# Treatment of Severe Refractory Thrombocytopenia in Brucellosis With Eltrombopag

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**Case Report**

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# Abstract

**Background:** Brucellosis is a common zoonotic illness in the world. Brucellosis is often characterized by hematologic abnormalities, including mild anemia, leukopenia, thrombocytopenia, or pancytopenia. However, severe refractory thrombocytopenia in brucellosis is very rare and easily misdiagnosed.

**Case presentation:** The patient was a 5-year-old girl with brucellosis who developed severe refractory thrombocytopenia (platelet count: $3\times10^9$/L) with complaints of epistaxis, skin petechiae and purpura. Most conventional treatments including glucocorticoids and intravenous immunoglobulin (IVIg) did not elevate her platelets, but eltrombopag worked well and her platelet count recovered rapidly. One week later, the patient's symptoms improved and the platelet count returned to normal.

**Conclusions:**

Patients with severe refractory thrombocytopenia, particularly resistant to IVIg and steroid treatment should be considered for second-line drugs such as eltrombopag. Our results also increase the application experience of eltrombopag in Chinese patients with severe refractory thrombocytopenia in brucellosis. To the best of our knowledge, this case is the first reported case of the successful treatment of severe refractory thrombocytopenia in brucellosis with eltrombopag.


# 1. Introduction

Brucellosis is one of the most widespread zoonotic disease and constitutes an important public health problem in many parts of the world, particularly in the Mediterranean and Middle East [1–3]. Brucellosis is a multisystem disease with non-specific clinical manifestations, which frequently leads to misdiagnosis and delayed treatment, and further increases the incidence of complications. Hence, the clinical manifestations of brucellosis are highly variable, ranging from minimal symptoms to severe fatalities [4]. The disease also produces a variety of abnormalities in hematological parameters, including mostly leukopenia and mild anemia but, rarely, pancytopenia and thrombocytopenia [5].

The frequency of thrombocytopenia among children with brucellosis has been reported to vary between 2.6 % and 6 % [6]. The mechanism of brucellosis associated thrombocytopenia is unclear and may be multifactorial, including immune destruction of platelets, marrow suppression, and hypersplenism [7]. However, severe refractory thrombocytopenia in brucellosis is rarely. Thus, it is still challenging to treat the patients with severe refractory thrombocytopenia before the diagnosis of brucellosis.

Recently, we successfully treated severe refractory thrombocytopenia in a child before the diagnosis of brucellosis using the thrombopoietin receptor agonist (TPO-RA), eltrombopag.

# 2. Case

5-year-old girl (weight 15 kg) was admitted to the Kunming Children's Hospital (Kunming, China) in May 2020 due to epistaxis for 2 days. The patient did not have fever, weight loss, nausea, sweating, and vomiting.

Physical examination showed the patient was pale, general petechiae, and purpura extremities. But no splenomegaly, hepatomegaly, or lymphadenopathy.

The results of blood tests before transfusion were shown in the Table 1 which indicated that the child suffered from moderate anemia (hemoglobin: 74 g/L) and severe thrombocytopenia (platelet count: $3\times10^9$/L). White blood cell (WBC) was $5.38\times10^9$/L. Activated thromboplastin time tests (APTT) were 31.9 s (normal, 28-44.5), prothrombin time (PT) was 13.3 s (normal, 11-14.5), international normalized ratio (INR) was 1.07 (normal, 0.8–1.5), ferritin was 212 μg/L (normal, 7-142), d-dimer (> 20 μg/nl) and fibrinogen degradation products (27.19 μg/nl) were increased, fibrinogen (1.54 g/L) was decreased. Complement C3 and C4 were normal. Immunoglobulin IgG was slight increased 17.4 g/L (normal range 5.9–14.3 g/L). Antinuclear antibodies and anti-dsDNA were negative. Coombs tests were negative. Abdominal ultrasonography was normal. No significant abnormalities in liver or kidney function were reported. She was given platelet infusion for epistaxis. Meantime, the patient also was given immunoglobulin (IVIg) intravenous (1g/kg/day) for 2 days and high dose methylprednisolone treatment (20 mg/kg/d for 3 days). Platelet counts which did not show any improvement,were $10\times10^9$/L and $7\times10^9$/L, at the beginning and end of the treatment, respectively.

