ORIGINAL ARTICLE

Clinical characteristics and intermediate-term outcomes of young patients with uncomplicated myopericarditis

Komplikasyonsuz miyoperikardit geçiren genç hastaların klinik özellikleri ve orta süreli izlem sonuçları

Kudret Keskin, M.D., Gökhan Çetinkal, M.D., Süleyman Sezai Yıldız, M.D., Serhat Sığırcı, M.D., Güneş Melike Doğan, M.D., Kadriye Orta Kılıçkesmez, M.D.

Department of Cardiology, Health Sciences University Şişli Hamidiye Etfal Training and Research Hospital, İstanbul, Turkey

ABSTRACT

Objective: Although the long-term prognosis of myopericarditis is good, recurrence continues to be a problem. In addition, there are concerns regarding the safety of the empirical use of anti-inflammatory drugs. This study was an investigation of the clinical outcomes of young patients with uncomplicated myopericarditis, the majority of whom received both nonsteroidal anti-inflammatory drugs and colchicine.

Methods: Patients aged 18 to 40 years who were admitted between May 2015 and May 2018 due to myopericarditis and had normal left ventricular function were included in the study. The primary outcome of the research was analysis of major adverse cardiac events (MACEs): all-cause mortality, myopericarditis recurrence, development of significant arrhythmia, heart failure, and cardiac tamponade. A total of 60 patients were included in the study. The median duration of follow-up was 19 months.

Results: A MACE occurred in 11.7% of the patients. None of the patients experienced heart failure, significant arrhythmia, cardiac tamponade, or all-cause mortality. Recurrence of myopericarditis was the only MACE observed. Most patients were treated with both nonsteroidal anti-inflammatory drugs and colchicine (96% and 95% of the patients, respectively). Univariate cox regression analysis indicated that only the maximum in-hospital C-reactive protein (CRP) level was associated with recurrence (hazard ratio: 1.01, 95% confidence interval: 1.01–1.02; p=0.04).

Conclusion: The intermediate-term prognosis of myopericarditis patients was excellent in terms of mortality. However, recurrence remains a challenge. The role of CRP, particularly in recurrence, should be explored further.

ÖZET

Amaç: Her ne kadar miyoperikarditin uzun dönem prognozunun iyi oldugu bildirilmiş olsa da, nüks gelişimi sorun olmaya devam etmektedir. Ayrıca, ampirik olarak kullanılan anti-enflamatuvar ilaçların güvenilirliği için de bazı endişeler bulunmaktadır. Bu nedenle, çalışmamızda komplikasyonsuz miyoperkardit geçirmiş ve çoğunluğu nonsteroid antienflamatuvar ilaç ve kolşisin ile tedavi edilmiş genç hastaların klinik sonuçlarını araştırdık.

Yöntemler: Mayıs 2015 ile Mayıs 2018 tarihleri arasında, miyoperikardit nedeniyle hastaneye yatan, normal sol ventrikül fonksiyonuna sahip, 18–40 yaş arası hastalar çalışmaya dahil edildi. Çalışmanın birincil sonlanım noktası, tüm nedenlere bağlı ölüm, miyoperikardit nüksü, aritmi, kalp yetersizliği ve kardiyak tamponad gelişimini içeren majör kardiyak olaylardı. Çalışmaya toplam 60 hasta dahil edildi. Ortalama izlem süresi 19 aydı.

Bulgular: Majör kardiyak olaylar hastaların %11.7'sinde meydana gelmiş olup bu oran, esas olarak miyoperikardit nüksüne bağlıydı. Hiçbir hastada kalp yetersizliği, belirgin aritmi, kalp tamponadı ve tüm nedenlere bağlı ölüm izlenmedi. Hastaların çoğu nonsteroid antienflamatuvar ilaçlar ve kolşisin ile tedavi edildi (sırasıyla, %96 ve %95). Tek değişkenli Cox regresyon analizinde, sadece hastane içi maksimum C-reaktif protein düzeyleri, nüks gelişimi ile ilişkili bulundu (HR: 1.01 [1.01–1.02, %95 GA], p=0.04).

