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*Case Report*

# Brucellosis complicated by myelofibrosis: report of five cases and review of literature

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**Abstract:** Myelofibrosis is a myeloproliferative tumor, that can be secondary to malignant hematologic or inflammatory diseases, such as chronic myeloid leukemia, polycythemia vera, primary thrombocythemia, multiple myeloma, disseminated tuberculosis, or vasculitis. However, few cases of brucellosis-associated myelofibrosis have been reported. Moreover, due to the rarity of this phenomenon, it is often overlooked by clinicians, resulting in misdiagnosis and mismanagement. Thus, brucellosis should be considered as a possible cause of myelofibrosis. In the present study, we report five cases of brucellosis, of which three had myelofibrosis. In addition, to further determine the potential link between brucellosis and myelofibrosis, we retrospectively analyzed the levels of various cytokines by collecting the clinicopathologic data of patients and using immunohistochemical staining. We found that brucellosis patients with myelofibrosis had elevated levels of cytokines such as interferon (IFN)-γ, interleukin (IL)-1β, basic fibroblast growth factor (b-FGF), vascular endothelial growth factor (VEGF), suggesting that the regulation of cytokines may play a central role in the development of myelofibrosis in patients with brucellosis.

**Keywords:** Brucellosis, myelofibrosis, interferon-γ, nuclear factor-κB

## Introduction

Here, we describe five cases of brucellosis, including three cases (patients 2, 4, and 5) of brucellosis accompanied by thrombocytopenia, pancytopenia, or leukopenia with anemia secondary to myelofibrosis, respectively. Brucellosis with myelofibrosis is a rare phenomenon, which leads to serious problems in the diagnosis, etiology, and treatment. Brucellosis is a globally widespread zoonotic disease, with a clinical presentation that varies depending on the site and duration of onset. This often leads to misdiagnosis and treatment delays, further increasing the incidence of complications [1]. Brucella infection can produce a variety of non-specific hematologic abnormalities, such as frequent mild anemia and leukopenia, and less frequently thrombocytopenia or pancytopenia. In addition, the bone marrow (BM) and spleen are usually affected in patients with brucellosis [2]. Pancytopenia during brucellosis can be explained by the direct inhibition of BM cell proliferation or by the indirect inhibition of hematopoiesis by soluble mediators released from activated macrophages or lymphocytes [3, 4]. Myelofibrosis is characterized by increased BM stromal fiber (composed of collagen and reticulin) deposition, decreased hematopoietic parenchymal cell numbers, and BM hematopoietic dysfunction [5]. Myelofibrosis is clinically common in patients with lymphoproliferative disorders such as lymphoma, leukemia, and multiple myeloma (MM). However, myelofibrosis can also develop in individuals with non-hematologic diseases (e.g., solid tumors, BM metastases, or autoimmune diseases) or following exposure to certain chemicals, infection, or radiotherapy [6]. Myelofibrosis is categorized into primary myelofibrosis (PMF) and secondary myelofibrosis (SMF). SMF is implicated in BM fibrous tissue proliferation and hematopoietic dysfunction, which can be caused by factors such as tumors and infection. However, few studies have linked myelofibrosis with brucellosis. To date, only one other report of a patient with brucellosis presenting with myelofibrosis exists. In this study, we describe the baseline conditions of five patients and further search for associations between brucellosis and mye-