On the third day of admission, the patient was suffered severe epistaxis and anemia. The patient was received platelet and red blood cell (RBC) infusion again. Bone marrow aspiration was performed after platelet infusion. Bone marrow aspiration revealed trilineage hematopoiesis, megakaryocytes hypercellularity. The entire bone marrow smear showed 623 megakaryocytes. Analysis of 100 megakaryocytes, the results showed granulosa megakaryocytes 82% and lamellar megakaryocytes 18%. Examination of bone marrow aspiration findings showed no malignancy. The patient was continually received methylprednisolone treatment (10 mg/kg/d for 3 days). However, the platelet count did not increase even after frequent platelet transfusions and receiving this regimen.

On the sixth day of admission, platelet count was dropped $1\times10^9$/L. Because the patient had continual severe epistaxis, the patient received platelet infusion again. Meantime, the patient was given oral treatment with 25 mg/d eltrombopag and prednisone (2 mg/kg/d orally).

On the seventh day of admission, the patient was given RBC infusion again due to severe anemia. After 3 days of eltrombopag and 3 days of prednisone intervention, the platelet count was increased to 9×109/L. The treatment continued.

On the tenth day of admission, the patient's blood culture demonstrated the growth of *Brucella melitensis*. Further history was obtained, and it was discovered the girl had contacted the goat and consumed unpasteurized goat milk. In consideration of the patient history, laboratory test results, positive *Brucella* serology, and *Brucella melitensis* on the blood culture, the patient was finally diagnosed with brucellosis

complicated with severe thrombocytopenia. The patient was started on empiric treatment with oral rifampin (30 mg/kg/d orally) and trimethoprim sulfamethoxazole (30 mg/kg/d orally, twice a day) for 5 days.

On the fifteenth day of admission, the patient's symptoms have improved. Her thrombocyte and blood values reached normal levels. the patient was discharged from the hospital and was advised to avoid unpasteurized diary. The changes of platelet count, Hb, and the treatment during admission were shown in Fig. 1.

# 3. Discussion

In our study, we presented the case of a child with severe refractory thrombocytopenia, epistaxis, general petechiae and purpura extremities as the presenting symptoms of *Brucella melitensis* infection, which is very rare and easily misdiagnosed. Furthermore, immunoglobulin and high dose methylprednisolone treatment did not elevate her platelets, but eltrombopag increased the platelets rapidly.

Brucellosis is a febrile zoonotic disease caused by intracellular Gram-negative coccobacilli of the Brucella species [8, 9]. The disease is primarily transmitted to humans through the consumption of unpasteurized dairy products or through occupational exposure to livestock [10, 11]. Brucellosis affects multiple organs and tissues, such as the osteoarticular system, gastrointestinal system, and central nervous system [12]. Thus, clinical manifestation is highly variable and may include undulating fevers, night sweats, joint pain and myalgia [13]. The most common signs of physical examinations are hepatomegaly, splenomegaly, and lymphadenopathy [14]. However, none of them are characteristic of brucellosis. So, it is very difficult to diagnose in brucellosis, especially in nonendemic area. The gold standard for diagnosis is blood culture or tissues culture, but often requires several weeks to yield results [15].

Brucellosis also produces a variety of hematologic complications abnormalities in hematological parameters, including mild anemia, leukopenia, thrombocytopenia, or pancytopenia, which can be confused with hematological disease [16]. Mild anemia and leukopenia are frequent in brucellosis, whereas severe thrombocytopenia and pancytopenia are less frequently observed [17]. Therefore, brucellosis is frequently misdiagnosed as a primary hematologic disease or malignancy. However, there are patients with brucellosis who have died because of intracranial bleeding due to thrombocytopenia [18]. In the literature, there are few case reports describing nose bleeding and severe refractory thrombocytopenia as a presenting feature of brucellosis. In our case, the patient was presented to us with suffered from severe epistaxis. Routine blood tests revealed moderate anemia and severe thrombocytopenia. The patient had no obvious clinical manifestation with brucellosis, which makes it especially difficult to diagnose. The patient was initially diagnosed immune thrombocytopenic purpura. The patient received intense platelet infusion,corticosteroids and intravenous immunoglobulin, which were the first-line treatments for immune thrombocytopenic purpura. However, symptoms did not improve.

