Report of a Severe Case of Pancytopenia Caused by Chronic Brucellosis in Tongliao City, Inner Mongolia Autonomous Region, China

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1. Abstract
Brucellosis is a type of zoonotic infectious disease that causes serious harm to public health. Inner Mongolia has become one of the most severely endemic areas of brucellosis in China. Human brucellosis is prone to involve multiple systems, which can cause a variety of complications. In this paper, we here reported a case of chronic brucellosis with pancytopenia, diagnosed and treated were retrospectively analyzed. hoping to promote awareness of brucellosis among clinicians and provide a basis for better clinical diagnosis and treatment.

2. Introduction
Brucellosis is a common zoonotic infectious disease with global distribution, accounting for at least 500,000 new cases annually [1]. It is widely prevalent in developing countries. According to the Statutory Infectious Diseases Report from China Centers for Disease Control (CDC), until May 23, 2021, a total of 26919 confirmed cases have been reported. Compared to the average for the same period from 2017 to 2019, the reported cases have risen by 70%. Especially in Inner Mongolia Autonomous Region shows the highest incidence rates for human brucellosis (HB), which reaches 34.5 cases per 100,000 in the first half of 2021 [2]. Due to the nonspecific and diverse clinical manifestations, HB is prone to misdiagnosis. Patients with Brucella infections commonly present with headache, fever, fatigue, night sweats, joint pain, and muscle aches. The bacteria can invade multiple systems, resulting in varying degrees of damage and dysfunction. For the impact of Brucella on the blood system, chronic brucellosis patients often have anemia, leukocyte reduction, leukopenia, or deficiency. Also, thrombocytopenia leads to the occurrence of purpura, or bleeding. The present study reports the case of a patient diagnosed with chronic HB associated with pancytopenia, The detailed are as follows.

3. Case Report
A 57-year-old female patient, who is employed primarily in livestock farming. In June 2020, the patient diagnosed with this disease. The clinical manifestations disappeared through the antibiotic treatment, and the whole blood cell generally turned to normal levels. Figure 1 portrayed the patient diagnosis, treatment, and outcome. On April 20, 2022, the patient again visited the hospital complaining of fever and fatigue. The patient underwent clinical detection. The results were: Brucella serology SAT: 1:200++++, WBC: 1.28 × 10^9/L, RBC: 3.63 × 10^{12}/L PLT: 115 × 10^9/L (Table 1). Then she was diagnosed with Brucellosis, along with pancytopenia. Treatment with rifampin and doxycycline was administered. During the treatment, the whole blood cell count...
of the patient kept decreasing. Thus, the patient went to a larger hospital outside the province for further diagnosis and treatment. After bone marrow examination, the patient was diagnosed with bone marrow hyperplasia and bone marrow suppression caused by sepsis.

On May 5, 2022, the patient returned to Tongliao city, Inner Mongolia, and were admitted to the intensive care unit of the Affiliated Hospital of Inner Mongolia University for Nationalities. The examination was conducted and the results showed: fever: 39℃, acute fever, face fatigue, drowsiness, no lymph nodes, liver spleen abnormalities. The patient lost about 20 kg, and had a 20-year history of lumbar disc disease. On imaging examination, the results showed: mild inflammation of the right lung, multiple small nodules, and no obvious abnormalities. Laboratory examination: Experimental results ruled out the possibility of common viral infections, autoimmune diseases, and malignant tumor. Brucella serum antibody (SAT: 1:200 + +), bone marrow culture is sheep type 3 Brucella and, multiple blood culture tests were negative. On May 10, whole blood was collected at Inner Mongolia University for Nationalities for a nucleic acid test and the results were positive. On May 24, whole blood was collected again for nucleic acid test and result were negative. The direct Coombs experiment showed a weak positive test.

According to the guide for treatment, The rifampicin and doxycycline antibiotics were administrated as well as the use of dexamethasone anti-inflammation, immunoglobulin infusion, recombinant human granulocyte stimulating factor, infusion of suspended red blood cells, and other symptomatic treatments were applied correspondingly. With this combined therapy for a week the patient felt much better with an improvement in whole blood index (Table 1). On June 5, the patient was transferred to the intensive care unit.

![Figure 1: Timeline of key dates about patient condition](image)