Sonuç: Miyoperikarditin prognozu orta vadede mortalite açısından çok iyi olmasına rağmen nüks bir sorun olmaya devam etmektedir. C-reaktif proteinin özellikle nüks üzerindeki rolü daha fazla araştırılmalıdır.

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Correspondence: Dr. Kudret Keskin. Halaskargazi Cad., Etfal Sokak, Şişli Hamidiye Etfal Eğitim ve Araştırma Hastanesi, 34250 İstanbul, Turkey.
Tel: +90 212 - 543 29 29 e-mail: keskinkudret@yahoo.com

Myopericarditis refers to inflammation of both the myocardium and the pericardium, with a more pronounced degree of inflammation in the pericardium. The etiology is varied; however, autoimmune diseases, hypersensitivity reactions, and infections, particularly viral infections, are the most common causes.[1] The true incidence is unknown due to underdiagnosis, but it is believed to affect approximately 1.5 million people worldwide per year.[2] A national study in Turkey reported an incidence of 0.5% in the pediatric population during viral outbreaks.[3] The diagnosis is established with definite acute pericarditis and myocardial involvement evidenced by elevated cardiac markers of injury. Left ventricular (LV) systolic function is assessed with echocardiography or cardiac magnetic resonance imaging (CMRI).[4]

However, gaps remain in our knowledge related to the management and long-term prognosis of myopericarditis. Nonsteroidal anti-inflammatory drugs (NSAIDs), which continue to be the mainstay of treatment for pericarditis, are used cautiously in myopericarditis due to the fear that it may increase mortality.[4] There have been suggestions that NSAID doses be reduced when the myocardium is involved.[5] Similarly, there are limited data related to colchicine use, though it has been shown to decrease recurrence rates in pericarditis, leading to a class I recommendation in the guidelines.[4] Thus, in previous studies the administration of colchicine in cases of myopericarditis has been limited to a maximum of 20%.[6] Although the long-term prognosis of myopericarditis is generally favorable, relapse continues to be a clinical problem, with the incidence estimated to be 10% to 15%.[7] It is difficult to predict which patients will develop recurrent attacks or experience serious events. Given the lack of data, the objective of this study was to examine clinical characteristics and major adverse cardiac events (MACEs) in uncomplicated myopericarditis patients, the majority of whom were treated with both NSAIDs and colchicine.

METHODS

Patients

The records of patients aged 18 to 40 years who were admitted to the cardiology clinic due to myopericarditis between May 2015 and May 2018 were investigated retrospectively and the baseline clinical characteristics, laboratory values, and echocardiogram results were evaluated. Patients were excluded if they had only pericarditis (normal troponin values), an LV ejection fraction <55%, equivocal test results, or concomitant autoimmune diseases.

Abbreviations:

CMRI	*Cardiac magnetic resonance imaging*
CRP	*C-reactive protein*
ECG	*Electrocardiogram*
EMB	*Endomyocardial biopsy*
LV	*Left ventricle*
MACE	*Major adverse cardiac event*
NSAID	*Nonsteroidal anti-inflammatory drug*

The diagnosis of myopericarditis was based on the criteria in the 2015 European Society of Cardiology pericardial disease guidelines: Patients who had definite signs and symptoms of pericarditis along with elevated cardiac injury markers.[4] The symptoms and signs pertinent to pericarditis were chest pain, pericardial friction-rub, widespread ST-segment elevation or PR depression on an ECG, and new or worsening pericardial effusion.

Clinical outcomes

MACE findings, defined as all-cause mortality, myopericarditis recurrence, and the development of significant arrhythmia (life-threatening or requiring specific antiarrhythmic drug), heart failure, or cardiac tamponade, were the primary endpoint of our study. Hospital records were reviewed to determine in-hospital mortality. MACEs resulting in intermediate-term mortality were investigated via direct patient contact, telephone interview, and the national e-pulse database. Patient statements and hospital records in the e-pulse database were reviewed for recurrence and arrhythmia. Evidence of hospital admission due to myopericarditis or any specific cardiac condition described in the definition of MACE, an elevated troponin level consistent with myopericarditis measured in the emergency department, and the administration of any cardiac drug, in particular, antiarrhythmic drugs, and any documentation of life-threatening arrhythmias were evaluated. Approval for the study was granted by the local ethics committee on August 28, 2018 (no: 2092).

