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Evaluation of *Brucella* pericarditis cases by pooled analysis method

Brucella perikarditi olgularının havuz analiz yöntemiyle değerlendirilmesi

Oğuz EVLİCE[1] (ID), Mustafa YILMAZ[2] (ID), Sevil ALKAN ÇEVİKER[3] (ID), Uğur KÜÇÜK[4] (ID)

ABSTRACT

Objective: Brucellosis is one of the most frequent zoonotic infectious diseases and is a global public health concern, particularly in developing countries. Brucellosis causes systemic symptoms and can affect different parts of the body. Brucellar pericarditis is a rare involvement of the cardiovascular system. This study aimed to investigate the clinical outcomes of *Brucella* pericarditis cases.

Methods: A pooled analysis study was conducted by searching four international online databases with the terms "*Brucella*" and "pericarditis" and their synonyms. The full texts or abstracts were screened using these keywords. The publications were examined in terms of the age and gender of cases, publication year and country, additional diagnosis, diagnostic methods, treatments, and outcomes.

Results: The study included 25 cases (14 males, 56%), with a mean age of 38.84 ± 9.7 (12-79) years. Systemic findings were present in 17 (68%) patients, and 17 (68%) had a cardiac presentation. 10 (40%) patients had retrosternal pain/ chest pain, 10 (40%) patients had pericardial frontman, and five (%10) cases had tachycardia. The most commonly used diagnostic method

ÖZET

Amaç: Bruselloz en sık görülen zoonotik enfeksiyon hastalıklarından biridir ve özellikle gelişmekte olan ülkelerde halk sağlığı sorunlarından biridir. Bruselloz sistemik semptomlara neden olabilmekte ve vücudun farklı bölgelerini etkileyebilmektedir. Brusella perikarditi kardiyovasküler sistemin seyrek görülen bir tutulumu olup bu çalışmada brusellozun perikardial tutulumunun klinik sonuçlarının araştırılması amaçlanmıştır.

Yöntem: Dört uluslararası çevrimiçi veri tabanının tam metin ve özetleri "*Brucella*" ve "perikardit" anahtar kelimeleri ile tarandı. Olguların yaş ve cinsiyet, yayın yılı ve ülkesi, tanı yöntemleri, aldıkları tedaviler ve klinik sonuçları havuz analizi yönetemiyle incelendi. İstatistiksel değerlendirmede tanımlayıcı istatistikler kullanıldı.

Bulgular: Çalışmaya yaş ortalaması 38.84 ± 9.7 (12-79) yıl olan 25 olgu (14 erkek, %56) dahil edildi. Hastaların 17 (%68)'sinde sistemik bulgular mevcuttu ve 17 (%68)'si kardiyak belirtilerle başvurmuştu. On (%40) hastada retrosternal ağrı/göğüs ağrısı, 10 (%40) hastada perikardiyal frotman ve beş (%10) olguda taşikardi saptandı. En sık kullanılan tanı yöntemi

[1]Turkish Ministry of Health, General Directorate of Public Health, Department of Communicable Diseases, Ankara
[2]Evliya Çelebi Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Kütahya
[3]Çanakkale Onsekiz Mart University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Çanakkale
[4]Çanakkale Onsekiz Mart University Faculty of Medicine, Department of Cardiology, Çanakkale

İletişim / Corresponding Author : Oğuz EVLİCE
Halk Sağlığı Genel Müdürlüğü, Adnan Saygun cad. No: 55 Sıhhiye / Ankara - Türkiye
E-posta / E-mail : oguzevlice@hotmail.com

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was a serological test (96%), and a positive blood culture result was determined in 64%. The Rose Bengal test was performed in seven cases, of which six had positive results. Complete recovery was reported for 22 cases, and death in two patients.

Conclusion: Although brucellosis is less common in many developed countries, it should be keep in mind differential diagnosis in endemic areas. Brucellosis is a rare cause of pericarditis and requires specific treatment. Standard tube agglutination tests are highly sensitive and specific in the diagnosis of brucellosis. This non-invasive, practical test should be used in the differential diagnosis of pericarditis.

Key Words: *Brucella*, brucellosis, brucellar pericarditis, pericarditis, cardiovascular system

serolojik testlerdi (%96) ve bunu kan kültürü pozitifliği takip ediyordu (%64). Rose Bengal testi yedi hastaya yapılmış olup altısında pozitifti. İyileşme 22 (%88) hasta için bildirilirken iki (%8) hasta kaybedilmişti.

