Japanese spotted fever (JSF), caused by the bacterium *Rickettsia japonica*, was first described in 1984 in Japan (1). It has been recognized in multiple countries in Asia, including Japan, South Korea, the Philippines, Thailand, and China (1–5), suggesting that it is endemic in Asia. In China, *R. japonica* has been detected in ticks from the central, southeast, and northeast regions (6–8). Since JSF cases were first found in Anhui Province in 2013 (5), a total of 39 have been reported in the Dabie Mountains on the borders of Henan, Anhui, and Hubei Provinces and in the Tianmu Mountains in Zhejiang Province on the eastern coast (Appendix Figure 1, https://wwwnc.cdc.gov/EID/article/29/1/22-0639-App1.pdf) (9–11).

The Study

Our study was approved by the ethics committees of the National Institute for Communicable Disease Control and Prevention (ICDC). During April–October 2021, five JSF cases were found in Zigui County, Hubei Province, in the Three Gorges area of China (Appendix Figure 1), including case 1, in which the patient died because of multiorgan failure. Among the 5 case-patients (3 female, 2 male), disease onset occurred during April–October (2 cases in spring, 3 in autumn); median age of case-patients was 53 years (range 47–70 years) (Table 1). All had histories of activity in fields, but none was aware of any tick bites. All initially manifested signs and symptoms of sudden fever (≥38.5°C), headache, chills, fatigue, chest tightness, shortness of breath, and dyspnea. All had rash and eschar (Appendix Figure 2), except for case-patient 1, who had no eschar. Case-patients 1, 3, and 5 experienced vomiting and case-patient 3 had abdominal pain. Medical laboratory tests (Table 2) showed that case-patients 1, 3, and 5 had thrombocytopenia and lymphopenia, case-patients 1 and 5 had neutrophilia, and case-patients 1 and 4 had mild anemia. All 5 patients had remarkably elevated levels of C-reactive protein and D-dimer, and except for case-patient 5, all had elevated liver-associated enzymes. Proteinuria was detected in case-patients 1, 2, 3, and 5. Case-patients 1, 3, and 5 had simultaneous edema and effusion and case-patient 5 showed multiple effusions (pelvic, pleural, pericardial, and ascites). Most laboratory tests were flagged as abnormal for case-patient 1, who died. She received an initial antimicrobial treatment (Appendix) at the village clinic without a causative agent being identified and already had severe sepsis (sequential organ failure assessment score = 12) by the time she was admitted to the hospital on day 8 after symptom onset. Disseminated intravascular coagulation was diagnosed, and she died of multiple organ failure on day 9 despite...
Japanese Spotted Fever, China

Table 1. Epidemiologic and clinical characteristics of patients with *Rickettsia japonica* infection, Zigui County, Hubei Province, China

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Case 1*</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Male</td>
<td>Male</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td>Age, y</td>
<td>58</td>
<td>47</td>
<td>68</td>
<td>57</td>
<td>70</td>
</tr>
<tr>
<td>Month of admission</td>
<td>Apr</td>
<td>Jun</td>
<td>Sep</td>
<td>Sep</td>
<td>Oct</td>
</tr>
<tr>
<td>Occupation</td>
<td>Farmer</td>
<td>Village teacher</td>
<td>Farmer</td>
<td>Farmer</td>
<td>Farmer</td>
</tr>
<tr>
<td>Possible causative exposures</td>
<td>Picking tea, tea garden</td>
<td>Collecting bamboo, bamboo groves</td>
<td>Herding sheep, woodland</td>
<td>Farm work, fields</td>
<td>Farm work and chopping wood, fields and woodland</td>
</tr>
<tr>
<td>Previous illness</td>
<td>Healthy</td>
<td>Healthy</td>
<td>Hypertension</td>
<td>Healthy</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Day of admission†</td>
<td>8</td>
<td>4</td>
<td>6</td>
<td>15</td>
<td>5</td>
</tr>
</tbody>
</table>

Signs and symptoms†

- Highest temperature, °C
  - 39.0
- Fever type
  - Continued
- Headache
  - Present
- Malaise
  - Present
- Myalgia
  - Present
- Chills
  - Present
- Eschar
  - Absent
- Rash (day)
  - Present (11)
- Hypotension (day)
  - Present (9)
- Dyspnea (day)
  - Present (9)
- Vomiting (day)
  - Present (9)
- Edema (day)
  - Face (9)
- Clouding of consciousness
  - Present
- Proteinuria
  - +++
- Anuria (day)
  - Present (9)
- Abdominal pain
  - Absent
- Pelvic effusion
  - Absent
- Pleural effusion (day)
  - Present (9)
- Pericardial effusion
  - Absent
- Ascites effusion
  - Absent

Table 2. Laboratory findings of the patients with *Rickettsia japonica* infection, Zigui County, Hubei Province, China*

