Clinical and sub-clinical characteristics of rickettsioses at 108 Military Central Hospital from 2020 to 2021

Trinh Van Son, Nguyen Thi Hiep, Nguyen Binh An, Nguyen Danh Anh, Vuong Phuc Duong

108 Military Central Hospital

Summary

Objective: Rickettsioses remains one of the most common infectious diseases in Vietnam, the atypical disease's manifestation often leads to misdiagnosis with other diseases and results in a delayed proper treatment. The study aimed to characterise the clinical and laboratory features of rickettsioses. *Subject and method:* This was a retrospective cohort study. The clinical and sub-clinical features of rickettsioses were described. All patients admitted to the 108 Military Central Hospital, Hanoi from May 2020 to September 2021. *Result*: There were 22 patients enrolled into the study and 15/22 (68.2%) hospitalised 5 days after fever onset. The most common clinical features were abrupt fever (100%), headache (100%), myalgia (100%), and skin hyperemia (100%). Some rare signs were recorded: Eschars (9.1%), lymphadenopathy (0%), and rash (4.8%). The laboratory findings showed 95% of the patients with elevated liver transaminases and 51.1% cases with thrombocytopenia. All of the patients were treated with doxycycline and 100% (22/22) fully recovered. The defervescence time was 74.9 ± 38.6 hours and the hospitalisation time was 7.1 ± 1.4 days. *Conclusion*: The study demonstrated that the appearance of longer than five days fever, severe headache, thrombocytopenia, and elevated liver transaminase could suggest a diagnosis of rickettsioses.

Keywords: Rickettsioses, scrub typhus, clinical and subclinical features.

1. Background

Rickettsioses belongs to a group of tick-borne diseases caused by members of the family *Rickettsiaceae*, which is comprised of two genera *Rickettsia* and *Orientia*. Originally, *Rickettsia tsutsugamushi* was considered a causative organism of Scrub typhus. Later, such pathogen has been classified to *Orientia family* and, Scrub typhus is still considered a rickettsiosis [1]. Rickettsia was one of the common causes of acute undifferentiated fever in Southeast Asia and Vietnam. However, the disease's atypical clinical characteristics may lead to a pitfall in diagnosis. Additionally, evidence of the emerging occurence of other rickettsioses in the region was presented [2].

Most common clinical features of rickettsioses include high fever with eschar sign, lymph node, and rash. After an incubation period without symptom, a full course of disease with fever, headache, skin rash, lymphadenopathy, eschar, myalgia, arthralgia, malaise, and cough will generally apprear [3]. Initial manifestations of rickettsioses are nonspecific and the more specific signs often develop several days after fever onset. However, this clinical process maybe just typical for Scrub typhus but not for other rickettsioses [4].

Received: *19 October 2021,* ***Accepted:*** *18 December 2021*

Correspondence to: *Trinh Van Son - Institute of Clinical Infectious Diseases, 108 Military Central Hospital*

Email: *sontv@108-icid.com*

Delayed empirical treatment may result in multiple organs failure.

Various study have identified more new causative organisms that belong to the genus *Rickettsia* [1]. Most of these new orginisms were found to cause atypical disease manifestaion while standard testings fail to identify them. Other clinical studies conducted in Vietnam reported the use of molecular diagnosis and genotyping of *Orientia tsutsugamushi*. These findings suggested that rickettsioses are more common than was thought and, were often underdiagnosed [4, 5]. Consequently, proper treatment was often delayed. The study aimed to charaterise the clinical and subclinical features and figure out the most valuable factors that help improve the diagnosis and treatment rickettsioses in Northern Vietnam.

2. Subject and method

2.1. Subject

The study involved 22 participates who were diagnosed rickettsioses by clinical features and confirmed by the realtime PCR method.

2.2. Method

This is a retrospective cohort study. We described the characteristics of clinical and laboratory rickettsioses from patients who were admitted to the 108 Military Central Hospital, Hanoi from May 2020 to September 2021. The clinical information and laboratory data of patients were recorded for analysis.

Inclusion criteria: All of the patients were hospitalized with the following criteria: unidentified acute fever (over than 3 days); clinical manifestations of suspected rickettsia infection, such as eschar, rash, lymphadenopathy, or eyes hyperemia, headache. The patient was diagnosed with rickettsioses when the real-time PCR result was positive with rickettsia.

2.3. Statistical analysis

Statistical analyses were performed using the SPSS software v.23.0 (IBM Corporation, Chicago, IL, USA). Categorical variables are given as frequencies with percentages. Continuous variables are given as mean ± SD (standard division).

2.4. Ethical statement

The research was an observational study and all participates allowed us to use their data for publication with a consensus. All patient data were anonymized before the analysis.