Sonuç: Bruselloz nadir görülen bir perikardit nedenidir ve özgün tedavi gerektirir. Bruselloz birçok gelişmiş ülkede sık görülmese de, endemik bölgelerde ayırıcı tanıda akılda tutulmalıdır. Standart tüp aglütinasyon testleri tanıda oldukça duyarlı ve özgüldür. Bu non-invazif, pratik test perikarditin ayırıcı tanısında kullanılmalıdır.

Anahtar Kelimeler: Brusella, bruselloz, brusella perikarditi, perikardit, kardiyovasküler sistem

INTRODUCTION

Brucellosis is a bacterial zoonosis transmitted directly or indirectly to humans from infected animals. Brucellosis is observed more frequently in developing countries and has been practically eradicated in developed countries (1). As *Brucella* spp. causes systemic infections, it should be considered in the differential diagnosis of many diseases (2,3). In endemic areas, it may be challenging to distinguish brucellosis from many other causes of fever. Osteoarticular, genitourinary, or hematological involvement are the most frequent complications of brucellosis, whereas cardiac involvement is a rare presentation of this disease. (4,5). Infective endocarditis (IE) (natural or prosthetic valves), myocarditis and pericarditis are rare cardiac involvements in patients with brucellosis, of which infective endocarditis is the most common type (5,6). Brucellar pericarditis is an extremely rare cardiovascular system involvement (5-7).

Although several recent studies have evaluated cardiovascular involvements of *Brucella* infections, the management and outcomes of brucellar pericarditis have not yet been discussed in detail. This study aimed to investigate cases of pericardial involvement of brucellosis and highlight key points in the literature through a discussion of the clinical characteristics and management of previously published brucellar pericarditis cases.

MATERIAL and METHOD

A search was made of four online international databases (Google Scholar, PubMed/Medline, Web of Science, and Scopus) for studies related to brucellar pericarditis published between January 1, 1950, and August 15, 2021. The database search was performed in the English language. The full texts (or the abstract when the full text was not available) were screened with the keywords, '*Brucella*' or '*Brucella* spp.' and 'pericarditis' or 'pericardial effusion' or 'cardiac

tamponade'. Publications reporting pediatric cases younger than 12 years were excluded. A total of 19 publications that were relevant to the topic were obtained from the literature search (Table 1) (8-26). The acquired data were analyzed and presented as mean standard deviation values, numbers, and percentages using the Statistical Package for the Social Sciences (SPSS) for Windows, version 23.0 (SPSS Inc., Chicago, IL, USA). In the statistical evaluation, descriptive statistics were used. Because the study was designed as a literature review, ethics committee approval was not necessary.

Table 1. Summary of published cases

No of cases	Author/Country/ year	Age/ Gender	Cardiac presentation	Microbiological diagnostic method and results	Therapy /duration	Outcome
1	Altas et al / Turkey/2018 (8)	12/F	Isolated pericarditis, pericardial effusion	Rose Bengal: + STA:+ Blood culture: Negative	Doxycycline rifampicin (for 6 weeks) and streptomycin (for two weeks)	Complete recovery
1	Chevalier et al/ France/1996 (9)	21/?	Pancarditis	Rose Bengal: NI* STA:NI* Blood culture: Positive (*B.melitensis*)	Doxycycline and rifamycine (1 week)	Exitus
1	Chocarro et al/ Spain /2002 (10)	17/M	Isolated pericarditis	Rose Bengal: + STA:+ Blood culture: Positive (*B.melitensis*)	Doxycycline +rifampicin+ TMP/SXT plus acetyl salicylic acid/ (8 weeks)	Complete recovery
1	Demirdağ et al/ Turkey /2005 (11)	50/F	Isolated pericarditis	Rose Bengal:+ STA:+ Blood culture: Positive (*B.melitensis*)	Doxycycline+ rifampicin (6 weeks)	Complete recovery
1	Garcia et al/ Spain/2004 (12)	29/M	Myopericarditis	Rose Bengal:- STA:+ Blood culture: Positive (*B.melitensis*)	Streptomycin +Doxycycline (6 weeks)	Complete recovery
2	Gatselis et al/ Greece/2011 (13)	17/M	Myopericarditis	Rose Bengal :NI STA:+ Blood culture: Positive (*Brucella spp.*)	Doxycycline +rifampicin (12 weeks) PLUS streptomycin (3 weeks)	Complete recovery
		34/M	Isolated pericarditis	Rose Bengal:NI STA:+ Blood culture: Positive (*Brucella spp.*)	Doxycycline +rifampicin (12 weeks)	Complete recovery
	Gomez-Huelgas et al /Spain/1986 (14)	39/F	Isolated pericarditis	Rose Bengal :NI Coombs:- Blood culture: positive (*B.melitensis*)	Doxycycline (4 weeks) + Streptomycin (2 weeks)	Complete recovery
2	Hatipoglu et al./ Turkey/2004 (15)	62/F	Isolated pericarditis	Rose Bengal:NI STA:+ Blood culture: negative Brucella SAT positivity in pericardial fluid	Gentamicin (2 weeks) + doxycycline and ciprofloxacin (6 weeks)	Complete recovery
		64/F	Isolated pericarditis	Rose Bengal: NI STA:+ Blood culture: Positive (*B.melitensis*)	Doxycyclin+ ofloxacin and rifampicin (24 weeks)	Complete recovery

