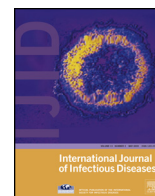




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## Brucellar pericarditis: a report of four cases and review of the literature

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## SUMMARY

**Background:** Brucellosis, a disease endemic in many countries including Turkey, is a systemic infectious disease. Cardiovascular complications are not frequent, and endocarditis is the main cardiac manifestation of brucellosis. Pericarditis in the absence of concomitant endocarditis is extremely rare. **Methods:** In this report, we present four patients with pericarditis caused by brucellosis in the absence of concomitant endocarditis, along with a review of the published literature on brucellar pericarditis. We also searched for clinically silent pericardial effusion among patients with brucellosis. We performed routine transthoracic echocardiography (TTE) on 72 consecutive patients with newly diagnosed brucellosis in the absence of any signs and symptoms of pericarditis over a period of 6 months. **Results:** Three of our patients with brucellar pericarditis recovered fully after antibiotics. The other patient received 6 days of antibiotic treatment, and her signs and symptoms regressed, but after this the patient was lost to follow-up. We did not detect pericarditis among the 72 newly diagnosed patients. **Conclusions:** Brucellar pericarditis is a rare clinical entity, and the morbidity and mortality in patients with brucellar pericarditis is low. Pericardiocentesis should only be performed in patients with cardiac tamponade. Moreover, the choice of antibiotics and the duration of treatment do not differ between brucellosis cases with or without isolated pericarditis. Although the prevalence of pericarditis in brucellosis is low, brucellar pericarditis should always be kept in mind in patients with acute or chronic pericarditis, especially in areas where brucellosis is endemic.

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## 1. Introduction

Brucellosis is a worldwide zoonotic disease, which is particularly endemic in the Mediterranean region, the Middle East, the Arabian Peninsula, Central and South America, Asia, and Africa.<sup>1</sup> According to data from the Turkish Ministry of Health in 2004, the disease is most common in the southeastern region of Turkey.<sup>2</sup> Humans are infected by close contact with an animal, or by the consumption of meat or dairy products infected by bacteria of the genus *Brucella*.<sup>3</sup>

Brucellosis is a systemic infection; skeletal muscle, spleen, liver, and bone marrow, rich in reticuloendothelial cells, are the most frequently involved sites. With its various clinical symptoms and signs, it is sometimes difficult to diagnose.<sup>4</sup> However, the incidence of cardiovascular complications in brucellosis, such as endocarditis, myocarditis, or pericarditis, is reported to be as low as 1% of all cases, with even fewer cases of myocarditis or pericarditis in the absence of concomitant endocarditis being reported. Indeed, myocarditis, pericarditis, and asymptomatic pericardial effusion

in brucellosis is thought to develop almost exclusively in the presence of endocarditis.<sup>5</sup>

We present the cases of four patients with brucellar pericarditis in the absence of concomitant endocarditis, and discuss these cases along with a review of the published literature on brucellar pericarditis.

## 2. Case reports

## 2.1. Case 1

A 79-year-old female patient was admitted to hospital due to 10 days of fever, dyspnea, fatigue, and generalized arthralgia. She also referred to weight loss and night sweats. Her medical history was unremarkable. She was living in a rural area and had a history of eating fresh cheese. On physical examination, only tachypnea, cardiac murmur, and hepatosplenomegaly were detected. Laboratory investigations revealed anemia, leukopenia, and thrombocytopenia, and an elevated C-reactive protein (CRP) level (Table 1). Brucellosis was suspected, and a Brucella standard tube agglutination (STA) test was positive at a dilution of 1:320. Electrocardiography (ECG) was normal, but chest radiography revealed cardiomegaly. Transthoracic echocardiography (TTE) showed

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**Table 1**  
Laboratory findings on admission of four patients with brucellar pericarditis

Parameter (normal range)	Case 1	Case 2	Case 3	Case 4
White blood cell count, $\times 10^9/l$ (4.1–11.2)	3.7	6.4	13.8	4.6
Lymphocytosis, % (10–50)	62	67	76	65
Hemoglobin, g/dl (F: 12–16, M: 14–18)	10.6	10.2	9.7	8.6
Platelets, $\times 10^9/l$ (150–400)	139	221	340	157
ESR, mm/h (0–15)	10	15	117	60
CRP, mg/dl (0–5)	8	8.72	149	93.3
ALT, IU/l (0–41)	32	27	40	36
AST, IU/l (0–40)	35	32	38	29
Urea, mg/dl (10–50)	41	36	61	39
Creatinine, mg/dl (0.5–0.9)	0.8	0.6	1.6	0.7

