KEY DIFFERENTIATING FEATURES BETWEEN SCRUB TYPHUS AND HEMORRHAGIC FEVER WITH RENAL SYNDROME IN NORTHERN CHINA

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Abstract. Both scrub typhus and hemorrhagic fever with renal syndrome (HFRS) are severely epidemic in northern China and often present with acute undifferentiated fever. To correctly distinguish the two diseases at an early stage, we collected and compared clinical and routine laboratory data of 46 patients with confirmed scrub typhus and 49 patients with confirmed HFRS presenting to the outpatient departments of three town hospitals in northern China. Most patients with HFRS but none of the patients with scrub typhus had hemorrhagic manifestations. Retro-orbital pain, lumbar back pain, flank tenderness, proteinuria, and occult blood in urine often occurred in patients with HFRS. However, skin eschar, regional lymphadenopathy, and maculopapular rash were more commonly found in patients with scrub typhus. In addition, platelet counts in patients with HFRS were significantly lower than in patients with scrub typhus. These findings will be useful for physicians to distinguish scrub typhus from HFRS.

INTRODUCTION

Scrub typhus is an infectious disease caused by Orientia tsutsugamushi transmitted by infected chigger mites and characterized by fever, an eschar at the chigger bite site, a rash, and lymphadenopathy. The disease is an important cause of acute undifferentiated fever in rural Asia, northern Australia, and the Western Pacific islands. It accounts for up to 23% of all febrile episodes in the endemic areas of the Asia-Pacific region. Scrub typhus has long been recognized to occur in southern China and is now being increasingly often described from the north since the first case reported in Mengyin County, Shandong Province, in 1986. In comparison with the severe and typical clinical manifestations of the disease in southern China, the scrub typhus in the north is relatively mild and self-limiting. Therefore, the disease in northern China is often regarded as mild or atypical scrub typhus. Diagnosis of scrub typhus is generally based on clinical manifestations and environmental exposure history. However, distinguishing diagnosis of scrub typhus from other acute undifferentiated fever illnesses, such as leptospirosis, murine typhus, malaria, dengue fever, and viral hemorrhagic fevers, is usually difficult because of their similar manifestations.

Hemorrhagic fever with renal syndrome (HFRS) is a rodent-borne disease caused by Hantavirus, with characteristics of fever, hemorrhage, kidney damage, and hypotension. China is the most severe endemic area of HFRS in the world, with 30,000–50,000 cases reported annually, which account for > 90% of total numbers worldwide. Shandong Province is the most severely affected province in China. Most patients with HFRS in the province are caused by Seoul type Hantavirus, and the disease usually occurs in spring and autumn-winter season with two incidence peaks.

From September to December of each year, both scrub typhus and HFRS are frequently reported in many rural areas of northern China, including Shandong Province, and often lead to acute undifferentiated fever. In addition, the two diseases are mainly associated with adult farmers. Clinically, it is difficult to distinguish both diseases at the early stages of illness because of their primary symptom similarities, and consequently, physicians often confuse them. To obtain simple and useful indices for distinguishing scrub typhus and HFRS at the early stage, we collected and compared the clinical and routine laboratory data at the time of admission to hospitals from the patients with serologically confirmed scrub typhus or HFRS in Shandong Province of northern China.

MATERIALS AND METHODS

Patients and study design. This study was conducted in Feixian County, Shandong Province, where both scrub typhus and HFRS are highly prevalent and often cause acute undifferentiated fever illness during autumn-winter seasons. From September to December of 2002–2004, adult patients (≥ 16 years old) with acute undifferentiated fever who presented to three town hospitals in northeastern Feixian County were considered. All the patients were farmers living in the countryside. During September to December every year, the farmers often work for long times in the crop field to gain peanuts, pachyrihus, and cotton, and to grow wheat. Thus they have many opportunities to be exposed to rodents and chigger mites in the field. In addition, they might catch infection by eating food or drinking water contaminated by rodent excretes and body fluids. After informed consent was obtained, 5 mL acute stage blood and urine were collected from each patient for routine laboratory examination. The febrile patients who had clinical manifestations, laboratory tests, and epidemiologic histories indicative of scrub typhus or HFRS were enrolled in the study. Briefly, the clinical manifestations included acute fever, headache, retro-orbital pain, lumbar back pain and flank tenderness, erythematous flushes on the face, neck, and upper bosom, hemorrhage on skin and mucosa, eschars, and maculopapular rashes on the trunk and
proximal limbs. The laboratory abnormalities concerned results suggestive of the two diseases, such as thrombocytopenia, proteinuria, and occult blood in urine. Epidemiologic exposure histories indicating that patients had worked in crop fields, been in contact with rodents, and eaten food or drunk water contaminated by rodents were also enrollment criteria. For suspected scrub typhus, chloramphenicol was administered orally at a dosage of 1.5–2.5 g, four times a day, for 4–5 days. Most of the patients with scrub typhus defervesced within 2 days after the treatment. For suspected HFRS, vigorous supportive treatment was given. In addition, intravenous ribavirin (750–1000 mg/d) for 5–7 days was given. Two to 4 weeks later after onset of treatment, 5 mL convalescent stage blood was also collected. Serum specimens were separated by centrifugation at 2,500g for 10 minutes and kept at −20°C until use. Febrile patients who had no clinical manifestations, routine laboratory examinations, or epidemiologic exposure histories indicative of scrub typhus or HFRS were excluded from the study. Patients with a history of known chronic medical problems or illness were also excluded. The study was approved by the Ethical and Scientific Review Subcommittee of the China Ministry of Public Health.