Table 1 (cont). Summary of published cases

No of cases	Author/Country/ year	Age/ Gender	Cardiac presentation	Microbiological diagnostic method and results	Therapy /duration	Outcome
1	Karagiannis et al./ Greece/2003 (16)	55/M	Cardiac tamponade	Rose Bengal: NI STA:+ IgG and IgA +	Doxycycline (6 weeks), streptomycin (2 weeks) and indomethacin (2 weeks)	Complete recovery
4	Kayaet al. / Turkey/2013 (17)	79/F	Isolated pericarditis	Rose Bengal: NI STA:+ Blood culture: Negative	Doxycycline+ rifampicin (8 weeks)	Complete recovery
		51/F	Isolated pericarditis	Rose Bengal: NI STA:+ Blood culture: Positive (*Brucella melitensis*)	Doxycycline + rifampicin	Lost to follow-up
		33/M	Isolated pericarditis	Rose Bengal: NI STA:+ Blood culture: Negative	Doxycycline+ rifampicin (8 weeks) and streptomycin (3 weeks)	Complete recovery
		51/F	Isolated pericarditis	Rose Bengal: NI STA:+ Blood culture: Negative	Doxycycline + rifampicin (8 weeks) and streptomycin (2 weeks)	Complete recovery
1	Khorasani et al. / Iran/2014 (18)	22/M	Myopericarditis	Rose Bengal: NI STA:+ Blood culture: *Brucella* spp.	Co-trimoxazole, rifampin doxycycline (12 weeks)	Complete recovery
1	Pedro et al. / Brazil/2012 (19)	31/M	Isolated pericarditis	Rose Bengal:+ Brucella IgG:-and IgM :+ STA: NI Blood culture: *Brucella* spp.	Doxycycline+ rifampicin (6 weeks)	Complete recovery
1	Sabzi et al. / Iran/2017 (20)	50/F	Isolated pericarditis	Rose Bengal: NI Wright test titer, Coombs wright and 2 mercaptoethanol (2ME): positive Blood culture: positive (*B. melitensis*)	Doxycycline + Rifampicin (6 weeks) and streptomycin (3 weeks) PLUS ibuprofen (6 weeks)	Complete recovery
1	Sarı et. al / Turkey/2012 (21)	25/M	Constructive pericarditis and cardiac tamponade	Rose Bengal:NI STA:+ Brucella IgG and IgM :+ Blood culture:NI Brucella SAT positivity in pericardial fluid	Doxycycline, rifampicin (8 weeks) PLUS prednisolone (2 weeks)	Complete recovery
1	Sırmatel/ Turkey/1993 (22)	?/M	İsolated pericarditis	Rose Bengal:NI STA:+ Blood culture:NI pericardial fluid culture: positive (*B. melitensis*)	Doxycycline + rifampicin (8 weeks)	Complete recovery

