

## *Brucella* prosthetic valve endocarditis: A case study

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### SOUHRN

Bakterie rodu *Brucella* jsou gramnegativní kokobacily, které typicky vyvolávají brucelózu projevující se nespecifickými symptomy, jako jsou horečka, únava a artralgie. Jedná se o multisystémové onemocnění, které může vést ke komplikacím, přičemž nejčastějším – i když vzácným – kardiovaskulárním projevem je brucelová endokarditida. Toto infekční onemocnění je odpovědné za 80 % případů úmrtí v souvislosti s brucelózou, často v důsledku srdečního selhání. K onemocnění primárně dochází po konzumaci nepasterizovaných mléčných výrobků. Vzhledem k rozmanitosti klinických projevů může diagnostika brucelózy představovat problém. Endokarditida umělé chlopně, vyvolaná bakteriemi rodu *Brucella*, se vyskytuje velmi vzácně a stanovení diagnózy brucelové endokarditidy a její léčba jsou obzvláště náročné. Popisujeme případ brucelové endokarditidy u muže ve věku nad 50 let s nevýznamnou anamnézou až na náhradu mitrální chlopně pro akutní revmatickou horečku. Po dobu déle než jeden rok trpěl recidivující horečkou, nočním pocením a úbytkem tělesné hmotnosti. Z laboratorních parametrů vykazovaly zvýšené hodnoty proteiny akutní fáze a jaterní enzymy, byla zjištěna hematurie a nízké hodnoty c3/c4, pozitivita antinukleárních protilátek a revmatoidního faktoru. Poslech srdce odhalil pansystolický šelest stupně 2/6 u mitrální chlopně, doprovázený slyšitelným zvukem kovové umělé chlopně. Byla provedena kultivace krevních vzorků odebraných v průběhu čtyř dnů z obou paží. První hemokultura prokázala růst gramnegativních bakterií po 72 hodinách, což vedlo k zahájení empirické léčby cefepimem a gentamicinem. Po pěti dnech byla prokázána přítomnost bakterie rodu *Brucella* a léčba byla změněna na podávání doxycylinu, rifampicinu, a gentamicinu. Od zahájení empirické léčby nebyl v kulturách zjištěn žádný růst. Následně bylo provedeno vyšetření transezofageální echokardiografií, která odhalila útvar o velikosti 13 mm odpovídající vegetacím na umělé mitrální chlopně. Pacient byl operován a v pooperačním období nebyly pozorovány žádné komplikace.

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### ABSTRACT

*Brucella* bacteria are Gram-negative coccobacilli that typically cause brucellosis, presenting with nonspecific symptoms like fever, fatigue, and arthralgia. It is a multisystem disease that can lead to complications, with brucella endocarditis being the most common cardiovascular manifestation, though rare. Brucella endocarditis accounts for 80% of brucellosis-related deaths, often due to heart failure. The disease is primarily contracted through unpasteurized dairy products. Diagnosing brucellosis can be challenging due to its diverse clinical features. Brucella-related prosthetic valve endocarditis is particularly rare and presents unique diagnostic and treatment difficulties. We present a case report of brucella endocarditis in a male patient in his 50s. His medical history was insignificant except a history of mitral valve replacement due to acute rheumatic fever. He had a history of relapsing fever, night sweat and weight loss over a year. There were diverse laboratory findings such as elevated acute phase reactants, liver enzymes, hematuria, low c3/c4, positive antinuclear antibody and rheumatoid factor. During cardiac auscultation, a pansystolic murmur grade 2/6 was detected at the mitral focus, accompanied by the audible sound of a metallic prosthetic valve. Blood cultures from both arms were taken over four days. The first culture showed Gram-negative bacterial growth at 72 hours, prompting empirical treatment with cefepime and gentamicin. After 5 days, *Brucella* was identified, and the treatment was adjusted to doxycycline, rifampicin, and gentamicin. No growth was seen in cultures taken after starting empirical treatment. Subsequently, a transesophageal echocardiogram was performed, revealing a 13 mm vegetative mass consistent with prosthetic mitral valve vegetations. The patient then underwent surgery, and no complications were observed in the postoperative period.