**Table 1.** Clinical baseline data of patients with brucellosis and myelofibrosis

| Feature | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 |
|---|---|---|---|---|---|
| Age/Gender | 47/M | 64/M | 53/F | 54/M | 50/F |
| History of close contact with sheep | + | NA | + | + | + |
| Onset symptoms | Fever | Headache | Arthralgia | Poor appetite | Edema of both lower limbs |
| Lymphadenectasis | NA | NA | + | NA | NA |
| WBC, (×10^9/L) | 4.23 | 2.34 | 2.62 | 5.58 | 2.63 |
| RBC, (×10^12/L) | 4.59 | 3.65 | 2.91 | 4.29 | 3.04 |
| PLT, (×10^9/L) | 67 | 240 | 200 | 24 | 54 |
| Comorbidities | NA | Multiple myeloma | NA | NA | NA |
| CRP, (mg/L) | 31.14 | 106.38 | 30.68 | 11.82 | 20.99 |
| PCT, (ng/mL) | 0.225 | 0.05 | 0.105 | 0.079 | 1.19 |
| ESR, (mm/h) | 28 | 99 | 49 | 25 | NA |
| Hepatomegaly | + | + | NA | NA | + |
| Splenomegaly | + | + | + | + | + |
| Hepatic dysfunction | NA | NA | NA | + | + |
| BAT | 1:400 | 1:50 | 1:800 | 1:200 | Negative |
| IgG | NA | NA | NA | + | + |
| Blood culture | Positive | NA | Positive | Positive | Positive |
| Mesh fiber dyeing | 0 | 1 | 0 | 2 | 1 |

Abbreviations: F, female; M, male; WBC, white blood cell; RBC, red blood cell; PLT, platelet; CRP, C-reactive protein; PCT, procalcitonin; ESR, erythrocyte sedimentation rate; BAT, Brucella agglutination test; IgG, immunoglobulin G; +, positive; NA, not available.

lofibrosis. Specifically, we perform a retrospective analysis of immunohistochemical data to determine whether the expression of cytokines such as platelet-derived growth factor (PDGF), basic fibroblast growth factor (b-FGF), vascular endothelial growth factor (VEGF), tumor necrosis factor (TNF)-α, interferon (IFN)-γ, interleukin (IL)-1β, IL-12, IL-6, IL-10, or transforming growth factor (TGF)-β was different in brucellosis patients with or without myelofibrosis and could thus inform early diagnosis and treatment strategies.

## Materials and methods

### *Patient selection*

A total of five patients were included in the study, which admitted to Hebei general hospital between June 2016 and January 2022. These patients with a median age at diagnosis of 53.6 years (range 47-64). The male/female ratio was 3:2, as shown in **Table 1**.

Myelofibrosis was diagnosed according to relevant guidelines [7], and the grading was according to the WHO (2016) grading standard of myelofibrosis [8].

Brucellosis was based on patient information, epidemiologic history, clinical presentation, and laboratory tests (**Table 1**) and reference to related literature [9].

### *Immunohistochemical staining*

Immunohistochemical staining was carried out using IHC Kit (Boster biological technology, China), the DAB Kit (Boster Biological Technology, China) and Mayer' Hematoxylin solution (Boster Biological Technology, China). Using one section of BM tissue section, the slides were deparaffinized, rehydrated, immersed in antigen retrieval solution, and incubated with endogenous peroxidase blocking solution for 10 min at room temperature, and washed with PBS buffer. Next, nonspecific binding was blocked with rabbit serum at 37°C for 30 min, and incubated overnight at 4°C with primary antibodies. After goat anti-rabbit IgG-HRP secondary antibodies were incubated at 4°C for incubated overnight, DAB and Mayer's Hematoxylin solution were followed, including VEGF (item no. bs-1313R), PDGF (item no. bs-0196R), bFGF (item no. A00121-3), IL-10 (item no. BA1201-1), IL-1β (item no. bs-0812R), TGF-β (item no. BA0290), IL-12 (item no. bs-14637R), TNF-α (item no. BA0131), INF-γ (item no. bs-0388R), IL-6 (item no. bs-4539R) antibodies were used. We performed immunohistochemical staining according to the instructions.

