore, it is important to study the association between bleeding and DIC as a risk factor of bleeding in patients with scrub typhus. This study aimed to determine the frequency and clinical association of DIC with scrub typhus.

2. Material and methods

2.1. Patients

A retrospective study was performed in patients confirmed to have scrub typhus infection at the Department of Internal Medicine of Chosun University Hospital, Republic of Korea, from September 1, 2004 to December 31, 2009. A total of 409 patients were enrolled in this study. After individual records of the patients were carefully reviewed by physicians, we excluded patients with the following: liver cirrhosis ($n = 4$) and systemic lupus erythematosus ($n = 1$), treatment with warfarin or aspirin ($n = 3$), and no measurement of coagulation parameters within 3 days of hospitalization ($n = 37$). Finally, 365 patients were included in the study.

The diagnosis of scrub typhus was confirmed when the indirect immunofluorescent antibody assay (IFA) IgM titer against *O. tsutsugamushi* increased to $>1:80$, the IFA titer against *O. tsutsugamushi* increased ≥ 4 times in paired serum samples, or when a positive reaction was observed in a nested polymerase chain reaction (PCR) targeting the 56-kDa gene of

* Corresponding author. Tel.: +82-62-220-3108; fax: +82-62-234-9653.

O. tsutsugamushi (Blacksell et al., 2007; Kim et al., 2013). We selected 36 hematology-oncology medical outpatients without any illness that could affect hemostasis as the healthy controls and measured their coagulation parameters. This study was approved by the Ethics Committee of the Chosun University Hospital.

2.2. Criteria for severe illness

Patients who met ≥ 2 of the following criteria or died within 30 days after scrub typhus infection were considered to have had severe illness: treatment in the intensive care unit, acute renal failure (dialysis or estimated creatinine clearance < 50 mL/min using the Cockcroft–Gault formula), radiologically verified thrombosis, need for platelet transfusion, shock (i.e., systolic blood pressure of 90 mmHg and need for intravascular fluid treatment or inotropic agents at any time during hospitalization), jaundice (total bilirubin level ≥ 2.5 mg/dL), meningoencephalitis, pericarditis, myocarditis, myocardial infarction, ARDS, and major bleeding. We defined major bleeding as evidence of clinical bleeding (i.e., melena, hematochezia, subdural hemorrhage, hemoptysis, and hemothorax) and > 1.5 g/dL reduction in hemoglobin concentration.

2.3. DIC scoring

The DIC score for each patient was calculated using the platelet count, D-dimer levels, prothrombin time (PT), and fibrinogen level according to the algorithm for the diagnosis of overt DIC recommended by the DIC scientific subcommittee of the International Society for Thrombosis and Hemostasis (ISTH; DIC1) (Taylor et al., 2001). In addition, we calculated the DIC score using the fibrinogen/C-reactive protein (CRP) ratio (DIC2) rather than the fibrinogen level (Table 1) to further enhance the diagnostic and prognostic power of the ISTH recommendation in the overt DIC template (Kim et al., 2007). A score ≥ 5 was compatible with overt DIC, whereas a score < 5 was indicative of non-overt DIC. However, non-overt DIC was not applied in this study because the protein C and antithrombin levels were not measured.

2.4. Statistical Analysis

Statistical analyses were performed using SPSS for Windows, version 19.0 (SPSS Inc., IBM, IL, USA). Fisher's exact and χ^2 tests were used for categorical variables, and an independent *t*-test was used for non-

categorical variables. The Mann–Whitney *U*-test was used for continuous non-normally distributed variables.

3. Results

3.1. Patients

Of the 365 patients, 64.9% were women, and the mean age of the patients was 63 years. Approximately 50% of hematology-oncology medical outpatients in the control group ($n = 36$) were women with a mean age of 44 years. None of the participants in the control group had overt DIC as defined by DIC1 and DIC2. Clinically significant bleeding was observed in 18 (4.9%) patients with scrub typhus. Fifty-one patients (14.0%) fulfilled the severe illness criteria. Five deaths occurred within 30 days after scrub typhus infection and were associated with bleeding ($n = 3$) and shock without bleeding ($n = 2$). Ten (2.7%) and 60 (16.4%) patients with scrub typhus had overt DIC as defined by DIC1 and DIC2, respectively.