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; F, female; M, male.

normal valves, however there was left ventricular hypertrophy with an ejection fraction of 60%, pulmonary hypertension, and marked pericardial effusion (7 mm of thickness) without signs of cardiac tamponade. A blood culture remained sterile. She was treated with oral doxycycline 100 mg twice daily plus oral rifampin 600 mg once daily for 2 months. Her symptoms regressed rapidly 7 days after the initiation of treatment, and no adverse drug reactions were observed during the follow-up. Echocardiographic studies at 3 weeks, 2 and 6 months after the start of treatment showed no pericardial effusion. After a follow-up duration of 9 months, our patient was well with no signs of relapse.

## 2.2. Case 2

A 33-year-old male patient was admitted to hospital with fever, weight loss, dyspnea, palpitations, fatigue, and generalized arthralgia of 15-day duration. He was working as a food handler. On physical examination, he had tachycardia and hepatosplenomegaly. Laboratory investigations revealed anemia, an elevated CRP level, and high erythrocyte sedimentation rate (ESR) (Table 1). The STA was found to be positive at a dilution of 1:160. Blood cultures were negative. An ECG showed sinus tachycardia, and chest radiography was normal. TTE showed normal valves but marked pericardial effusion of 13 mm in thickness. There were no signs of cardiac tamponade. Pericardial effusion was also observed on thoracic computed tomography (CT) (Figure 1A). In accordance with these findings, a diagnosis of Brucella-related pericarditis was made and our patient was treated with oral doxycycline 100 mg twice daily for 2 months plus intramuscular streptomycin 1 g once daily for the first 3 weeks. His symptoms regressed rapidly 4 days

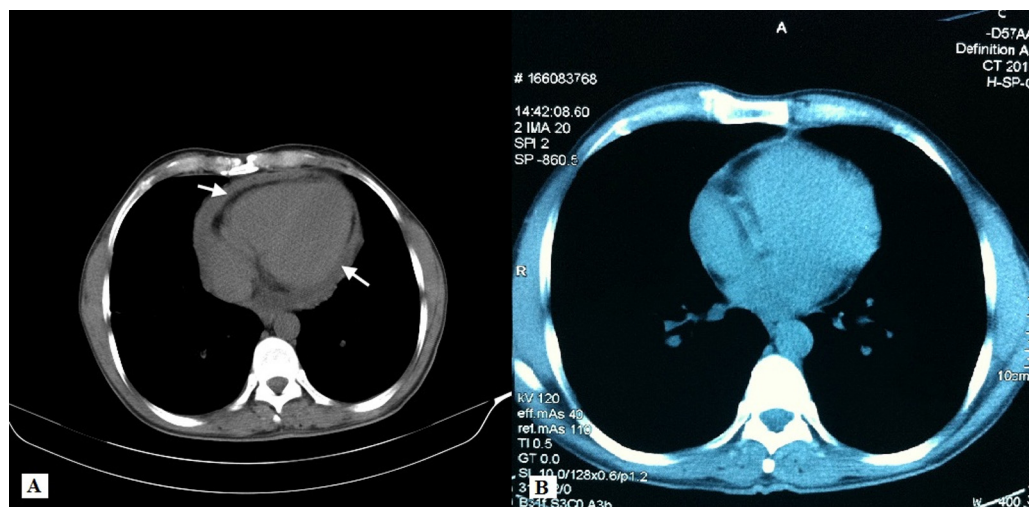
after the initiation of treatment. TTE and thoracic CT were normal 1 month after the beginning of treatment (Figure 1B), and he showed no signs of relapse during 7 months of follow-up.