**Table 2.** Immunohistochemical findings of BM pathology of brucellosis and myelofibrosis

| | Case 1 | Case 2* | Case 3 | Case 4 | Case 5 |
|---|---|---|---|---|---|
| IL-6 | (+) | (+++) | (+) | (+) | (+) |
| IL-10 | (++) | (++) | (+) | (+) | (++) |
| IL-12 | (++) | (++) | (+) | (+++) | (+) |
| IL-1β | (++) | (+++) | (++) | (+++) | (++) |
| TNF-α | (+) | (±) | (+) | (+) | (±) |
| TGF-β | (±) | (+) | (+++) | (+) | (++) |
| INF-γ | (+) | (++) | (+) | (++) | (+) |
| VEGF | (+) | (++) | (+) | (++) | (+) |
| PDGF | (++) | (++) | (++) | (+) | (++) |
| b-FGF | (+) | (++) | (+) | (++) | (+) |

Abbreviations: Immunohistochemical evaluation calculated based on IS added to ES. IS double-blind reading by experienced pathologists, ES was calculated by the semi-quantitative software Image J. All five cases were brucellosis patients, of which three (case 2, 4, 5) had myelofibrosis. *: Strong expression of IL-6 and IL-1β in MM with Brucella patients.

*Determination of immunohistochemical staining*

Immunohistochemical slides were evaluated by pathologists with no information on patient clinical data. The presence of brown chromogen within the cytoplasm was interpreted as positive staining. No cell nuclear staining was observed in any case. Unaffected tissue was used as the external positive control to check the validity of the immunoreaction. Evaluation of the different staining patterns of cytokines was performed as previously described. Immunohistochemistry (IHC) was included Intensity of staining (IS) and Extent Score (ES). IS was graded on a 0-3 scale (0 = absent staining, 1 = weak staining, 2 = moderate staining, 3 = strong staining). ES was calculated by the semi-quantitative software Image J, used to assess the area and density of the dyed region and the integrated optical density (IOD) value of the IHC section, and five categories (0-4) of percentage of immunopositive cells were identified: <5%; 5-25%; 26-50%; 51-75%; >75%. IS was summed to ES to obtain the final score; 0-1, (-, Negative); 2-3, (+, weak positive); 4-5, (++, positive); 6-7, (+++, strong positive).

## Results

To explore a possible link between brucellosis and myelofibrosis, we evaluated the expression of IL-1β, IFN-γ, and TGF-β by retrospectively analyzing immunohistochemical data (**Table 2** and **Figure 1**). We found that patients with brucellosis and myelofibrosis (patients 2 and 4) were strongly positive (+++) for IL-1β, positive (++) for IFN-γ, and weakly positive (+) for TGF-β. By contrast, a brucellosis patient without myelofibrosis (patient 3) was positive (++) for IL-1β, weakly positive (+) for IFN-γ, and strongly positive (+++) for TGF-β (**Table 2**). Based on the literature we reviewed, the elevated production of cytokines such as TGF-β, b-FGF, PDGF, VEGF, and IL-12 provides a favorable environment for the development of myelofibrosis [10]. In the present study, we focused on the role of the pro-inflammatory cytokines IL-1β and IFN-γ in the development of myelofibrosis; our hypothesis regarding the pathogenesis of myelofibrosis as a complication of brucellosis is outlined in **Figure 2**.

## Discussion

Brucellosis is a chronic infectious disease caused by Brucella bacteria. Blood culture is the gold standard for the diagnosis of brucellosis. Laboratory testing is routinely used to diagnose brucellosis patients who have high C-reactive protein levels and low platelet counts. Some brucellosis patients also have high erythrocyte sedimentation rates, low whole blood cell counts, and signs of liver dysfunction. In this study, three of the five brucellosis patients had myelofibrosis, which is a very rare combination. We found only one previous report of a brucellosis patient presenting with myelofibrosis, which suggested that brucellosis should be considered as a possible cause of myelofibrosis in endemic areas, and that the development of myelofibrosis may be due to excessive production of cytokines such as TGF-β [11].