Table 1: Blood routine clinical indicators results

<table>
<thead>
<tr>
<th>Clinical indicators</th>
<th>Date</th>
<th>Reference range</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4.2</td>
<td>4.28</td>
<td>5.6</td>
</tr>
<tr>
<td>White blood cell</td>
<td>1.28</td>
<td>0.25</td>
<td>0.23</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>0.04</td>
<td>0.02</td>
<td>0.04</td>
</tr>
<tr>
<td>Neutrophil rate</td>
<td>2.3</td>
<td>5.9</td>
<td>17.4</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>0.85</td>
<td>0.24</td>
<td>0.18</td>
</tr>
<tr>
<td>Lymphocyte rate</td>
<td>95.5</td>
<td>90.1</td>
<td>78.3</td>
</tr>
<tr>
<td>Monocyte</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Monocyte rate</td>
<td>1.1</td>
<td>4.3</td>
<td>4.3</td>
</tr>
<tr>
<td>Red blood cell</td>
<td>3.63</td>
<td>2.34</td>
<td>1.89</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>117</td>
<td>79</td>
<td>59</td>
</tr>
<tr>
<td>Platelet</td>
<td>115</td>
<td>60</td>
<td>72</td>
</tr>
<tr>
<td>Hypersensitive C-reactive protein</td>
<td>110</td>
<td>84.68</td>
<td>113.4</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>7.3</td>
<td>7.5</td>
<td>7.4</td>
</tr>
<tr>
<td>Aspartic aminotransferase</td>
<td>15.6</td>
<td>15.9</td>
<td>17.1</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>15.6</td>
<td>17.7</td>
<td>33.7</td>
</tr>
<tr>
<td>Direct bilirubin</td>
<td>11.2</td>
<td>13.4</td>
<td>28.8</td>
</tr>
<tr>
<td>Indirect bilirubin</td>
<td>4.6</td>
<td>4.7</td>
<td>4.9</td>
</tr>
</tbody>
</table>
4. Discussion

Brucella is a facultative intracellular parasite and gram-negative CoC bacterium that uses different strategies and expresses different virulence factors to evade the host immune response [3]. Brucella can persist in human macrophages, and it is difficult for the human immune system to remove this form of intracellular parasite. Many untreated antibiotic treatments or antibiotics have poor efficacy and can cause brucellosis chronicity or relapse. When immunity drops, Brucella parasites in macrophages multiply and cleave them to infect more phagocytes. When phagocytes spread throughout the body through lymphatic and blood circulation, they multiply and lyse, which can cause a strong immune response in the body.

In addition to the common clinical manifestations such as fever, fatigue, hyperhidrosis, and back pain, the most prominent features were pancytopenia and significant weight loss. Furthermore, the bone marrow puncture report suggested that the myeloid hyperplasia was extremely reduced and the bone marrow hematopoiesis was suppressed. The mechanism of bone marrow suppression is unknown, which may be caused by the release of Brucella itself or the produced metabolites, endotoxins, or because the immune inflammatory response of the body suppresses bone marrow hematopoiesis. Myelosuppression is an important cause of pancytopenia. In addition to myelosuppression, the severe pancytopenia in the short term should also be closely associated with the consumption of blood cells.

Neutrophils, the largest proportion of white blood cells in the blood, play the role of the first line of defense against microbial invasion and are an important part of human innate immunity. After the emergence of bacteria in the body, it will quickly phagocytose and kill the pathogen, while releasing cytokines to activate innate immunity. Because Brucella is a hidden pathogen, its special structure can resist the killing mechanism of these neutrophils. Infected neutrophils cannot release cytokines to activate innate immune [4], and Brucella LPS core part of lipid A can induce the premature death of neutrophils [5]. In this patient, the cells died prematurely after neutrophils phagocytose Brucella, and the neutrophils were low before the onset, so the white blood cells in the patient will be reduced. With too few leukocytes, a large number of Brucella released are phagocytosed by monocytes, macrophages, dendritic cells, producing cytokines, and antigen presentation leading to the rapid activation of adaptive immunity. This patient had been previously infected with Brucella, and large numbers of Brucella bacteria entering the blood could also rapidly activate memory T lymphocytes to release inflammatory factors. Extensive release of pro-inflammatory factors IL-2, IL-6, TNF-α, IFN-γ, and IL-12 activates monocyte macrophages to kill intracellular Brucella, activate pro-inflammatory TH1 cell immunity, and rapidly remove Brucella in patients. At the same time, the body will also release a large number of inflammatory factors, resulting in the formation of inflammatory factors storm. In some animal trials, Brucella infec-
mechanism hidden, Brucella can form a relatively calm and normal state between the pathogen and the host. The patient was diagnosed with brucellosis in 2020, and although there were no clinical symptoms. The leukocyte level has been low and may have been in chronic infection. The TH1 pro-inflammatory response that was determined by cytokine test results was not strong enough to clear Brucella. NK cells are the important immune cells of the body, and they play an important role in the clearance of Brucella infection [14-16]. It is also known from the relative count results of NK cell lymphocyte subsets that although the function of NK cells cannot be known due to the lack of corresponding detection, the number of NK cells tested has been far below the normal range. This also suggests that immune depletion is already present or already quite severe [17]. Brucella is endocytosed by monocyte macrophages through neutrophils, red blood cells, platelets, and is re-hidden in monocyte macrophages by Trojan horse. So the patient still has a long way to go before a complete recovery. Patients should take antibiotics on a regular basis, completely, and in conjunction with regular examination and guidance. At the same time, patients should strengthen their own nutrition, get adequate rest and enage in appropriate exercise to strengthen the recovery of their own immune function.

5. Conclusion

Chronic human brucellosis associated with pancytopenia is potential, severe complication. Diagnostic and treatment of human brucellosis remain challenging despite medical advances. Clinicians should be aware of the precise identification for the brucellosis results in proper therapy and a favorable outcome.

6. Funding

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7. Ethics approval and consent to participate

In this report, the requirement for ethics approval was waived by the Research Ethics Committee of Inner Mongolia Minzu University. (No. NM-LL-2022-05-31-01)

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