Eltrombopag, a thrombopoietin receptor agonist, stimulates megakaryocyte proliferation and maturation[19]. Eltrombopag license for chronic immune thrombocytopenia (ITP) treatment in both pediatric and adult patients when the first-line therapy or splenectomy fail [20]. Eltrombopag improves T and B regulatory cells functions, suppresses T-cells activity, and inhibits monocytes activation in pediatric patients with immune thrombocytopenia (ITP) [21]. The combination of eltrombopag with an oral immunosuppressant and an androgen in patients with refractory severe aplastic anemia is feasible and could restore multi-lineage hematopoiesis[22]. Eltrombopag is an effective alternative to intravenous immunoglobulin for perioperative treatment of immune thrombocytopenia [23]. It was reported that a patient with severe refractory thrombocytopenia in chronic myelomonocytic leukemia who had treatment failures with prednisone, IVIG, thrombopoietin and cyclosprin A. But the platelet counts were markedly increased after using eltrombopag [24]. Above results suggest that eltrombopag has a unique function in the treatment of severe refractory thrombocytopenia. Therefore, the patient was received eltrombopag on the sixth day of her admission. After 3 days of treatment, the platelet count was increased to $9\times10^9$/L. On the tenth day of her admission, the patient was diagnosed with brucellosis and started on antibiotic therapy. It was reported that the patients with brucellosis recovered completely, and their thrombocytopenia returned to normal by 2 to 4 weeks after antibiotic treatment of brucellosis [25]. Interesting, we founded our patient's thrombocyte level reached normal rapidly. It suggests that eltrombopag promote the rapid recovery of platelets, shorten the course of thrombocytopenia, and then reduce the incidence of complications.

In conclusion, our results show that thrombocytopenia secondary to brucellosis, which is ineffective with first-line drugs, should be treated with thrombopoietin receptor agonists such as eltrombopag as soon as possible.

# 4. Conclusion

Thrombocytopenia can be caused by brucellosis. However, severe refractory thrombocytopenia is very rare and easily misdiagnosed. Patients with severe refractory thrombocytopenia, particularly resistant to IVIg and steroid treatment should be considered for second-line drugs such as eltrombopag. Our results also increase the application experience of eltrombopag in Chinese patients with severe refractory thrombocytopenia in brucellosis.

# Declarations

### Ethics statement

The studies involving human participants were reviewed and approved by The Kunming Children's Hospital research ethics committee. Written informed consent to participate in this study was provided by the participants' legal guardian.

### Consent for publication

Written informed consent for publication this case report and accompanying images were obtained from the patients' parents.

### Data availability statement

All datasets generated for this study are included in the article/supplementary material.

### Competing interests

The authors declare that they have no competing interests.


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### Authors' contributions

T.L.H. designed the study. R.P. analyzed the data. X.T., Q.L.L., C.Y.S., Y.B.L., and Y.L. treated patients and helped draft the manuscript. B.H.S., C.H.Y, and N.L. performed data collection. X.WZ., analyzed the data and wrote the manuscript.


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# Tables

**Table 1** Laboratory test results of the patient at the time of admission.

| Test | Result | Unit | Reference |
|---|---|---|---|
| WBC | 5.38 | $10^9$ /L | 4-10 |
| Lymphocyte | 1.63 | $10^9$ /L | 1.0-3 |
| Neutrophil | 3.45 | $10^9$ /L | 1.8-6.4 |
| RBC | 2.88 ↓ | $10^{12}$ /L | 3.5-5.5 |
| Hb | 74 ↓ | g/L | 110-160 |
| PLT | 3.0 ↓↓ | $10^9$ /L | 100-300 |
| RET | 1.72 ↑ | % | 0.5-1.5 |
| CRP | 5.11 | mg/L | 0-10 |
| APTT | 31.9 | s | 28-44.5 |
| Fibrinogen degradation products | 27.19 ↑ | μg/nl | <5 |
| Fibrinogen | 1.54 ↓ | g/L | 2.0-4 |
| PT | 13.3 | s | 11-14.5 |
| d-dimer | >20 ↑ | μg/nl | <0.5 |
| Ferritin | 212.0 ↑ | μg/L | 7-142 |
| International normalized ratio (INR) | 1.07 | | 0.8-1.5 |

WBC: white blood cell; RBC: red blood cell; Hb: Hemoglobin; RET: reticulocyte, PLT: platelet; CRP, C-reactive protein; APTT: activated thromboplastin time tests; PT: prothrombin time.