Table 1 (cont). Summary of published cases

No of cases	Author/Country/ year	Age/ Gender	Cardiac presentation	Microbiological diagnostic method and results	Therapy /duration	Outcome
1	Soudbakhsh et. al / Iran/2011 (23)	35/M	İsolated pericarditis	Rose Bengal :NI STA:+ 2-Mercaptoethanol, anti-*Brucella* IgG and IgM :+ Blood culture: negative bone marrow and pleural fluid cultures: negative	Doxycycline+ rifampicin (12 weeks) and streptomycin (2 weeks)	Complete recovery
1	Tatlı Kıs&Kıs/ Turkey/2020 (24)	19/M	İsolated pericarditis	Rose Bengal :+ Coombs:+ Blood culture: positive (*Brucella spp.*)	Doxycycline + rifampicin TMP/SXT and ibuprofen (12 weeks)	Complete recovery
2	Ugartemendia et al./ Spain/1985 (25)	48/F	Pericardial effusion+ cardiac tamponade	Rose Bengal:NI STA:+ Blood culture: positive (*B. melitensis*)	TMP/SXT + streptomycin, tetracycline (3 weeks) PLUS prednisone (6 weeks)	Complete recovery
		52/M	Pericardial effusion+cardiac tamponade	Rose Bengal:NI STA:+ Blood culture: positive (*B. melitensis*)	TMP/SXT + streptomycin, etracycline, and rifampicin (3 weeks)	Exitus
1	Zorlu et al. / Turkey /2017 (26)	50/M	İsolated pericarditis	Rose Bengal :+ STA:+ anti-Brucella IgG and IgM :+ Blood culture: positive (*Brucella spp.*)	Doxycycline +rifampicin (12 weeks)	Complete recovery

ECG:Electrocardiography, PE: Physical examination, EF: Ejection fraction, NI: no information, STA : standard tube agglutination, TTE: Transthoracic echocardiography, TEE: Trans Esophageal Echocardiography, TMP/SXT:Trimetoprim/sulfametoksazol

RESULTS

The evaluation comprised 19 publications reporting 25 cases, including 14 (56%) males and 11 (44%) females with a mean age of 38.84 ±9.7 years. Concomitant systemic brucellosis was determined in 72.2% of the patients, and 68% had a cardiac presentation. Retrosternal pain/chest pain (40%) and tachycardia (40%) were the most common symptoms of brucellar pericarditis. The most commonly used diagnostic method was a serological test (96%), and blood culture positivity was determined in 64% (*Brucella melitensis* in 10 cases, *Brucella* spp. in 6 cases). The Rose Bengal test was performed in seven cases, of which six had positive results. Complete recovery was recorded in 22 cases, mortality developed in two, and one patient was lost to follow-up. The results of the analyses of the cases are shown in Table 2.

DISCUSSION

Cardiovascular involvement of brucellosis includes endocarditis, myocarditis, pericarditis, and mycotic aneurysms (7,20,27,28). Endocarditis is the most common cardiovascular complication, accounting for approximately 1% of all brucellosis cases, and mortality in brucellosis is mainly attributed to endocarditis (1,29). The clinical manifestations of brucellar pericarditis range from no symptoms or

Table 2. Pooled analyses of published cases

	n (=25)	%
Gender (male)	14	56
Cardiac presentation* (two different presentations in some cases)		
Isolated brucellar pericarditis	17	68
Cardiac tamponade	4	16
Myopericarditis	3	12
Pancarditis	1	4
Constructive pericarditis	1	4
Concomitant clinical findings		
Systemic brusellosis	17	68
Lobar pneumonia	1	4
Pleural effusion	3	12
Lomber pain	1	4
Paraspinal abscess	1	4
Brucellosis and tuberculosis co-infection	1	4
Swelling in the testis	1	4
NI	3	12
none	2	8
***Brusella spp*. isolation of blood cultures**		
B. melitensis	10	40
Brucella spp.	6	24
Laboratory tests		
Blood cultures	22	88
Pericardial fluid cultures	1	4
Serological testes	24	96
Pericardial fluid serological tests	2	8
Histopathological examination	1	4
PE findings		
NI	5	20
Retrosternal pain/ chest pain	10	40
Pericardial frotman	5	20
Tachycardia	10	40
ECG findings		
ST elevation	2	8
NI	8	32
T wave abnormalities (negative t wave in leads, ST elevation)	6	24
Normal	3	12
Atrial fibrillation	1	4
Low QRS complexes	2	8
TTE findings		
Pericardial effusion	21	84
Abscess formation	1	4
Additional therapies		
Acetyl salicylic acid	2	8
İndomethacin	1	4
Corticosteroids	2	8
Outcome		
Complete recovery	22	88
Exitus	2	8
Lost to follow-up	1	4