The mechanism of brucellosis pathogenesis has not been fully defined. A variety of virulence factors such as lipopolysaccharide and Virb/T4ss, released by Brucella species, enter the body through damaged skin or mucous membranes by binding to Toll-like receptors (TLRs) 2, 4, and 9. These virulence factors then inhibit the secretion of cytokines such as IFN-γ, IL-12, TNF-α, IL-6, and IL-10, which in turn inhibits the function of macrophages, eventually leading to recurrent or chronic infection [12-14]. TLR9 recruits a series of signaling molecules through intracellular myeloid differentiation factor 88

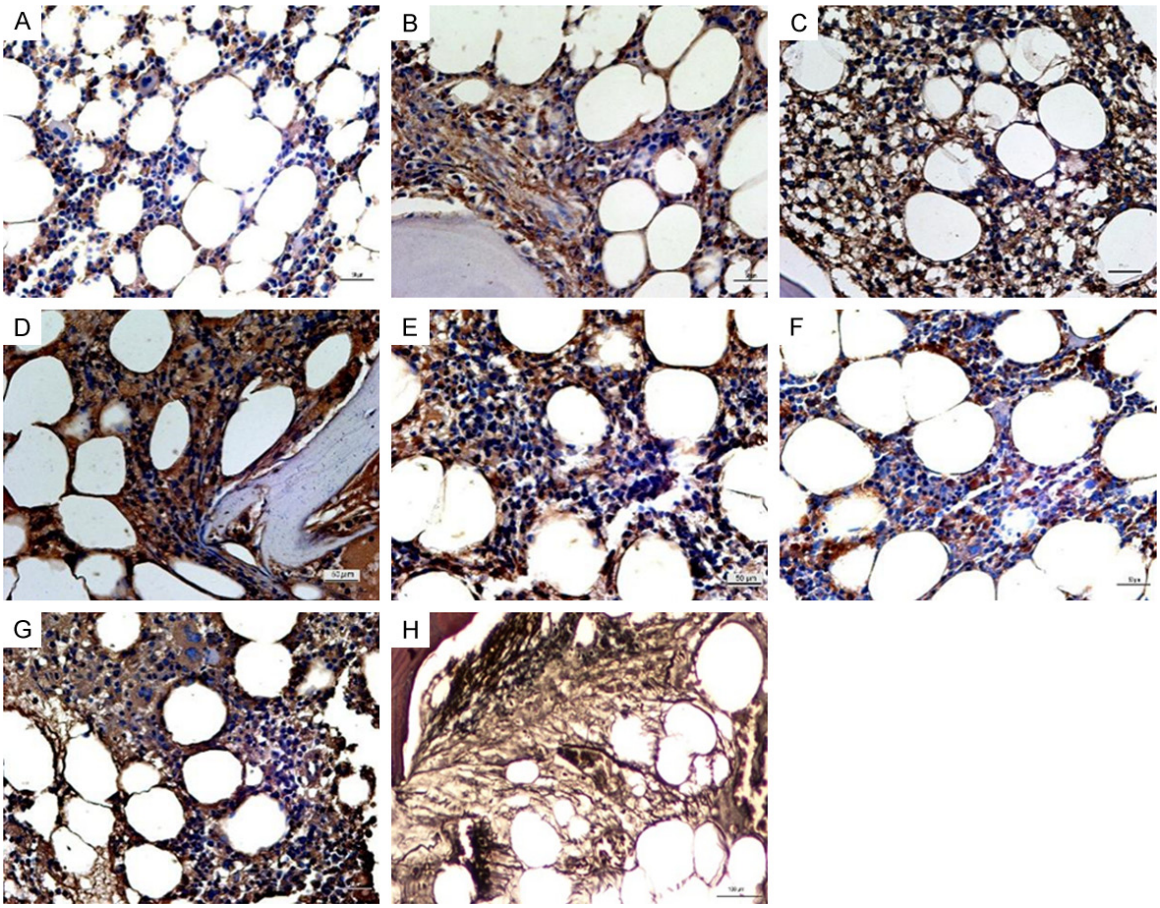


**Figure 1.** Immunostaining and reticulin fiber silver staining of BM pathology in cases of brucellosis with myelofibrosis. A: IL-6 ×400, strongly positive (+++) (Scale bar: 50 μm). B. IL-10 ×400, strongly positive (+++) (Scale bar: 50 μm). C. IL-12 ×400, strongly positive (+++) (Scale bar: 50 μm). D. IL-1β ×400, strongly positive (+++) (Scale bar: 50 μm). E. VEGF ×400, positive (++) (Scale bar: 50 μm). F. IFN-γ ×400, positive (+++) (Scale bar: 50 μm). G. TGF-β ×400, strongly positive (+++) (Scale bar: 50 μm). H. Reticulin fiber staining ×200, MF-2 (Scale bar: 100 μm).