## 2.3. Case 3

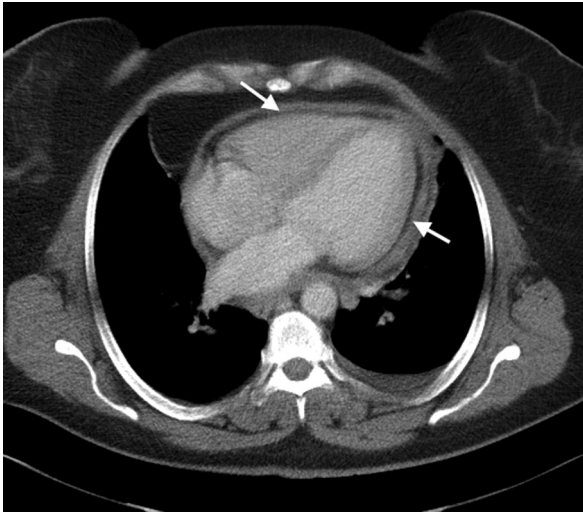
A 51-year-old female patient was admitted to the cardiology outpatient clinic with fever, chest pain, dyspnea, palpitations, and fatigue persisting for a month. She also had a history of generalized arthralgia, headache, and night sweats, was working as a stock farmer, and had been drinking raw cow milk. On physical examination, the only abnormalities were a systolic murmur (grade 3/6) and hepatosplenomegaly. Laboratory investigations revealed anemia, leukocytosis, elevated CRP level, and high ESR, with elevated serum urea and creatinine levels (Table 1). The STA was positive at a dilution of 1:320, and *Brucella melitensis* was isolated from two blood cultures. An ECG was normal, but chest radiography revealed cardiomegaly. TTE and thoracic CT showed pericardial effusion, without any signs of cardiac tamponade (Figure 2). Oral doxycycline 100 mg twice daily plus oral rifampin 600 mg once daily were started. Her symptoms regressed rapidly 6 days after the initiation of treatment, and the patient was discharged. The patient was then lost to follow-up.

## 2.4. Case 4

A 51-year-old female patient was admitted to our clinic due to fever, dyspnea, fatigue, generalized arthralgia, and chest pain of 3-week duration. She was living in a rural region and drinking raw cow milk. A physical examination was normal other than



**Figure 1.** (A) Pericardial effusion in thoracic CT (arrows). (B) Thoracic CT is normal after 1 month of treatment.



**Figure 2.** Thoracic CT showing pericardial effusion (arrows).

tachycardia. Laboratory investigations revealed anemia, elevated CRP, and a high ESR (Table 1). An ECG showed sinus tachycardia. The STA was positive at a dilution of 1:320. Blood cultures were sterile. TTE suggested minimal pericardial effusion, and there were no signs of cardiac tamponade. Oral doxycycline 100 mg twice daily plus intramuscular streptomycin 1 g once daily were started. Her symptoms regressed 4 days after the initiation of treatment. Streptomycin was stopped due to raised serum urea and creatinine levels after 10 days of treatment, and oral rifampin 900 mg once daily was added. Doxycycline and rifampin were maintained for 2 months. A TTE was normal at the end of treatment. She showed no signs of relapse after 6 months of follow-up.

### 3. Discussion

Brucellosis is a significant health problem in Turkey.<sup>6</sup> The disease is a systemic infection and the clinical presentation varies widely from asymptomatic and mild to severe disease. Infected animals and their products, particularly unpasteurized milk and dairy products, are common sources of infection.<sup>1</sup> Our patients had a history of eating fresh cheese or drinking raw cow milk.

The spleen, liver, and bone marrow are the most frequently involved sites. Cardiovascular, gastrointestinal, osteoarticular, urogenital, hematological, and neurological complications may arise.<sup>7</sup> Cardiovascular complications (endocarditis, pericarditis, and myocarditis) are extremely rare.<sup>5</sup> Brucellar endocarditis is the most common cardiovascular involvement of the disease and usually involves the aortic valve and less frequently the mitral valve. The covers damaged due to rheumatic fever, congenital malformations, or scleroderma are more likely to be affected.<sup>1</sup> It has a subclinical course and poor prognosis without any surgical treatment.<sup>8</sup> Replacement of the affected valve is necessary after 5–7 days of antibiotic therapy.<sup>9</sup> In the study of Taşova et al.,<sup>10</sup> endocarditis was found in only one of 238 cases of brucellosis. In another study, Gur et al.<sup>11</sup> reported two cases of brucellar endocarditis in the presence of concomitant myocarditis and pericarditis in a series of 283 cases with brucellosis. In cases of endocarditis, myocarditis and pericarditis are frequent, but pure pericarditis or myocarditis appears to be exceptional as the main feature of the disease.<sup>12,13</sup> Indeed, by searching the MEDLINE database for published articles using the words ‘pericarditis’ and ‘brucellosis’, we identified only 13 reports in the literature of adult patients with brucellosis, including 16 patients with brucellosis-related pericarditis in the absence of concomitant endocarditis,<sup>5,12,14–24</sup> of which 10 had appropriate information for analysis

(Table 2). In a study of 530 cases from Spain, only one patient had isolated brucellar pericarditis.<sup>14</sup> A case of pure brucellar pericarditis proven by blood culture has been reported by Gatselis et al.<sup>5</sup> Anguita et al.<sup>15</sup> reported two cases of *B. melitensis* pericarditis. Cuisinier et al.<sup>16</sup> reported acute pericarditis in a patient with relapsed brucellosis. Two reports of pure *Brucella* pericarditis with culture of *B. melitensis* from pericardial effusion have been reported by Ugartemendía et al.<sup>17</sup> Karagiannis et al.<sup>18</sup> reported a case with serologically diagnosed brucellosis developing acute pericarditis, without endocarditis. In this case, pericardiocentesis was required because of cardiac tamponade.