3. Result

3.1. Clinical features

Table 1. Clinical findings of patients with rickettsioses

Variables		Rickettsioses (n = 22) n (%)	Variables	Rickettsioses (n = 22) n (%)
Age (years) Median (Minimum-Maximum)		48 (24 - 74)	Skin hyperemia	22 (100)
Sex (male)		17 (77.3)	Rash	1 (4.8)
Pre-existing conditions		4 (18.2)	Eyes hyperemia	20 (90.9)
Live in Hanoi		17 (77.3)	Eschar	2 (9.1)
Rainy season (May-Oct)		18 (81.8)	Lymphadenopathy	0 (0)
Fever	Abrupt	22 (100)	Edema	0 (0)
	Chill	0/22 (0)	Lung rales	0 (0)
	Hyperpyrexia	22 (100)	Liver enlargement	1 (4.8)
Headache		22 (100)	Spleen enlargement	0 (0)
Myalgia		22 (100)	Altered mental status	0 (0)

The median age was 48 years (range 24 - 74), with the most cases appearing in the rainy season (81.8%). Our results reported less eschar (9.1%), skin rash (4.8%), and no cases with lymphadenopathy. However, all of the patients had skin hyperemia and 90.9% of cases had eyes hyperemia. We observed no respiratory and intestinal signs in our participants.

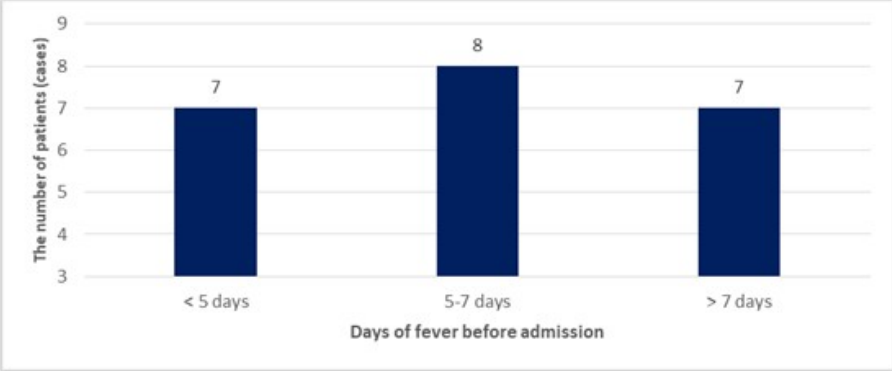

Figure 1. Distributions the duration of fever before admission

We reported 15/22 (68.2%) patients who were admitted hospital after 5 days of onset fever. The mean fever duration before admission was 7.1 ± 1.4 days (range 5 - 10 days).

3.2. Laboratory characteristics

Table 2. Hematology and biochemical parameters of 22 cases with rickettsioses

Hematology parameters (mean ± SD)		Biochemical parameters (mean ± SD)	
WBC (G/L)	6.6 ± 2.0	Urea (mmol/L)	4.2 ± 2.2
Neu (%)	71.9 ± 10.2	Creatinine (µmol/L)	73.3 ± 15.9
Lym (%)	18.5 ± 7.4	SGOT (UI/L)	169.2 ± 129.0
RBC (T/L)	4.5 ± 0.4	SGPT (UI/L)	160.6 ± 145.9
HGB (g/L)	136.3 ± 10.2	Bilirubin-Total (µmol/L)	13.4 ± 8.7
HCT (L/L)	40.4 ± 3.2	Protein (g/L)	68.9 ± 5.9
PLT (G/L)	127.5 ± 60.6	Albumin (g/L)	36.4 ± 1.8
Prothrombin (%)	96 ± 13	CRP (ng/mL)	108.6 ± 20.8

Note: WBC: White blood cells; Neu: Neutrophils; Lym: Lymphocytes; RBC: Red blood cells; HGB: Hemoglobin; HCT: Hematocrit; PLT: Platelet; SGOT: Serum glutamic-oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase; CRP: C-reactive protein.

We observed less change of hematology parameter with lower platelet (127.5 ± 60.6G/L). There were not any cases of acute kidney injury. However, we reported elevation of liver transaminase with 169.2 ± 129.0UI/L of SGOT and 160.6 ± 145.9UI/L of SGPT.

Table 3. The change of laboratory data in rickettsioses

Variables	Rickettsioses (n = 22), n (%)
Respiratory injury in chest X-ray	0 (0)
Leucopenia (WBC < 4G/L)	2 (9.1)
Thrombocytopenia (PLT < 140G/L)	13 (59.1)

Liver transaminases elevation (SGOT/SGPT > 40UI/L)	21 (95.5)

Note: WBC: *White blood cells; PLT: Platelet; SGOT: Serum glutamic-oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase.*

In this study, there were 2 out of 22 cases with leucopenia, 13 out of 22 cases with thrombocytopenia, and 21 out of 22 patients with increasing liver transaminases. There were not any cases of respiratory injury in the chest X-ray.

3.3. Treatment outcome

All of the patients were treated with doxycycline and support therapies. 100% (22/22) cases were excellent responses without death. The defervescence time was 74.9 ± 38.6 hours and the duration of hospital stay was 7.1 ± 1.4 days.