(Myd88) to activate nuclear factor (NF)-κB signaling, which elicits an inflammatory cytokine response, culminating in IFN-α production. MyD88 is also involved in the activation of T cells, and especially in mediating the T cell response to IL-18, which induces IFN-γ production [15]. In addition, TLRs inhibit the expression of the long non-coding RNA Gm28309, which also leads to the activation of the NF-κB pathway and promotes the expression of IL-1β [16]. Our immunohistochemical results are in agreement with those of the above studies and suggest that the expression of cytokines such as IL-1β and IFN-γ plays a role in brucellosis pathogenesis.

To further delineate the relationship between brucellosis and myelofibrosis, we needed to investigate myelofibrosis pathogenesis. To date, most studies have shown that myelofibrosis is associated with chronic inflammation and the JAK-STAT and NF-κB signaling pathways [17, 18]. The constitutive activation of JAK-STAT signaling is triggered by mutations in Janus kinase 2 (JAK2), calreticulin (CALR), and the myeloproliferative leukemia virus (MPL) oncogene. The most common mechanism of structural JAK-STAT pathway activation involves the V617F mutation in JAK2, which results in the release of TGF-β, PDGF, and b-FGF from platelet a-granules. This in turn promotes type I, III, and IV collagen synthesis and ultimately leads to myelofibrosis development. Also, fibrosis can develop following a reduction in the levels of matrix metalloproteinases-3 (MMP3) and an increase in the synthesis of metallopeptidase inhibitor 1 (TIMP-1) [19]. In addition to “driver” mutations, chronic inflammation [20, 21] (as ob-