The cause of cardiac damage in brucellosis is uncertain. It may be due to a direct effect of the microorganism, as suggested by pericardial fluid cultures or by local deposits of immunocomplexes seen in cardiac biopsies.<sup>5</sup> Chest pain, dyspnea, and fever are common in pericarditis. There is pericardial friction rub in half of the cases.<sup>19</sup> The diagnosis is based on the demographic and epidemiologic characteristics of the disease, the presence of symptoms, results of serological tests, and isolation of the microorganism by blood, bone marrow, or pericardial fluid culture.<sup>5</sup> In our series, fever and dyspnea were the common symptoms in all patients. Echocardiograms showed pericardial effusion without any additional endocardial abnormalities, and none of the cases had cardiac tamponade. Surgical intervention (i.e., pericardiocentesis) and pericardial fluid culture were performed in only three patients among the total number of 16 cases found in the literature with brucellar pericarditis. Two of these patients presented with cardiac tamponade, and pericardiocentesis was performed as a therapeutic approach.<sup>17,18</sup> In the rest of the cases, the diagnosis was made by means of serology, blood culture, ECG, TTE, and radiology, as well as from the clinical picture. Diagnosis was based on TTE, radiology, and a positive serology in three of our patients, and in the other, positive serology with the isolation of *B. melitensis* from blood in addition to TTE and radiology. We conclude that pericardiocentesis, which is performed in order to carry out pericardial fluid analysis (culture), is not essential in cases with brucellar pericarditis in the absence of cardiac tamponade.

Forty-five days of combined antibiotic treatment is sufficient in cases of pericarditis due to *Brucella*. Trimethoprim–sulfamethoxazole may be added to rifampin–doxycycline therapy in patients with serous membrane involvement.<sup>19</sup> Three of our patients received combined antibiotic therapy for 2 months (rifampin–doxycycline or doxycycline–streptomycin). We administered rifampin and doxycycline to the other patient for 6 days, and her signs and symptoms regressed, but she was then lost to follow-up.

*Brucella* endocarditis is a clinical picture with a high mortality, and this situation can be fatal even if antibiotic treatment is started immediately, with the addition of surgical interventions.<sup>1</sup> When we searched the literature, the survival rate is high in patients with brucellosis accompanied by ‘pure pericarditis’. Indeed, only one of the 16 described patients died, and that patient had cardiac tamponade and also hepatic cirrhosis.<sup>17</sup> In our series, three patients completed antibiotic treatment, and were doing well after follow-up durations of 6–9 months. They were completely asymptomatic and without any pathological echocardiogram findings.

Corticosteroids can be used in neurobrucellosis, but there is no consensus on the use of steroids in brucellar pericarditis.<sup>3</sup> In the literature, there are only four cases with brucellar pericarditis who received anti-inflammatory treatment (prednisone in two cases, indomethacin in one, and acetylsalicylic acid in one patient) in addition to antibiotics (Table 2).<sup>17,18,20,21</sup> The other cases ( $n = 7$ ) did not receive any anti-inflammatory medications, and six of them recovered fully with antibiotics alone. We also did not