#### Keywords:

*Brucella*

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## Introduction

*Brucella* bacteria are aerobic, immobile, non-spore-forming, Gram-negative coccobacilli. Initially, brucellosis typically presents with nonspecific symptoms such as fever, fatigue, night sweats, and arthralgia.<sup>1</sup> Human brucellosis is a serious multisystem disease that can impact various organs. It may lead to some complications and relapses. Although cardiovascular complications are uncommon, endocarditis is the most frequently observed cardiovascular manifestation of brucellosis with 1.4%.<sup>2</sup> *Brucella* endocarditis accounts for 80% of *Brucella*-related deaths.<sup>3</sup> Death, particularly in cases where diagnosis is delayed, occurs as a result of heart failure. It can affect both natural and prosthetic heart valves. The consumption of unpasteurized milk and dairy products is a significant risk factor for brucellosis.<sup>4</sup> Diagnosing brucellosis can be difficult due to its systemic nature and diverse clinical presentations. *Brucella*-related prosthetic valve endocarditis is exceptionally uncommon and presents substantial diagnostic and therapeutic hurdles, especially concerning

the optimal duration of treatment, selection of antibiotic regimens, and determining the timing or necessity of surgical intervention.<sup>5</sup>

In this case report, we will present a challenging case of *Brucella* prosthetic valve endocarditis characterized by a complex diagnostic process and extensive clinical and laboratory findings.

## Presentation of case

A male patient in his 50s, residing in a rural area, presented with a year-long history of weight loss, night sweats, and nausea, accompanied by the recent onset of fever and back pain. Before his admission to our clinic, he had sought the opinions of various medical specialists at different hospitals regarding these constitutional symptoms. Over the past year, he underwent routine laboratory tests and thoracoabdominal computerized tomography (CT) scans, which revealed mild hepatosplenomegaly, anemia, mildly elevated liver enzymes, non-nephrotic proteinuria,

**Table 1 – Laboratory findings**

Test	Results	Reference range	Units
WBC	2.8	4–10.3	10 <sup>3</sup> /μL
Neutrophils	1.8	2.1–6.1	10 <sup>3</sup> /μL
Hemoglobin	9	12–16	g/dL
Hematocrit	26.6	36–46	%
MCV	86.2	80.7–95.5	fL
RDW	19.1	11.8–14.3	%
Platelets	120	156–373	10 <sup>3</sup> /μL
Creatinine	1.22	0.9–1.3	mg/dL
AST	47	0–50	U/L
ALT	26	0–50	U/L
GGT	267	0–55	U/L
ALP	272	30–120	U/L
LDH	279	125–220	U/L
Total bilirubin	1.08	0.30–1.20	mg/dL
Direct bilirubin	0.26	0–0.20	mg/dL
Total protein	10.39	6–8.3	g/dL
Albumin	2.62	3.5–5.2	g/dL
IgM	235	40–230	mg/dL
IgG	4694	700–1600	mg/dL
Ferritin	364	18–306	ng/ml
CRP	77	0.2–5	mg/L
Procalcitonin	0.67	0–0.05	ng/ml
ESR	93	0–15	mm/h
RF	626	0–14	IU/mL
C3	73.4	90–180	mg/dL
C4	7.49	10–40	mg/dL

ALP – alkaline phosphatase; ALT – alanine transferase; AST – aspartate transferase; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; GGT – gamma glutamyl transferase; LDH – lactate dehydrogenase; MCV – mean corpuscular volume; RDW – red cell distribution width; RF – rheumatoid factor; WBC – white blood cell.

microscopic hematuria, significantly high serum globulin levels, elevated erythrocyte sedimentation rate, positivity for antinuclear antibodies (ANA), increased level of rheumatoid factor (RF), low C3/C4 levels, elevated C-reactive protein (CRP) levels, and hypodense lesions in the liver and spleen. The patient had received empirical antibiotic therapy multiple times; however, while he experienced intermittent improvements, his symptoms never completely resolved. In summary, during this one-year period, the patient sought multiple consultations based on these findings: hematology for the evaluation of lymphoproliferative disorders and plasma cell dyscrasias, nephrology for proteinuria and hematuria, gastroenterology for hepatosplenomegaly and mildly elevated liver enzymes, and rheumatology for elevated acute phase reactants and positivity for autoantibodies. As a result, he had not undergone thorough investigations and struggled with maintaining consistent follow-up appointments until presenting to our clinic.