Statistical analysis

Distribution of the study data was assessed using the Kolmogorov-Smirnov test. Continuous variables were reported as mean±SD or median and interquartile range. Categorical variables were reported as numbers and percentages. Continuous variables were compared

between groups using an independent sample t-test or the Mann-Whitney test. Categorical data were compared using a chi-square test or Fisher's exact test. Univariate Cox regression analysis was performed to predict myocarditis relapse. A receiver operating characteristic curve was created to assess the cut-off value for the level of C-reactive protein (CRP) and Cohen's kappa statistic was used to determine sensitivity and specificity. A 2-tailed p value <0.05 was considered statistically significant. All of the analysis was performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 60 patients were included in the final analysis. Baseline clinical characteristics, laboratory values, and medications are presented in Table 1. The mean age was 24.6±6.1 years and the majority of the patients were male (n=58, 96.7%). All of the patients had preserved LV function with a mean discharge LV ejection fraction of 60.2±4.3%. The mean maximum troponin I and CRP level during the hospital stay was 1012.3±3438.4 ng/mL and 67.7±64.4 mg/dL, respectively. No obstruction was detected in the coronary angiography of 18 (30%) patients. Electrocardiogram results indicated that 27 (45.0%) patients had dynamic ST-T wave changes and 23 (38.3%) presented with ST elevation mimicking acute coronary syndrome. During discharge, use of NSAIDs and colchicine was recommended for 58 (96.0%) and 57 (95.0%) patients, respectively.

Primary end-point was observed in 7 (11.7%) patients which were the cases of recurrent myopericarditis at all. The follow-up data of 5 patients was available at our hospital records, however, the follow-up details of the remaining 2 patients have been retrieved from the national e-pulse system. During a median 19 months (min-max: 10–28 months) of follow-up, there was no instance of all-cause mortality. None of the patients developed heart failure, significant arrhythmia, or cardiac tamponade. Outcomes are presented in Table 2.

All 7 of the patients who had a recurrence were male (mean age: 22.1±1.1 years). During the index admission, there was 1 case of mild pericardial effusion, 3 patients demonstrated ST segment elevation on electrocardiogram results, and 1 underwent coronary angiography in order to rule out acute ischemia.

Table 1. Baseline clinical characteristics and laboratory parameters of the study patients

	Patients (n=60)
Age (years), mean±SD	24.6±6.1 (16–40)
Gender (male), n (%)	58 (96.7)
Hypertension, n	0
Diabetes mellitus, n	0
Prior myocarditis, n (%)	2 (3.3)
Discharge LVEF (%), mean±SD	60.2±4.3
Hospital stay (days), mean±SD	4.5±1.7
Dynamic ECG changes, n (%)	27 (45.0)
ST elevation on ECG, n (%)	23 (38.3)
Pericardial effusion, n (%)	11 (18.3)
Coronary angiography, n (%)	18 (30.0)
Endomyocardial biopsy, n	0
Prodromal symptoms*, n (%)	56 (93.3)
Maximum leukocyte (x10^3), mean±SD	11.0±3.3
Hemoglobin (g/dL), mean±SD	14.3±1.2
Platelet (x10^3), mean±SD	224.8±83.7
In-hospital maximum Troponin I (ng/L)#	7.0 (1.8–24.9)
In-hospital maximum CRP (mg/dL)#	43.2 (19.7–93.1)
ALT (IU/mL), mean±SD	30.8±5.8
AST (IU/mL), mean±SD	45.5±34.2
Glucose (mg/dL), mean±SD	106.2±16.0
Creatinine (mg/dL), mean±SD	0.8±0.1
Discharge therapy, n (%)	
Colchicine	57 (95.0)
NSAID	58 (96.0)
Steroid	1 (1.6)
NSAID use after discharge (days), mean±SD	11.0±3.0
Colchicine use after discharge (months), mean±SD	2.0±0.3 (1–6)