**Table 2**  
Adult patients with brucellar pericarditis published in the literature

Author, year (Ref.)	Cases, <i>n</i>	Age, years/sex	Clinical presentation	ECG findings	TTE findings	Serum agglutination	Blood cultures	Pericardial fluid cultures	Antibiotic treatment (duration, weeks)	Anti-inflammatory treatment (duration, weeks)	Follow-up time, months	Outcome
Ugartemendía et al., 1985 (17)	2	48/F	Fever, chest pain	NA	PE	1/320	<i>B. melitensis</i>	<i>B. melitensis</i>	Co-trimoxazole, streptomycin, oxytetracycline (3)	Prednisone (6)	18	Cure
		52/M	Fever, chest pain	NA	PE, calcific aortic stenosis	1/640	<i>B. melitensis</i>	<i>B. melitensis</i>	Co-trimoxazole, streptomycin, oxytetracycline, rifampin (3)	None	18	Death
Gomez-Huelgas et al., 1986 (12)	1	29/M	Fever, retrosternal pain	Sinus tachycardia, low QRS complexes	PE	Negative	<i>B. melitensis</i>	NA	Doxycycline (4), streptomycin (2)	None	NA	Cure
Rivera et al., 1988 (22)	1	55/M	Fever, chest pain	NA	PE	1/640	<i>B. melitensis</i>	NA	Rifampin, doxycycline (NA)	None	NA	Cure
Martínez et al., 2002 (21)	1	17/M	Retrosternal pain	ST elevation, T negativity	Pericardial thickening	1/640	<i>B. melitensis</i>	NA	Doxycycline, rifampin, co-trimoxazole (8)	Acetylsalicylic acid	12	Cure
Karagiannis et al., 2003 (18)	1	55/M	Fever, dyspnea	Atrial fibrillation	PE	1/1280	Negative	Negative	Doxycycline (6), streptomycin (2)	Indomethacin (2)	6	Cure
Hatipoğlu et al., 2004 (23)	2	62/F	Fever, dyspnea, chest pain	NA	PE	1/640	Negative	NA	Doxycycline, ciprofloxacin (6), gentamicin (2)	None	NA	Cure
		64/F	Dyspnea, hip pain	NA	PE	1/320	<i>B. melitensis</i>	NA	Doxycycline, rifampin, ofloxacin (24)	None	6	Cure
Demirdağ et al., 2005 (19)	1	50/F	Fever, dyspnea, chest pain	Sinus tachycardia	Left ventricular hypertrophy, PE	1/160	<i>B. melitensis</i>	NA	Rifampin, doxycycline (6)	None	NA	Cure
Gatselis et al., 2011 (5)	1	34/M	Fever, arthralgia	Sinus rhythm	PE	1/2560	<i>Brucella spp</i>	NA	Doxycycline, rifampin (12), streptomycin (3)	None	12	Cure
Our series	4	79/F	Fever, dyspnea, arthralgia	Sinus rhythm	Left ventricular hypertrophy, PE	1/320	Negative	NA	Rifampin, doxycycline (8)	None	9	Cure
		33/M	Fever, dyspnea, palpitation	Sinus rhythm	PE	1/160	Negative	NA	Doxycycline (8), streptomycin (3)	None	7	Cure
		51/F	Fever, dyspnea, chest pain	Sinus rhythm	PE	1/320	<i>B. melitensis</i>	NA	Rifampin, doxycycline	None	NA	NA
		51/F	Fever, dyspnea, chest pain	Sinus tachycardia	PE	1/320	Negative	NA	Rifampin, doxycycline (8)	None	6	Cure

ECG, electrocardiography; F, female; M, male; NA, not available; PE, pericardial effusion; TTE, transthoracic echocardiography.

administer any anti-inflammatory treatment to our patients, and a cure was achieved and maintained in three of the cases (Table 2).

Since the prevalence of pericarditis in brucellosis is low, in order to test this in our patient cohort, we also tried to investigate the frequency of clinically silent pericardial effusion among patients with brucellosis. We performed routine TTE in 72 consecutive patients with newly diagnosed brucellosis in the absence of any signs and symptoms of pericarditis over a period of 6 months (between March and September 2012). None of these patients had pericardial effusion, so after this finding, we can say that TTE is a necessary diagnostic procedure only in patients with brucellosis who have signs and symptoms of pericarditis.

In conclusion, brucellar pericarditis is a rare clinical entity, and the morbidity and mortality in patients with brucellar pericarditis is low, in contrast to cases presenting with endocarditis. Sampling the pericardial fluid for culture is not necessary in order to make the diagnosis of brucellar pericarditis, and pericardiocentesis should only be performed in patients with cardiac tamponade. Moreover, the choice of antibiotics and the duration of treatment do not differ between brucellosis cases with and without isolated pericarditis. Adding anti-inflammatory drugs to the therapy may be beneficial in selected cases with brucellar pericarditis, but this treatment modality is most probably not essential. A prospective controlled randomized trial is necessary to answer this question. Although the prevalence of pericarditis in brucellosis is low, brucellar pericarditis should always be kept in mind in patients with acute or chronic pericarditis, especially in areas where brucellosis is endemic.

*Conflict of interest:* No conflict of interest to declare.

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