His medical history included a prosthetic mitral valve replacement (MVR) performed four years prior, as well as surgery six months earlier due to a hemorrhagic cerebrovascular event (CVE). He reported no known allergies or other significant medical conditions. The patient experienced elevated body temperature, which typically rose in the evenings and persisted for a duration of 4 to 5 days. Following this period, there were subsequent days characterized by an absence of fever. Upon physical examination, his temperature was 38 °C, heart rate was 96 beats per minute and rhythmic, and blood pressure was 128/81 mmHg. During cardiac auscultation, a pansystolic murmur grade 2/6 was detected at the mitral focus, accompanied by the audible sound of a metallic prosthetic valve. Traube's space exhibited dullness, and both the liver and spleen were palpable 4 cm below the costal margin. Additionally, petechial rashes were observed on the lower extremities, while the remainder of the physical examination findings were unremarkable.

Laboratory tests showed a white blood cell count of  $2.8 \times 10^3/\mu\text{L}$ , hemoglobin 9 g/dL, hematocrit 26.6%, platelet count  $120 \times 10^3/\mu\text{L}$ , erythrocyte sedimentation rate 93 mm/hour, total protein 10.39 g/dL, albumin 2.62 g/dL, lactate dehydrogenase (LDH) 279 U/L, alkaline phosphatase (ALP) 272 U/L, and gamma-glutamyl transferase (GGT) 267 U/L. Other laboratory tests were within normal limits (Table 1). The patient was admitted to the internal medicine department for further investigation.

Blood cultures were taken from both the right and left arms of the patient for four consecutive days. In the first blood culture, a signal indicating Gram-negative bacterial growth was detected at 72 hours. Given the patient's preliminary diagnosis of infective endocarditis, empirical treatment with cefepime and gentamicin was initiated. After the first doses of both antibiotics were administered, another blood culture was taken (as previously planned). Ultimately, *Brucella* growth was detected in the first culture after 5 days, and the treatment was adjusted to doxycycline 200 mg/day, rifampicin 600 mg/day, and gentamicin 3 mg/kg/day. Although *Brucella* signals were observed in all blood cultures taken before the initiation of empirical treatment, no growth was detected in the blood culture taken after the first doses of the



Fig. 1 – PET/CT showing increased FDG uptake around the mitral valve

empirical treatment. Serological tests were not requested because *Brucella* growth was already detected in the cultures. Additionally, serological tests are often positive in the Turkish population, even when brucellosis is not active, as Turkey is a high-risk endemic area for brucellosis.

An abdominal MRI was requested to further investigate the hypodense lesions, which were determined to be chronic infarct areas in the spleen. Additionally, when the FDG PET/CT images previously requested by hematology were reevaluated by our team, increased FDG uptake around the mitral valve was observed (Fig. 1). Despite the performance of three transthoracic echocardiograms, no vegetations were detected on the cardiac valves. Subsequently, a transesophageal echocardiogram was conducted, which revealed a 13 mm vegetative mass consistent with prosthetic mitral valve vegetations. The diagnosis of *Brucella* prosthetic valve endocarditis was established following the culture of *Brucella* from blood samples and the identification of vegetations on the prosthetic mitral valve via transesophageal echocardiography. A multidisciplinary council, comprising specialists from cardiology, cardiovascular surgery, infectious diseases, and internal medicine, convened and determined that the patient should undergo surgical intervention. Postoperative monitoring revealed no complications. The patient received antibiotic therapy for approximately six months, during which no relapses of brucellosis were observed. Upon investigation for brucellosis, it was discovered that both the patient and his wife had been consuming unpasteurized milk. The patient's spouse, who resides in the same household, reported exhibiting similar symptoms; however, the severity of her symptoms was relatively milder. Although the patient's wife tested positive

for Rose Bengal and Wright serological tests (1/640) for brucellosis, she exhibited no clinical signs of infective endocarditis. Her brucellosis was effectively managed with antibiotic treatment.

