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Recurrent pericarditis: a case report and literature review

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Background. Recurrence affects about 30% (20% to 50%) of patients within 18 months after the initial episode of acute pericarditis resulting in subsequent rehospitalizations. Bearing in mind high treatment costs of patients admitted to hospital with acute and recurrent pericarditis, there is a need to optimize the treatment of both of these conditions.

Materials and methods. We present a case of recurrent pericarditis. The first episode of pericarditis was diagnosed in 2006. Three months later the patient was hospitalized due to clinical symptoms suggesting recurrence of a past condition. Ten years after the initial episode of acute pericarditis the patient was hospitalized for the treatment of recurrent pericarditis. The search for etiology of the disease was unsuccessful, the patient received treatment with nonsteroidal anti-inflammatory drugs; empiric antimicrobial therapy was also administered.

Results and conclusions. Acute pericarditis is the most common disease of the pericardium encountered in clinical practice. Colchicine has been demonstrated as a first-line drug to be added to conventional anti-inflammatory therapies in patients with a first episode of pericarditis or its recurrences in order to improve the response to therapy and reduce recurrences. Despite a large amount of new data, there are still several issues that require additional research and clarification, including the search for new individualized therapies, the best duration of treatment for patients with pericardial diseases, and optimization of patient follow-up in order to collect data on long-term outcomes that would allow shortening the duration of in-patient treatment and reduction of recurrences.

Keywords: acute pericarditis, recurrent pericarditis, transthoracic echocardioscopy, fever, leukocytosis

INTRODUCTION

The pericardium is a thin avascular sac composed of two layers, serosal and fibrous. It prevents acute distension of cardiac chambers and optimizes diastolic filling. A physiologic amount of pericardial fluid (approximately 30 to 50 ml) allows the heart to move freely within the pericardial sac (1). The main pericardial syndromes encountered in clinical practice include pericarditis (acute, subacute, chronic, and recurrent), pericardial effusion, cardiac tamponade, constrictive pericarditis, and

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pericardial masses. Manifesting with or without pericardial effusion, acute pericarditis is the most common inflammatory pericardial syndrome encountered in clinical practice (2). The frequency of pericarditis varies from country to country and there is no reliable data on the morbidity of the Lithuanian population. Data collected from the Finnish National Registry showed a total standardized incidence rate of hospitalizations for acute pericarditis of 3.32 per 100,000 person-years with the incidence rate 2.02 times higher among men compared to women in general admitted population (3). It is important to emphasize that pericarditis is diagnosed in approximately 0.1% of patients hospitalized for chest pain and in 5% of patients admitted to the emergency department for chest pain unrelated to acute myocardial infarction (2, 4).

Recurrent pericarditis is the most troublesome complication of acute pericarditis occurring within 18 months in 30% (20% to 50%) of patients after the first episode of acute pericarditis as it can lead to repeated hospitalizations, additional treatment costs, and development of cardiac tamponade or, more rarely, constrictive pericarditis in some patients (5, 6).

We present case of recurrent pericarditis. On his first admission to the hospital, the patient received medical care at Vilnius University Hospital Santaros klinikos and was treated for acute pericarditis. A relapse of pericarditis was suspected three months after the patient was discharged from the hospital (most likely due to insufficient duration of treatment of the past condition). Ten years after the initial episode of acute pericarditis, the patient was hospitalized for the treatment of the recurrence of the disease.

Several issues and unsolved questions occur in clinical practice concerning therapeutic tactics, indications for hospitalization, and treatment duration for patients with pericarditis. These issues require additional attention considering the frequency of this pathology in the population and incidence rates of hospitalization bearing in mind that the majority of patients are those of working age. With attention to these matters, it is important to review new available treatment options (the recent studies recommend Colchicine on top of the standard anti-inflammatory therapy in order to improve the response to medical therapy, to improve remission rates, and to prevent recurrences) (2, 5), draw attention to complex clinical cases as well as search for etiology that may determine the prognosis and success in the treatment of pericardial diseases.

CASE REPORT

A 46-year-old male was admitted to hospital for treatment of recurrent pericarditis. The patient was hospitalized for treatment of acute pericarditis in 2006 complaining of chest and right shoulder pain. Other complaints at that time included a mild cold and fever lasting for several days prior to admission. The blood test showed leukocytosis – WBC 11.08 × 10^9/l (with a shift to the left) and elevated CRP 86.5 mg/l. The electrocardiogram (ECG) showed a sinus rhythm, ST segment elevation in leads I, II, III, and aVF. ECG findings remained without any changes during the hospitalization period. Mild left ventricular hypertrophy and impaired left ventricular diastolic function were seen on the transthoracic echocardiogram (TTE). The patient's condition improved with the administration of non-steroidal anti-inflammatory drugs (NSAIDs) and he was discharged after a nine-day stay in hospital with complete resolution of symptoms.

Three months after discharge, the patient was brought to the emergency department complaining of chest pain and shortness of breath present at limited physical activity and at rest. Other complaints included palpitations and fever as high as 38.5°C. The ECG showed sinus tachycardia with inverted T-wave in all ECG leads. The TTE showed pericardial effusion distributed around the heart (0.8–1 cm). Leukocytosis with a shift to the left and elevated CRP were present (WBC 12.8 × 109/l, CRP – 203 mg/l). Based on this clinical picture, recurrent pericarditis was diagnosed and the patient was hospitalized. The patient developed renal insufficiency during the period of admission (serum creatinine was 168 micromol/L). The renal function recovered after stimulating diuresis. The patient received treatment with NSAIDs (diclofenac) and 6 million units of penicillin per day intravenously. The chest computed tomography (CT) scan performed before discharge from hospital revealed a thickened pericardium of 4 mm and fibrotic changes is both lungs. A conclusion that a disease relapse

occurred, most likely, due to patient terminated treatment of acute pericarditis earlier against medical recommendation was made. Because of a slow onset, prolonged disease course, fibrotic heart and lung changes on the CT, tuberculous pericarditis was suspected but as tuberculosis was not confirmed, this diagnosis was ruled out. Seven days from admission to the hospital the patient's condition improved and he was discharged. Patient had no complaints after hospitalization.