Data collection. We developed record forms about scrub typhus and HFRS that were filled out by the physicians working in the three town hospitals of Feixian County. The forms included questions regarding demographic characteristics such as age, sex, education level, and occupation. Epidemiologic information included onset date, place, exposure history, clinical manifestations, and routine laboratory examinations such as white blood cell (WBC) counts, platelet counts, hemoglobin (HGB), hematocrit (HCT), proteinuria, and occult blood in urine.

Confirmatory diagnosis. After the provisional diagnosis by physicians based on clinical manifestations, routine laboratory examinations, and epidemiologic exposure histories, IgM and IgG antibodies against pooled Karp, Kato, and Gilliam strains of O. tsutsugamushi antigens were measured by an indirect fluorescent antibody assay (IFA) to confirm the diagnosis of scrub typhus.4,7,18 Some acute stage blood samples of suspected patients with scrub typhus were tested by polymerase chain reaction (PCR) targeting the scrub typhus antigen 56-kd (Sta56) protein gene, if their convalescent sera were unavailable.4,18,19 The confirmatory diagnosis of scrub typhus was made when there was seroconversion, a 4-fold or greater rise in serum IgG antibody titers between acute and convalescent sera, or the PCR assay was positive.4,7,18,19 IgM and IgG antibodies to Hantavirus of patients with suspected HFRS were measured by enzyme-linked immunosorbent assay (ELISA) and IFA, respectively. Some acute stage blood samples of patients with suspected HFRS were tested by nested reverse transcription-PCR (RT-PCR) targeting Hantavirus S gene if their convalescent sera could not be obtained.15,17,20 The confirmatory diagnosis of HFRS was made when there was seroconversion, a 4-fold or greater rise in serum IgG titers between acute and convalescent sera, or the nested RT-PCR was positive.15 The patients with acute undifferentiated fever who were confirmed neither as scrub typhus nor as HFRS by serologic or PCR tests and were excluded from the study.

Statistical analyses. Statistical analyses were performed using the χ2 test (or Fisher exact test) for categorical percentages and Mann-Whitney U test for continuous variables. A difference was considered statistically significant if P < 0.05. Ranges were indicated by interquartile range (IQR).

RESULTS

During the 12-month study period, a total of 130 patients with acute undifferentiated fever were assessed. Forty-six were diagnosed as scrub typhus, and one of them died. This patient, who was 70 years old, was initially misdiagnosed and treated as HFRS by country infirmary. He was sent to Shangye town hospital with serious multiple system organ failure and eventually died after all efforts for rescuing him failed. Forty-nine patients were diagnosed as HFRS, and two of them died. Both of them were older than 70 years of age, and they were first misdiagnosed as having a common cold by the country infirmary and delivered to Shangye town hospital with severe shock. Thirty-five patients were identified as neither scrub typhus nor HFRS by serologic or PCR tests and were excluded from the study.

Many clinical characteristics of patients with scrub typhus at the time of admission to hospitals were similar to those of patients with HFRS (Table 1). However, patients with HFRS had a shorter fever history than individuals with scrub typhus (P < 0.001, Mann-Whitney U test). Erythematous flushes on the face, neck, and upper bosom, hemorrhagic manifestation (including conjunctival suffusion and mucosal injection of pharynx, petechiae, and/or ecchymoses appeared on the palate, pharynx, axillary skin folds, and bulbar conjunctiva), retro-orbital pain, lumbar back pain and flank tenderness, proteinuria, and occult blood in urine were more common in patients with HFRS than in cases with scrub typhus. However, skin eschar, regional lymphadenopathy, and maculopapular rash were exclusively or more frequently observed in patients with scrub typhus (Table 1).