4. Discussion

In this study, we focus on clinical and subclinical findings of rickettsioses and found that over 5 days onset of fever, severe headache, the elevation of liver transaminases, and thrombocytopenia are the most common manifestations of rickettsioses. Our results also show that lymphadenopathy, rash, or eschar are very rare and all of the patients were excellent response with doxycycline therapy.

Previous studies demonstrated that eschar, lymphadenopathy, and rash were common in scrub typhus, ranging from 53.4% to 87% [4, 6]. However, the signs are less common in other rickettsioses, such as murine fever [4]. In the study, we observed rare eschar (9.1%), rash (4.8%), and lymphadenopathy (0%). Most of our cases lived in Hanoi (77.3%) and the diagnostic test is not differential between scrub typhus and other rickettsioses. So that, our patients may suffer from murine typhus or spotted fever. Other studies from the location showed murine typhus had fewer eschars, lymphadenopathy than scrub typhus. Moreover, patients who lived in cities were suffered from other rickettsioses than scrub typhus [4, 5].

The laboratory data of rickettsioses reported thrombocytopenia, liver injury, acute kidney injury, and pneumonia [7]. Our results showed 95.5% liver transferases elevation, 59.1% thrombocytopenia. Other studies in the epidemic area found a high rate of patients with serum aminotransferases elevation and thrombocytopenia [4, 5, 8]. The presence of liver transaminases elevation was variable with ranging 54% - 92% and thrombocytopenia was presented from 22% to 45% [7]. Analysis of the data showed that the elevation of liver transaminases was valuable to diagnose rickettsioses, especially in suspected cases without eschars [8].

Early approaching clinical manifestations to early diagnosis and treatment is very important for physicians. Additionally, doxycycline therapy is very effective and also cheap, safe. The results found that early empirical treatment led to a good outcome with no death, 74.9 ± 38.6 hours of the mean length of fever gone away and 7.1 ± 1.4 days of the mean duration of hospital stay. Other researches showed similar outcomes with from 0.2% to 0.4% of deaths [5]. On another hand, the mortality is up to 6% with untreated rickettsioses [3]. In conclusion, based on clinical and subclinical features, including over 5 days fever, severe headache, the elevation of liver transaminases, and thrombocytopenia, physicians should approach the diagnosis of rickettsioses with real-time PCR method and choose empirical therapy.

There are some limitations of the study. This is an observational study at a hospital with small participants. Additionally, the diagnostic tests cannot be differential between *Rickettsia* and *Orientia*. So that, the clinical features and laboratory data are not typical for each group. In the future, we will collect the samples to the sequence of species of rickettsia and develop methods for the differential diagnosis of types of rickettsioses.

5. Conclusion

The study demonstrated that the appearance of longer than five days fever, severe headache, thrombocytopenia, and elevated liver transaminase could suggest a diagnosis of rickettsioses.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Author's contributions

TVS drafted the manuscript. VPD, NTH, NBA, and NDA were involved in the revision of the manuscript. All authors reviewed and approved the submission.

Funding

The study did not require any funds.

References

1. Abdad MY, Abou Abdallah R, Fournier PE et al (2018) *A Concise review of the epidemiology and diagnostics of rickettsioses: Rickettsia and Orientia spp.* J Clin Microbiol 56(8):e01728-17.
2. Aung AK, Spelman DW, Murray RJ et al (2014) *Rickettsial infections in Southeast Asia: Implications for local populace and febrile returned travelers.* The American journal of tropical medicine and hygiene 91(3): 451-460.
3. Rajapakse S, Weeratunga P, Sivayoganathan S et al (2017) *Clinical manifestations of scrub typhus.* Transactions of The Royal Society of Tropical Medicine and Hygiene 111(2): 43-54.
4. Trung N.V., L.T. Hoi, V.M. Dien et al (2019) *Clinical manifestations and molecular diagnosis of scrub typhus and murine typhus, Vietnam, 2015-2017.* Emerging Infectious Disease journal 25(4): 633.
5. Hamaguchi S., N.C. Cuong, D.T. Tra et al (2015) *Clinical and epidemiological characteristics of scrub typhus and murine typhus among hospitalized patients with acute undifferentiated fever in northern vietnam.* Am J Trop Med Hyg 92(5): 972-978.
6. Ogawa M, Hagiwara T, Kishimoto T et al (2002) *Scrub typhus in Japan: Epidemiology and clinical features of cases reported in 1998.* Am J Trop Med Hyg 67(2): 162-165.
7. Blanton LS (2019) *The rickettsioses: A practical update.* Infectious disease clinics of North America 33(1): 213-229.
8. Su TH, Liu CJ, Shu PY et al (2016) *Associated factors and clinical implications of serum aminotransferase elevation in scrub typhus.* Journal of Microbiology, Immunology and Infection 49(6): 941-946.