PPE: Physical examination, ECG:Electrocardiography, EF: Ejection fraction, NI: No information, TTE: Transthoracic echocardiography

mild symptoms to cardiac tamponades (17,19). İn this pooled analysis, 17 (%68) isolated brucellar pericarditis, four (%16) cardiac tamponade, three (%12) myopericarditis, one (%4) pancarditis, one (%4) constructive pericarditis were found.

Pericarditis in the absence of concomitant endocarditis is extremely rare, and there were seen to be only 25 cases in four international databases.

The highest number of cases was reported from Türkiye with 12 cases. In a study from Spain, isolated brucellar pericarditis was detected in only one of 530 cases. It was reported that of the 530 brucellosis cases, 1.5% (8/530) showed cardiac involvement, and only one patient (0.2%) was diagnosed with pericarditis without concurrent endocarditis (30). In another study, Gür et al. reported endocarditis with concomitant myocarditis and pericarditis in only two of a total of 283 cases (31). As the myocardium and pericardium are contiguous, brucellar myocarditis and pericarditis may coexist. Myocarditis clinical manifestations range from subclinical disease (asymptomatic ECG abnormalities) to fulminant heart failure. It should be considered that there may be ECG abnormalities and global left ventricular dysfunction on echocardiography (5,28,32,33).

Two theories have been proposed regarding the development mechanism of brucellar pericarditis. Cardiac damage may occur due to the direct effect of *Brucella* infection on pericardial tissue (demonstrated in pericardial fluid obtained by pericardiocentesis), or immune complexes may be involved (25).

The pericardial involvement of brucellosis should be differentially diagnosed from viral, pyogenic, tuberculous, and fungal pericarditis. Most enteroviral myocarditis or pericarditis cases occur in newborns, adolescents, or young adults. Pyogenic pericarditis is usually secondary to cardiothoracic operations as an extension of the infection from the lungs or pleural cavities. Tuberculous pericarditis is a common cause of chronic pericardial effusion, especially in developing countries where active tuberculosis and HIV are endemic (34-36).

The diagnosis of brucellar pericarditis is based on the clinical and epidemiological characteristics of the disease, the patient's symptoms, echocardiography and computed tomography findings, results of serological tests, and isolation of the microorganism, especially by blood culture analysis (30,31). Retrosternal pain, fever, and dyspnea are common symptoms (20,30). Echocardiography is the most widely used imaging technique, as it is sensitive, simple, non-invasive, and allows localization and estimation of the quantity of pericardial fluid (37). Pericardiocentesis may yield an etiological agent, but it is negative in the majority of patients. When an invasive procedure is necessary for diagnosis, pericardiotomy with biopsy and drainage is preferable to pericardiocentesis because of the higher diagnostic rate (20,38). The standard tube agglutination test (STA) is the most frequently utilized test for detecting Brucella antibodies. STA in the diagnosis of brucellosis are very sensitive and specific. Clinical evidence and agglutination test values ≥1/160, or Coombs' test with a fourfold increase in agglutination, were used as a diagnosis of brucellosis (39). This non-invasive, practical test should be used in the differential diagnosis of pericarditis.

There have been no reports in the literature of any specific, evidence-based therapeutic regimen for brucellar pericarditis in the absence of endocarditis. Brucellar endocarditis almost always requires surgery plus antibiotic treatment, while surgery is not indicated in brucellar pericarditis unless tamponade develops. Brucellar pericarditis is treated with at least two drugs (an aminoglycoside, a tetracycline, and/or rifampin), and treatment is usually applied for at least six weeks (13,40).

Although brucellosis is less common in many developed countries, it should be considered a differential diagnosis in endemic areas. Brucellosis should be considered in the etiology of pericarditis. Agglutination tests should be used in the differential diagnosis of pericarditis. Further studies are needed to evaluate and discuss the management and treatment of this disease.

ETHICS COMMITTEE APPROVAL

* This study does not require Ethics Committee Approval.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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