Figure 1 shows that the median platelet (PLT) count in the patients with HFRS was significantly lower than for the scrub typhus group (P < 0.001, Mann-Whitney U test). The age-adjusted odds ratio (OR) was 125 (95% confidence interval [CI] = 14–1,453) for the association between having HFRS and a platelet count < 100 × 109/L. The median counts of the WBCs in patients with HFRS showed no significant difference with that of patients with scrub typhus (P = 0.76, Mann-Whitney U test; Table 2). Similarly, the median HCT in the HFRS group also had no significant difference with that in the scrub typhus group (P = 0.28, Mann-Whitney U test).

DISCUSSION

IFA, ELISA, PCR, and other tests are recognized as sensitive and effective methods for early diagnosis and distinguishing scrub typhus from HFRS.4,15,18,20 However, these diagnostic tests are usually not available in town hospitals located in rural and undeveloped areas of China. Physicians working in these places have to distinguish scrub typhus from HFRS only according to clinical manifestations, routine laboratory examinations, and exposure histories. If physicians are not familiar with the differences of early clinical and routine laboratory characteristics between scrub typhus and HFRS, misdiagnosis of the two diseases often occurs.3,11,15 By comparing and analyzing the early clinical and routine laboratory data of 46 patients with confirmed scrub typhus and 49 pa-
Patients with confirmed HFRS, this study identified the following differences between the two diseases. Most patients with HFRS but none of the patients with scrub typhus had hemorrhagic manifestations; retro-orbital pain, lumbar back pain, flank tenderness, proteinuria, and occult blood in urine more often occurred in the patients with HFRS; skin eschar, regional lymphadenopathy, and maculopapular rash mainly appeared in patients with scrub typhus; obvious thrombocytopenia was mainly observed in patients with HFRS. These findings will be useful for physicians working in the rural and undeveloped areas to correctly distinguish the two diseases at an early stage.

Previous studies have shown that alanine aminotransferase (ALT), serum creatinine, and blood urea nitrogen (BUN) were always normal in patients with uncomplicated scrub typhus but would be expected to be raised in quite a bit in patients with HFRS. Because of economic reasons, most farmer patients were unwilling to pay for any more biochemical tests than simple blood routine tests. Therefore, unfortunately, serum creatinine was not tested in this study.

Early diagnosis of scrub typhus often depends on recognition of the eschar, rash, and exposure history of the patient.21 Within 2 days after the chigger feeds, a skin papule appears that slowly becomes a small bulla that sloughs to leave a flat shallow ulcer. By the time the patient is symptomatic, the ulcer is covered with a black eschar 1–2 cm in diameter. The chigger has a predilection for attacking secrete and moist sites of human body, such as groin, scrotum, axillae, etc. However, in moist skin folds, the eschars may be absent.22 Previous studies from different new epidemic areas in northern China showed that the percentages of patients with scrub typhus with eschars varied from 15% to 100%.4,23 In our study, 67% (31/46) of patients with scrub typhus had eschars. However, this is quite a bit higher than the usually reported figure. The reason may be that the physicians in our study team have worked there for many years and are very familiar with eschars. In addition, we carried out a thorough body examination for every patient with acute fever, and no

### Table 1

Clinical characteristics of the studied patients at the time of admission to hospitals