# Figures

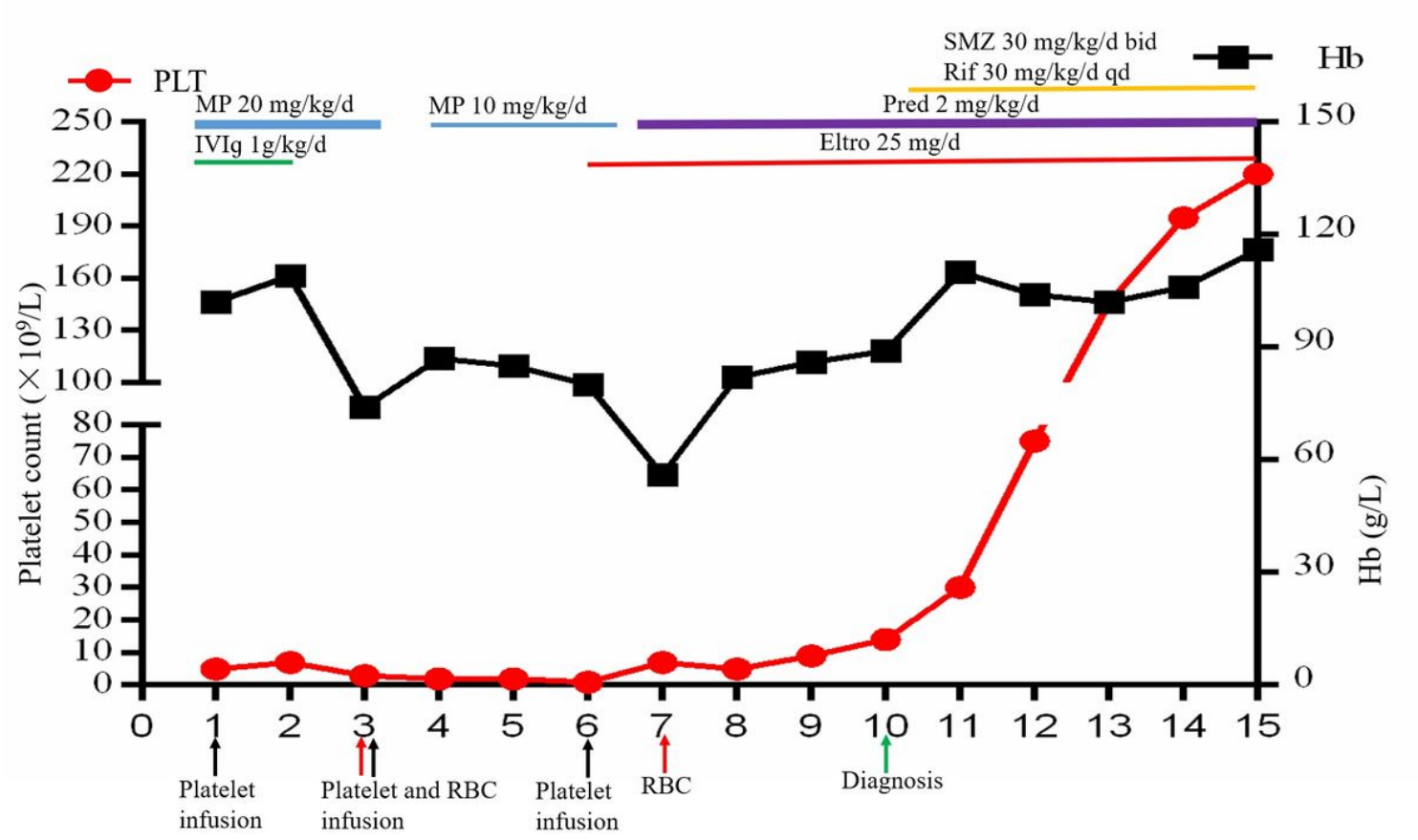


**Figure 1**

The changes of platelet count and hemoglobin during the treatment on admission. The patient was initially treated with intravenous immunoglobulin (IVIg), methylprednisolone (MP), platelet and RBC transfusion which were not effective. Then eltrombopag was initiated. The platelet count was increased to 9×109/L 3 days later. On the tenth day of her admission, the girl was diagnosed with brucellosis and started on antibiotic therapy. The patient's thrombocyte level reached normal rapidly. The horizontal axis represents the days of admission, the left vertical axis represents the platelet count, and the right vertical axis represents hemoglobin. IVIg: immunoglobulin; MP: methylprednisolone; eltro: eltrombopag; Pred: prednisone; SMZ: sulfamethoxazole; Rif: rifampicin.