<table>
<thead>
<tr>
<th>Laboratory findings*</th>
<th>Reference value</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte, × 10⁹ cells/L</td>
<td>4.0–10.0</td>
<td>9.09</td>
<td>5.50</td>
<td>7.78</td>
<td>8.45</td>
<td>9.15</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>110–150 (F), 120–160 (M)</td>
<td>109</td>
<td>130</td>
<td>127</td>
<td>105</td>
<td>115</td>
</tr>
<tr>
<td>Platelets, × 10⁹/L</td>
<td>100–300</td>
<td>45</td>
<td>99</td>
<td>72</td>
<td>110</td>
<td>82</td>
</tr>
<tr>
<td>Lymphocytes, × 10⁹ cells/L</td>
<td>0.8–3.5</td>
<td>0.52</td>
<td>0.72</td>
<td>0.91</td>
<td>2.29</td>
<td>0.64</td>
</tr>
<tr>
<td>Neutrophils, × 10⁹ cells/L</td>
<td>1.8–6.3</td>
<td>8.11</td>
<td>2.55</td>
<td>5.80</td>
<td>5.80</td>
<td>7.90</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>0.8–8.0</td>
<td>199.53</td>
<td>72.8</td>
<td>77.00</td>
<td>72.00</td>
<td>111.72</td>
</tr>
<tr>
<td>PCT, µg/L</td>
<td>&lt;0.5</td>
<td>5.64</td>
<td>0.38</td>
<td>2.14</td>
<td>0.4</td>
<td>0.54</td>
</tr>
<tr>
<td>D-dimer, µg/mL</td>
<td>0–0.5</td>
<td>4.200</td>
<td>2.081</td>
<td>2.160</td>
<td>1.090</td>
<td>1.080</td>
</tr>
<tr>
<td>TBil, mg/L</td>
<td>3–13</td>
<td>38.0</td>
<td>12</td>
<td>12</td>
<td>9.3</td>
<td>11</td>
</tr>
<tr>
<td>DBil, mg/L</td>
<td>0–2.5</td>
<td>24.0</td>
<td>2.0</td>
<td>3.4</td>
<td>2.7</td>
<td>2.0</td>
</tr>
<tr>
<td>TBA, µmol/L</td>
<td>&lt;10</td>
<td>43.1</td>
<td>3.9</td>
<td>8.6</td>
<td>4.8</td>
<td>4.9</td>
</tr>
<tr>
<td>TP, g/L</td>
<td>60–80</td>
<td>48.7</td>
<td>62.9</td>
<td>52.3</td>
<td>58.2</td>
<td>65</td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>35–55</td>
<td>23.8</td>
<td>36.2</td>
<td>30.6</td>
<td>35.6</td>
<td>35.9</td>
</tr>
<tr>
<td>A/G</td>
<td>1.5–2.5</td>
<td>1.0</td>
<td>1.4</td>
<td>1.4</td>
<td>1.6</td>
<td>1.2</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>0–35</td>
<td>21</td>
<td>69</td>
<td>177</td>
<td>167</td>
<td>16</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>0–40</td>
<td>114</td>
<td>88</td>
<td>167</td>
<td>111</td>
<td>29</td>
</tr>
<tr>
<td>BUN, mmol/L</td>
<td>2.9–7.5</td>
<td>7.81</td>
<td>3.81</td>
<td>10.80</td>
<td>2.38</td>
<td>7.54</td>
</tr>
<tr>
<td>Creatinine, mg/L</td>
<td>40–100 (F), 50–110 (M)</td>
<td>93.2</td>
<td>84.9</td>
<td>74.1</td>
<td>58.2</td>
<td>83.9</td>
</tr>
<tr>
<td>Uric acid, µmol/L</td>
<td>150–357 (F), 200–416 (M)</td>
<td>378</td>
<td>301</td>
<td>259</td>
<td>182</td>
<td>210</td>
</tr>
<tr>
<td>LDH, U/L</td>
<td>100–300</td>
<td>587</td>
<td>412</td>
<td>403</td>
<td>433</td>
<td>368</td>
</tr>
<tr>
<td>Creatine kinase, U/L</td>
<td>18–198</td>
<td>257</td>
<td>186</td>
<td>51</td>
<td>48</td>
<td>125</td>
</tr>
<tr>
<td>α-HBDH, U/L</td>
<td>8–90</td>
<td>401</td>
<td>294</td>
<td>254</td>
<td>317</td>
<td>323</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>135–145</td>
<td>137</td>
<td>141</td>
<td>132.9</td>
<td>131.4</td>
<td>136.5</td>
</tr>
</tbody>
</table>

*Fatal case.
†Day on which sign or symptom manifested in patient, when applicable. The day when the patient first experienced headache and fatigue was defined as Day 0.
‡Difficulty determining fever type because of drug intervention.
§Urine protein concentration: –, <0.1 g/L; +, 0.1–0.2 g/L; +, 0.2–1.0 g/L; ++, 1.0–2.0 g/L; ++++, 2.0–4.0 g/L.