LVEF: Left ventricular ejection fraction; ECG: Electrocardiogram; CRP: C-reactive protein; ALT: Alanine transaminase; AST: Aspartate transaminase; NSAID: Nonsteroidal anti-inflammatory drug; SD: Standard deviation. *Prodromal symptoms refers to preceding upper respiratory tract or gastrointestinal infections and fever. #Numbers represent median (Q1-Q3).

The results of univariate Cox regression analysis, which included age, ST elevation on ECG, presence of pericardial effusion, and maximum serum troponin I and C-reactive protein (CRP) level as covariates, are presented in Table 3. The only variable associated with myopericarditis recurrence was the in-hospital maximum CRP level (hazard ratio: 1.01, 95% confi-

Table 2. Major adverse cardiac events

	Patients (n=60)
In-hospital death	0
In-hospital arrhythmia	0
Post-discharge events	
Median follow-up, months; median (Q1-Q3)	19 (10–28)
Myocarditis recurrence	7 (11.7%)
Time for recurrence, months; median (Q1-Q3)	24 (1.5–27)
Hospitalization	7 (11.7%)
Cardiac tamponade	0
Heart failure	0
Arrhythmia treatment	0
All-cause mortality	0

Table 3. Univariate Cox logistic regression analyses of variables related to myopericarditis recurrence

	Univariate analysis		
	HR	95% CI	*p*
Age	0.95	0.79–1.13	0.59
Maximum cTnI	0.98	0.90–1.07	0.75
Maximum CRP	1.01	1.01–1.02	0.04
ST elevation	1.09	0.21–5.25	0.91
Pericardial effusion	1.28	0.14–11.35	0.82

HR: Hazard ratio; CI: Confidence interval; cTnI: Cardiac troponin I; CRP: C-reactive protein.

dence interval: 1.01–1.02; p=0.04). Values above 80 mg/dL had a 70% sensitivity and 75% specificity for future events. CRP value and myopericarditis recurrence are illustrated in Figure 1.

DISCUSSION

Recurrence of myopericarditis was the only MACE recorded in this study. No case of all-cause mortality, heart failure, or significant arrhythmia was identified during follow-up. Similarly, no complications were observed during the index hospitalization. Cox regression analysis showed that only the in-hospital maximum serum CRP level, which reflected the severity of inflammation, was associated with recurrence. In addition, it was noteworthy that all of the cases of recurrence were male patients.

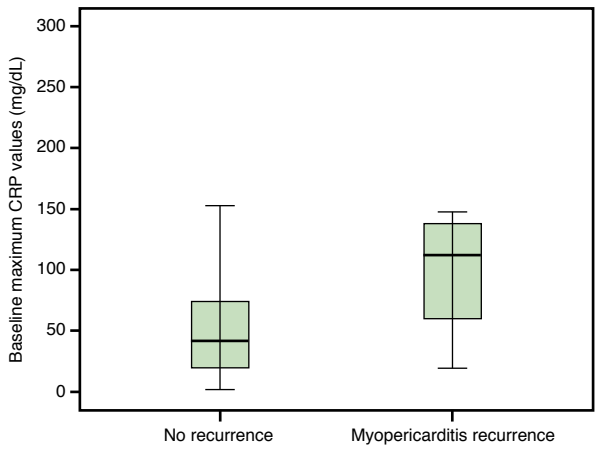

Figure 1. Serum C-reactive protein level and the recurrence of myopericarditis.