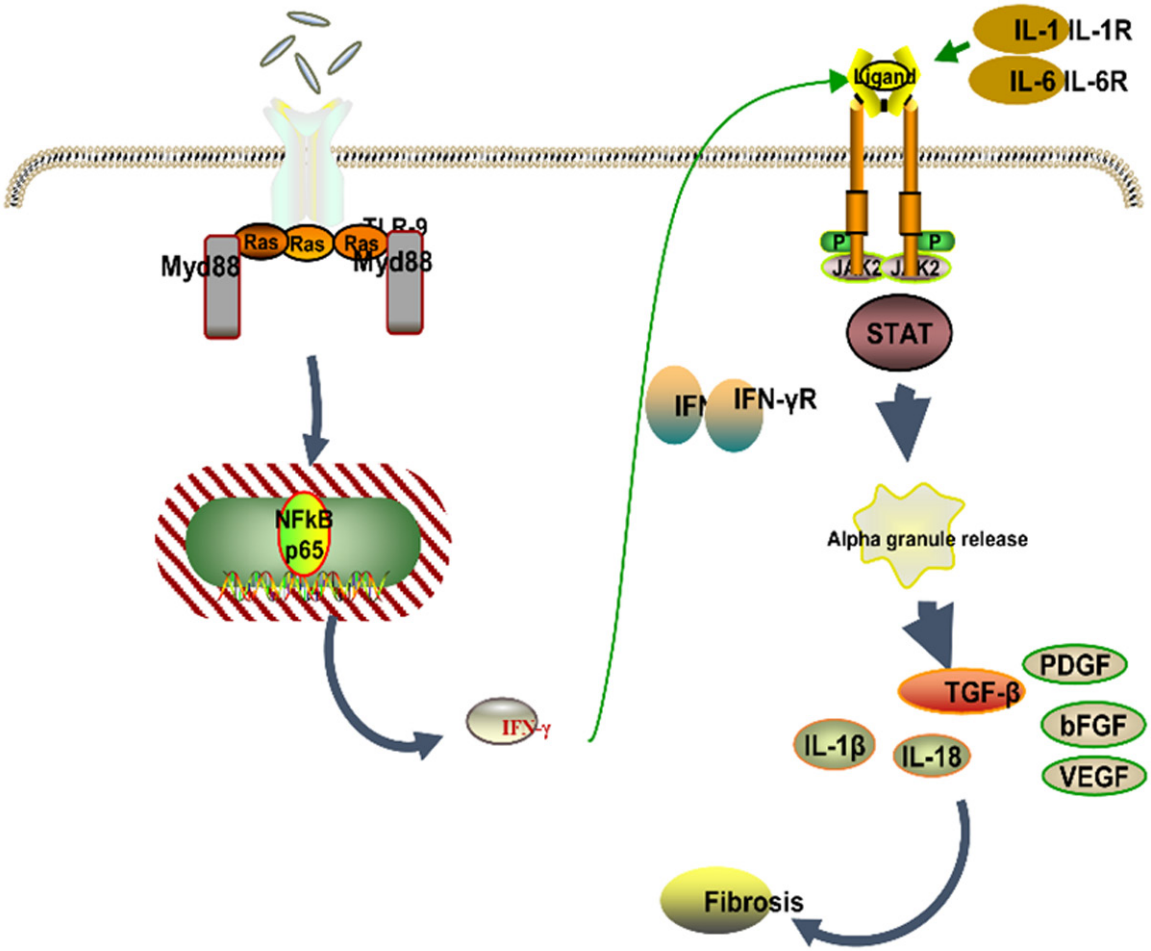


**Figure 2.** Our hypothesis regarding the pathogenesis of brucellosis with myelofibrosis is that Brucella may activate NF-κB through Myd88 in TLR9, resulting in the binding of IFN-γ to its receptor. This may further activate the JAK-STAT pathway activation and promote the expression of factors that promote the occurrence of myelofibrosis. Similarly, the binding of IL-1 and IL-6 to their respective receptors could also activate the JAK-STAT pathway and lead to myelofibrosis.

served in disseminated tuberculosis, vasculitis, and autoimmune diseases) [22-25] is considered to be a hallmark of myelofibrosis; however, studies in this research area are limited. The specific mechanisms implicated in SMF development are still under investigation; however, they are likely to involve TGF-β, PDGF, b-FGF, and IL-1β, as well as various adhesion molecules. In our previous study, we showed that the production of cytokines such as b-FGF, TNF-α, TGF-β, PDGF, IL-1β, IL-6, and IL-10 may contribute to the development of SMF [10]. We subsequently demonstrated that the overexpression of TGF-β was closely related to myelofibrosis pathogenesis [26]. In line with these findings, Rafiei et al. reported that polymorphisms of the TGF-β-encoding gene may be related to the occurrence of brucellosis, although this remains controversial [27, 28]. In the present study, we characterized three patients with brucellosis and myelofibrosis; however, the link between these conditions is not fully understood. To the best of our knowledge, our study is the second to report the association between myelofibrosis and brucellosis. Brucellosis is characterized by chronic inflammation, which is associated with NF-κB pathway overactivation and the subsequent increase in the expression of cytokines such as IL-1β and IFN-γ [29]. Similarly, in myelofibrosis, the activation of the JAK-STAT pathway increases the production of TGF-β, PDGF, b-FGF, and IL-1β. Therefore, the relationship between brucellosis and myelofibrosis may be explained by