## Discussion

Our patient presented numerous and varied clinical and laboratory findings. Due to a delay in diagnosis, these diverse symptoms progressively worsened. The following findings, which we believe are related to *Brucella* endocarditis in our case, can be listed as: recurrent fever, fatigue, and weight loss that had persisted for over a year (constitutional symptoms); an unexplained hemorrhagic stroke six months ago (the first clinical finding that brought the patient to the hospital); non-nephrotic proteinuria, hematuria, spontaneous ecchymoses, back pain, splenic infarctions, rheumatoid factor (RF) positivity, antinuclear antibody (ANA) positivity, reduced C3/C4 levels, normocytic anemia, elevated acute phase reactants, increased erythrocyte sedimentation rate, elevated serum immunoglobulin levels, rouleaux formation on peripheral blood smear, hepatosplenomegaly, and increased uptake around the mitral valve on FDG-PET/CT. Fadul et al. presented a case of *Brucella* endocarditis complicated by embolic stroke, similar to our case; however, our patient experienced a hemorrhagic stroke.<sup>6</sup> Immunological phenomena can be observed in endocarditis, such as in *Brucella* endocarditis, including positive RF, ANA, and endocarditis-related glomerulonephritis findings, as we presented in our case.<sup>7</sup> FDG-PET/CT has become an important tool for the evaluation and diagnosis of endocarditis in recent years, with a sensitivity of 86% for the diagnosis of prosthetic valve IE.<sup>8</sup> The FDG-PET/CT scan provided important findings for the diagnosis of IE in our case.

Considering that *Brucella* is transmitted through contact with animals and consumption of animal products such as milk, it is important to clinically evaluate and screen close contacts, such as household members, of individuals diagnosed with *Brucella*; as shown in this case, *Brucella* was also detected in the patient's wife.<sup>4</sup>

In our case, *Brucella* growth in the blood cultures taken before the initiation of empirical treatment appeared on the fifth day. However, no growth was observed in the blood culture taken after the first dose of empirical cefepime/gentamicin treatment. *Brucella* is a slow-growing infectious agent and more difficult to culture in blood compared to other pathogens. The sensitivity of blood cultures ranges from 10% to 90%.<sup>9</sup> Therefore, it is crucial to obtain blood cultures under appropriate conditions from patients with suspected brucellosis before initiating empirical treatments.

Sometimes, even when everything points to infective endocarditis, the diverse clinical and laboratory findings can obscure this reality. Our patient had presented to the hospital multiple times with different complaints and had been evaluated for various differential diagnoses before coming to us. However, if we had simplified the case to that of a patient with recurrent fever and a history of mitral valve replacement surgery, the first consideration would have been infective endocarditis. It is crucial to

adopt a holistic approach to patients and to search for the most appropriate clinical pattern in a multifaceted disease such as infective endocarditis.

## Conclusion

Brucellosis can present with a variety of clinical features, which can mislead physicians. A holistic approach, along with identifying the most appropriate pattern that explains the majority of findings, is crucial for the diagnosis of infective endocarditis due to brucellosis. *Brucella* typically infects humans through unpasteurized dairy products, and it is important to screen the households of index patients. As *Brucella* is a slow-growing bacterium in cultures, it is essential to collect blood samples for culture before starting empirical treatment.

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## Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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## Ethical statement

The present study followed international and national regulations and was in agreement with the Declaration of Helsinki, and ethical principles. Our institution does not require ethical approval for reporting individual cases or case series.

## Informed consent

Written informed consent was obtained from the patient and his wife for their anonymized information to be published in this article.

## Availability of data and materials

All are available upon reasonable request.

## Authors' contribution

HD was a major contributor to the writing of the manuscript, and all authors (HD, AÜ, İEA, EÖ, MOT) commented on subsequent versions. All authors (HD, AÜ, İEA, EÖ, MOT) contributed to data collection, treatment, and patient follow-up. All authors (HD, AÜ, İEA, EÖ, MOT) read and approved the final manuscript.

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