The degree of LV dysfunction appears to play a key role in future cardiac events, whether it is myocarditis alone or when inflammation of the pericardium is more pronounced. Ammirati et al.[8] recently conducted a thorough analysis of myocarditis patients based on LV function and demonstrated that cardiac events increased substantially in patients who presented with heart failure, significant LV dysfunction, or ventricular tachycardia. Patients with preserved LV function had a favorable long-term outcome, with only a 0.3% all-cause mortality rate. Similarly, a comprehensive meta-analysis of patients with myopericarditis also demonstrated that patients with preserved LV function had an excellent long-term outcome with no reported mortality. Despite favorable outcomes, however, the recurrence rate was 10%.[6] Our findings were consistent with the literature. We observed no fatalities and had a similar recurrence rate over a 19-month follow-up period.

When it comes to treatment, there are several controversial issues. Contrary to pericarditis, in which NSAIDs and colchicine constitute the main pillar of therapy, the safety of these agents has been questioned when the myocardium is involved. Some experimental models have indicated that the administration of NSAIDs in the context of myocarditis may enhance inflammation and lead to increased mortality.[9,10] The administration of colchicine is also a concern.[11] There are some indications based on preclinical studies suggesting that it may increase mortality.[12] Therefore,

the clinical data for the use of these drugs in cases of myopericarditis remains inconclusive, but nevertheless, these agents are used empirically in clinical practice. Since both NSAIDs and colchicine were administered to the majority of our patients (>95%) in our study without complication, it may be that when LV function is preserved, the use of both agents may be safe without a dose reduction. To the best of our knowledge, no prior study has reported such a high rate of colchicine use in these patients. However, we acknowledge that the mean duration of colchicine use was only 2 months after discharge. It is unknown whether a longer duration of colchicine use would have led to lower recurrence rates. Nevertheless, our findings suggest that these agents can be sued safely both in-hospital and short-term after discharge.

One other noteworthy finding of our study was the male predominance, which has been reported in the literature and is believed to be due to hormone levels, particularly estrogen.[13] Some studies have reported that natural killer cells play a significant role in gender bias in Coxsackievirus-induced myocarditis. Zhou et al.[14] observed that ovariectomized female mice with decreased estrogen levels exhibited substantially increased enrichment of cardiac IFN-gþ natural killer cells and displayed significantly aggravated myocarditis. Estrogen-treated male mice demonstrated less cardiac infiltration with significantly alleviated viral myocarditis. However, there are no clinical studies investigating this gender gap in myocarditis and more research is needed.

Another finding of our research was the relationship between the in-hospital CRP level and future myopericarditis recurrence. Unlike the troponin level, which has been shown to have no prognostic value in these cases, CRP may hold promise as a marker of inflammation.[6] There are a limited number of studies that have reported a correlation between serum CRP level and myocardial damage detected using CMRI and late gadolinium enhancement.[15] A CRP level >80 mg/dL had a 70% sensitivity and 75% specificity for the prediction of recurrence. A prognostic role of CRP in myocarditis needs to be confirmed in large-scale studies.

Finally, obtaining an endomyocardial biopsy (EMB), while recommended by the European Society of Cardiology guidelines for all patients with myocarditis, should be reassessed in the context of myopericarditis.[1] Given the low incidence of events in myopericarditis and the complications related to an EMB, the diagnostic and therapeutic yield is likely to be low.[16] Therefore, the need for an EMB should be individualized according to the patient, and probably confined to those with LV dysfunction.

There are some limitations to this study. In addition to being a single-center, retrospective study, the number of patients was relatively small due to the rarity of the disease. Although an EMB is not required in uncomplicated cases according to the American Heart Association guidelines, the lack of EMB and CMR results is a limitation.[17] We also did not perform coronary angiography on all of the study patients because most were young without any risk factors for coronary artery disease and the likelihood of acute coronary syndrome was too low to justify an invasive procedure.

Conclusion

Patients with uncomplicated myopericarditis and preserved LV systolic function had an excellent intermediate-term prognosis with regard to mortality and the development of heart failure or significant arrhythmia. The in-hospital maximum CRP level during index hospitalization for myopericarditis may predict recurrence at intermediate-term follow-up.

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Anahtar sözcükler: Antienflamatuvar tedavi; kolşisin; miyoperikardit; nüks.