Using a PCR assay, we detected 6 rickettsial genes (*groEL*, *gltA*, *ompA*, *ompB*, *sca*, and 17kDa gene) in a blood specimen from case-patient 1. In addition, we

continuous intensive therapy. The other 4 patients recovered without sequelae after receiving doxycycline or minocycline treatment (Appendix).
amplified groEL, gltA, and 17kDa genes from case-patients 2, 3, and 5 but only gltA and 17kDa from case-patient 4. For all 5 patients, the genomic sequences of each amplified target gene were 100% identical to each other; phylogenetic analysis revealed that the causative agent was most closely related to R. japonica (Figure). We submitted the obtained sequences to GenBank (accession nos. OM966424–8 for gltA,

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**Figure.** Bootstrap consensus phylogenetic tree constructed based on partial sequences of 17kDa (A), gltA (B), groEL (C), ompA (D), ompB (E), and sca4 (F) amplified from blood specimens from 5 spotted fever patients in Japan (yellow shading). We aligned sequences using MUSCLE within MEGA6 software (http://www.megasoftware.net). We analyzed phylogenetic relationships using the neighbor-joining method with 1,000 bootstrap replicates; boot values are shown next to the branches. Genbank accession numbers for the *Rickettsia* strains retrieved are indicated.
OM966422 for ompA, OM966423 for ompB, OM966412-6 for 17kDa, OM966417 for sca4, and OM966418-21 for groEL). We obtained 1 stable rickettsial isolate, designated R. japonica strain YC21, from the blood of case-patient 1 using Vero cell cultures (Appendix Figure 3) and obtained the whole genomic sequence from the isolate (GenBank BioProject PRJNA812951). Phylogenetic analysis based on core genes suggested that R. japonica strain YC21 was most closely related to R. japonica strain LA16/2015 (Appendix Figure 4); 30 virulence-associated genes of R. japonica strain YC21 (Appendix Table 2), predicted using the virulence factor database (http://www.mgc.ac.cn/VFs), were completely homologous to those of strain LA16/2015.

We used an immunofluorescence assay using R. japonica strain YC21 as coating antigen (a cutoff of 1:64 was determined by testing negative and positive samples) and R. rickettsii (Focus Diagnostics, http://focusdiagnostics.in) to test serum-specific antibodies from the 5 JSF patients and 100 healthy subjects recruited locally. Case-patients 2 and 3 were confirmed to have JSF on the basis of a ≥4-fold increase in R. rickettsii–specific and R. japonica–specific IgG titers between acute and convalescent phase serum (Appendix Table 3). At baseline, 12/100 (12%) of the healthy local donors tested positive (range, 1:128–1:1,024; geometric mean, 512) for R. japonica–specific IgG.

We measured cytokine and chemokine levels in the serum samples collected from the JSF patients (during acute phase) and 6 healthy donors (Appendix Table 4). The levels of interferon (IFN) γ, interleukin (IL) 6, IL-10, IL-1α, macrophage inflammatory protein 1β, IL-8, IFN gamma-induced protein 10, and monocytic chemoattractant protein 1 in the 4 surviving JSF patients were significantly higher than in the healthy donors (p <0.01), consistent with previous reports, except for the exclusion of tumor necrosis factor α (12–14). In the case-patient who died, serum levels of IL-6, IL-10, and IFN-γ were 10-fold higher than those in the surviving case-patients and the levels of IL-4, INF-α, granulocyte-macrophage colony-stimulating factor, monocytic chemoattractant protein 1, macrophage inflammatory protein 1β, and IP-10 were 2-fold higher, suggesting that R. japonica infection might cause an unregulated hyperinflammatory state, potentially leading to cytokine release syndrome (14).

**Conclusion**

We identified 5 cases of JSF, including 1 in which the patient died, in Zigui County in the Three Gorges Area of China, where JSF has not previously been identified. Furthermore, our study revealed a high prevalence (12%) of R. japonica among residents, suggesting a new endemic area for JSF in China and indicating that JSF might be more widespread than previously thought. We should be alert to the potential risk for JSF, especially in areas where R. japonica is detected in vectors (Appendix Figure 1). The JSF cases were confirmed by PCR detection and serologic tests. A strain of R. japonica isolated from the blood of the patient who died was revealed to be most closely related to strains LA16/2015 and LA4/2015 detected in Zhejiang Province, suggesting that a virulent strain of R. japonica might have spread widely across China.

Delayed treatment is one of the worst prognostic factors for patients with JSF, and as a neglected infectious disease, it might not be considered during differential diagnosis. In our study, the patient who died manifested a faint rash, but without eschar, which resulted in delayed diagnosis and provision of correct antimicrobial treatment when she first visited the rural clinic. Profiling the patient’s serum cytokine and chemokine levels indicated notably elevated IL-6, IL-10, and IFN-γ, characteristic of potential cytokine release syndrome. The primary findings on patient cytokines levels benefit understanding of immune response to R. japonica infection.

Our findings highlight the threat of JSF to public health in China. Healthcare workers, especially in rural areas where residents are at increased risk for tick exposure, should be aware of this potentially deadly infectious disease. Long-term surveillance and investigation of local hosts and vectors of R. japonica are necessary to improve the prevention and treatment of JSF.

**Acknowledgments**

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References

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