3.2. Platelets and coagulation tests

Patients with scrub typhus had a significantly lower median platelet count than the control group (137×10^9 platelets/mL vs. 258.5×10^9 platelets/mL; $P < 0.0001$). Patients with scrub typhus had a significantly longer median PT (12.2 s vs. 10.4 s; $P < 0.0001$) and higher median levels of fibrinogen, D-dimer, and fibrin/fibrinogen degradation products (FDP) compared to the control group (Fig. 1-1). Patients with scrub typhus and DIC showed a significantly lower median platelet count than those without DIC (78.5×10^9 platelets/mL vs. 152.5×10^9 platelets/mL; $p < 0.0001$). In addition, patients with scrub typhus and DIC had a significant lower median fibrinogen score and higher median score of D-dimer and fibrin/FDP ratio than those without DIC (Fig. 1-2).

3.3. Coagulation, DIC score, and clinical bleeding

Clinically significant bleeding was observed in 18 (4.9%) patients, including gastrointestinal bleeding ($n = 15$), subdural hemorrhage ($n = 1$), hemothorax ($n = 1$), and hemoptysis ($n = 1$). The characteristics of these patients are summarized in Table 2. Bleeding occurred 9.3 days after symptom onset and significantly more frequently in men (12/129) than in women (6/237; $p = 0.004$). Of the patients with bleeding, 3 (16.7%) men and no women died. Three (16.7%) and 10 (55.6%) patients in the bleeding group had overt DIC as defined by DIC1 and DIC2, respectively. The incidence of overt DIC was higher in the bleeding group than in the non-bleeding group (Table 3). Further, in the bleeding group, thrombocytopenia ($< 100,000$ platelets/mm³) was observed more frequently, the mean fibrinogen level was lower, the FDP and D-dimer levels were higher, and the fibrinogen/CRP-ratio was lower (Table 3) than those in the non-bleeding group. However, the mean platelet count, PT prolongation, and hypofibrinogenemia (< 100 mg/dL) did not significantly differ between the 2 groups (Table 3).

3.4. Coagulation, DIC score, and clinical severity

Fifty-one (14.0%) patients presented with severe complications of scrub typhus, and 12 of these patients had bleeding complications. A higher number of men had severe scrub typhus as compared to women ($P = 0.024$). Patients with severe scrub typhus had a significantly lower mean platelet count and more-frequent thrombocytopenia ($< 100,000$ platelets/mm³) compared to those with less-severe complications. In addition, patients with severe scrub typhus showed a significant increase in the D-dimer and FDP levels and decrease in the fibrinogen level and fibrinogen/CRP ratio (Table 4). PT prolongation and hypofibrinogenemia were observed significantly more frequently in patients with severe scrub typhus (Table 4) than in those with

Table 1
Scores of templates for overt disseminated intravascular coagulation in patients with scrub typhus.

	Score	DIC1	DIC2
Platelet count, 10^9 platelets/L	2	< 50	< 50
	1	50–100	50–100
	0	> 100	> 100
Fibrin-related marker (D-dimer, mg/L or FDP, μ g/mL)	3	Strong increase	Strong increase
	2	Moderate increase	Moderate increase
	0	Normal range	Normal range
Prothrombin time, s	2	≥ 6	≥ 6
	1	3–6	3–6
	0	< 3	< 3
Fibrinogen, mg/dL	1	< 100	n/a
	0	≥ 100	n/a
Fibrinogen/CRP-ratio	1	n/a	< 104
	0	n/a	≥ 104

DIC1, scoring with the disseminated intravascular coagulation scientific subcommittee of the International Society for Thrombosis and Hemostasis; DIC2, scoring with the fibrinogen/CRP-ratio instead of fibrinogen; FDP, fibrin/fibrinogen degradation products; CRP, C-reactive protein; n/a, not available.

A strong increase corresponded to a D-dimer level ≥ 1 mg/L or FDP level ≥ 20 μ g/mL. A moderate increase corresponded to 0.5 mg/L \leq D-dimer level < 1 mg/L or 5 μ g/mL \leq FDP level < 20 μ g/mL.

Download English Version:

<https://daneshyari.com/en/article/5665903>

Download Persian Version:

<https://daneshyari.com/article/5665903>

[Daneshyari.com](https://daneshyari.com)