the interaction between NF-κB and JAK-STAT pathways, whereby the IFN-γ released as a result of NF-κB signaling may further activate the JAK-STAT pathway. Similarly, the binding of IL-1β and IL-6 to their respective receptors could also activate the JAK-STAT pathway and lead to myelofibrosis development [21]. In this study, we found that three of the five patients with brucellosis had myelofibrosis. However, we could not make a conclusive diagnosis of PMF in these patients as we did not evaluate the presence of mutations in the JAK2, CALR, or MPL genes, which are implicated in myeloproliferative neoplasms. In addition, our ability to definitively diagnose PMF was limited by the fact that 10% of PMF patients do not have mutations in these three genes [30]. We speculate that as the disease progressed in the three brucellosis patients with myelofibrosis, they experienced BM invasion, which is highly characteristic of SMF.

Based on our findings, we proposed the following possible mechanism of myelofibrosis induction by brucellosis. The expression of IL-1β, b-FGF, and VEGF (seen in the three brucellosis patients with myelofibrosis) likely provided a favorable microenvironment for the development of myelofibrosis. In addition, the occurrence of brucellosis is related to NF-κB pathway activation. The pro-inflammatory genes upregulated as a result of NF-κB signaling may drive the progression of myelofibrosis. We found that case 2 and 4 were positive (++) for IFN-γ, and weakly positive (+) for TGF-β. By contrast, case 3 was weakly positive (+) for IFN-γ, and strongly positive (+++) for TGF-β. Specially, the strongly positive of IL-6 and IL-1β may be related to MM. This is consistent with the report that the increase in TGF-β production in patients with brucellosis is closely related to the inhibition of IFN-γ production [14]. In our study, the expression of IFN-γ, VEGF, and b-FGF increased with the development of myelofibrosis. Based on this observation and the relevant literature, we speculate that myelofibrosis is induced by multiple pathways, which may have shared cytokines (e.g., IFN-γ is implicated in both the JAK-STAT and NF-κB pathways).

The pathogenesis of brucellosis is complex, especially as patients with the disease are prone to relapse, meaning that treatment needs to be administered early, combined with other forms of treatment, and if necessary, extended to prevent recurrence [31]. In our study, patients 1 and 2 received doxycycline and six rounds of rifampicin treatment, which ultimately led to the improvement of their disease. Meanwhile, patient 5, who only received doxycycline had a worse outcome and had to be referred to a specialized hospital because of chronic low-grade fever, indicating that combination treatment was more effective than monotherapy. Consistently, the World Health Organization (WHO) has approved a combination therapy for brucellosis, which can effectively avoid recurrence and drug resistance compared with traditional monotherapy [32]. We recommend that patients presenting with a fever of unknown origin, myalgia, fatigue, joint pain, lymphadenectasis, and hemogram abnormalities in the absence of common diseases should be tested for brucellosis. Moreover, brucellosis patients with increased levels of pro-inflammatory cytokines such as IL-1β and IFN-γ should be monitored for myelofibrosis, which could be caused by chronic inflammation. Early diagnosis of myelofibrosis is the key to effective treatment.

In this study, only patient 2 presented with MM (positive for IGH/CCND1 gene locus fusion, standard risk). Because of the combination of brucellosis and MM in this patient, they were able to receive drugs targeting both conditions rapidly and their outcome finally improved. The patient experienced no other complications and no disease recurrence. However, the other two brucellosis patients with myelofibrosis were not treated in our hospital and were not tracked. We stress the importance of obtaining a timely diagnosis of myelofibrosis and initiating treatment of any complications possibly related to myelofibrosis prognosis as early as possible.

## Conclusion

This study reported the occurrence of myelofibrosis in three of five patients with brucellosis. Our immunohistochemical results suggest that the regulation of cytokines, such as IFN-γ, b-FGF, VEGF, IL-1β, and IL-6, may contribute to the development of myelofibrosis. However, because our study was limited to three patients, further research is needed to explore the pathogenesis of brucellosis and myelofibrosis.

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Written informed consent for this case report has been obtained from the patient.

## Disclosure of conflict of interest

None.

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