<table>
<thead>
<tr>
<th></th>
<th>Patients with scrub typhus (N = 46)</th>
<th>Patients with HFRS (N = 49)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>42 (18–75)</td>
<td>40 (18–80)</td>
<td>0.86†</td>
</tr>
<tr>
<td>Male/female</td>
<td>25/21</td>
<td>28/21</td>
<td>0.78‡</td>
</tr>
<tr>
<td>Median days of fever before admission (range)</td>
<td>5 (2–9)</td>
<td>4 (2–6)</td>
<td>0.37‡</td>
</tr>
<tr>
<td>Temperature (°C) (range)</td>
<td>38.5 (37.0–40.0)</td>
<td>38.0 (36.9–40.0)</td>
<td>0.67‡</td>
</tr>
<tr>
<td>Chill</td>
<td>31 (67%)</td>
<td>35 (71%)</td>
<td></td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>39 (85%)</td>
<td>47 (96%)</td>
<td></td>
</tr>
<tr>
<td>Myalgia and prostration</td>
<td>46 (100%)</td>
<td>48 (98%)</td>
<td>1.00‡</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>21 (46%)</td>
<td>28 (57%)</td>
<td>0.26‡</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>19 (41%)</td>
<td>25 (51%)</td>
<td>0.34‡</td>
</tr>
<tr>
<td>Hemorrhagic manifestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctival suffusion and mucosal injection of pharynx</td>
<td>0 (0%)</td>
<td>40 (82%)</td>
<td>&lt; 0.001‡</td>
</tr>
<tr>
<td>Petechiae and/or eccymoses appeared on the palate, pharynx, axillary skin folds, and bulbar conjunctiva</td>
<td>0 (0%)</td>
<td>41 (84%)</td>
<td>&lt; 0.001‡</td>
</tr>
<tr>
<td>Aches</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>46 (100%)</td>
<td>48 (98%)</td>
<td>1.000§</td>
</tr>
<tr>
<td>Retro-orbital pain</td>
<td>8 (17%)</td>
<td>39 (80%)</td>
<td>&lt; 0.001‡</td>
</tr>
<tr>
<td>Lumbar back pain</td>
<td>5 (11%)</td>
<td>45 (92%)</td>
<td>&lt; 0.001‡</td>
</tr>
<tr>
<td>Flank tenderness</td>
<td>1 (2%)</td>
<td>29 (59%)</td>
<td>&lt; 0.001‡</td>
</tr>
<tr>
<td>Skin eschars</td>
<td>31 (67%)</td>
<td>0 (0%)</td>
<td>&lt; 0.001§</td>
</tr>
<tr>
<td>Maculopapular rashes appeared on the trunk and proximal limbs</td>
<td>35 (76%)</td>
<td>0 (0%)</td>
<td>&lt; 0.001§</td>
</tr>
<tr>
<td>Regional lymphadenopathy</td>
<td>28 (61%)</td>
<td>3 (6%)</td>
<td>&lt; 0.001§</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>8 (17%)</td>
<td>5 (10%)</td>
<td>0.31‡</td>
</tr>
</tbody>
</table>

* P < 0.05.
† By Mann-Whitney U test.
‡ By χ² test.
§ By Fisher exact test.
eschar was neglected from the patients with suspected scrub typhus.

The locations of eschars in this study were at the axilla (nine patients), umbilicus (two patients), waist (two patients), groin (two patients), breast (two patients), face (two patients), arm (two patients), back (two patients), around anus (one patient), foreskin of penis (one patient), labium (one patient), scrotum (one patient), neck (one patient), behind ear (one patient), buttocks (one patient), and foot (one patient). It is difficult to search for evidence of an eschar unless through a thorough examination of the body.24 However, individuals living in rural areas are often reluctant to accept a thorough body examination because of cultural or other reasons. Besides, most physicians working in the new epidemic areas of northern China are not familiar with scrub typhus and its eschars. Therefore, it is difficult not only for young but also for the experienced physicians to make a confirmatory diagnosis of scrub typhus at an early stage, let alone correctly distinguishing scrub typhus from HFRS.

Previous studies from different new epidemic areas in northern China showed that the percentages of patients with scrub typhus with conjunctival suffusions varied from 14% to 60%.4,23 However, conjunctival suffusions were not found in patients with scrub typhus in this study. The experienced physicians in our team were very familiar with conjunctival suffusions. They found conjunctival suffusions in 82% of patients with HFRS but not in patients with scrub typhus. We assume the reason may be that conjunctival suffusions in patients with scrub typhus were much more subtle and transient than that in patients with HFRS and thus difficult to find.

Initial manifestations of scrub typhus may mimic a variety of febrile illnesses. Dengue fever, leptospirosis, malaria, HFRS and other diseases that cause acute undifferentiated fevers in Asia are often difficult to distinguish from each other.4,6–11,15 The clinical manifestations of dengue fever can be similar to that of scrub typhus and even more so to HFRS. However, dengue fever mainly occurs in southern China, such as Guangdong, Hainan, and Guangxi Province. This disease was not found until now in the studied area.25 Leptospirosis is also mainly present in the south and drainage areas of the Yangtse River, and it has occurred only sporadically in the Shandong Province.26 Malaria was seriously epidemic ~30 years ago in China, including the studied area.27 Through intensive control efforts, very few leptospirosis cases have occurred, and malaria was basically eradicated from the Shandong Province.26,27 During our study period, neither lepto-
REFERENCES