In 2016, ten years after the treatment of recurrent pericarditis, the patient was brought by ambulance to Vilnius University Hospital Santaros klinikos with chest discomfort relieved with nitroglycerin. Other relative symptoms included shortness of breath, weakness, and fever as high as 38°C with chills. The patient had a history of smoking and was suffering from hypertension. On admission, the patient had fever of 38.1°C, blood pressure was 130/80 mmHg, pulse – 100 beats per minute, no murmur was noted on examination, and no oedema of the limbs was present. The blood test showed leukocytosis with a shift to the left (WBC 13.66 × 10^9/l), elevated CRP – 42.4 mg/L, and D-dimer – 800 mkg/L levels. In the emergency department, cardiac-enzyme levels were found to be normal. Based on laboratory findings, the patient's medical history, and the data of previous hospital admissions, recurrent pericarditis was suspected and the patient was hospitalized for further treatment and clinical investigation. The patient's high fever persisted, so blood and urine culture tests were done but both were negative for bacteria. The ECG showed sinus tachycardia and an inverted T wave in leads V1–V6 (Figure).

A moderate-sized pericardial effusion (1.7 cm) was seen on the TTE. The patient received Sol. Amoxiclavi 1.2 g twice daily, NSAIDs (prolonged-release diclofenac tablets 75 mg per day), oral perindopril, beta-blockers, and Aspirin. The patient's condition improved with the prescribed treatment, and the fever and inflammation markers started decreasing: leukocytosis 13.66 → 13 → 10.45 × 109/l, CRP 42.4 → 33.5 → 9.8 mg/L. A repeat TTE showed moderate-sized and hemodynamically insignificant pericardial effusion (less than 1 cm echo-free space apically and around the left atrium). ECG showed a sinus rhythm without other significant changes. The patient was discharged six days from admission to hospital with complete resolution of the symptoms. He was recommended to continue taking aspirin and beta-blockers, and to continue the treatment of hypertension. The patient was also urged to give up smoking and to control his body weight, and benefits of regular physical activity were also emphasized. The patient had no complaints of chest pain since the latest hospital admission; hypertension was controlled adequately.

DISCUSSION

Recurrent pericarditis is diagnosed with a documented first episode of acute pericarditis, a symptom-free interval of four-to-six weeks or longer, and evidence of subsequent recurrence of pericarditis (6). Usually symptoms of disease relapse manifest within 18–24 months, but a precise upper limit of time has not been established (5).

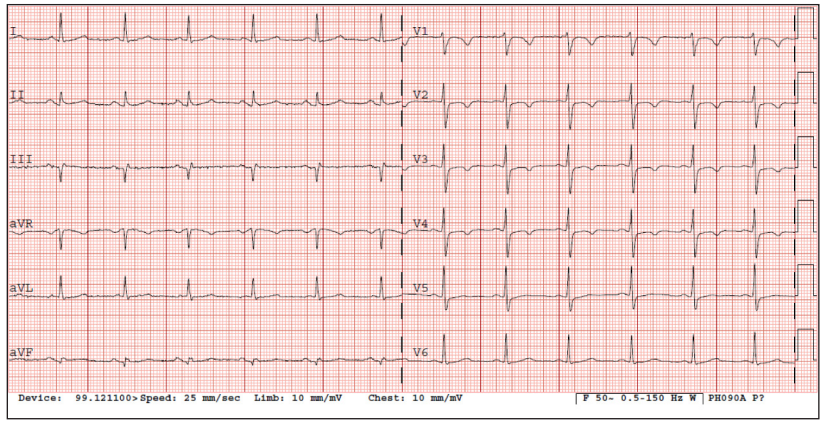

Figure. ECG (18 March 2016.). Sinus rhythm, inverted T wave in the anterior-septal wall

In developed countries, the etiology of both acute and recurrent pericarditis is often not identified and pathogenesis of recurrence is generally presumed to be immune-mediated with manifestation of the disease being a result of inadequate treatment or insufficient duration of treatment of the first episode of acute pericarditis (6). However, according to the literature, in up to 20% cases of recurrent pericarditis, additional virological studies conducted on pericardial fluid and tissue reveal a viral etiology with viruses also being the most common etiological agents of acute pericarditis (6). Viruses and other etiological agents of pericardial diseases are listed in Table 1.

Mycobacterium tuberculosis is the most common cause of pericarditis of known origin and a common cause of a protracted course of pericarditis, especially in the developing world (6, 1). In the clinical case discussed tuberculous pericarditis was suspected due to thickened pericardium and pericardial effusion observed during TTE, findings of fibrotic changes in the lungs, and gradual disease onset with such non-specific symptoms as fatigue and anorexia dominating the clinical picture. Despite these symptoms and clinical findings, tuberculous pericarditis diagnosis was ruled out.

The diagnosis of recurrent pericarditis is established according to the same criteria as those used for acute pericarditis. These criteria can be found in guidelines prepared by the European Society of Cardiologists (6). The clinical diagnosis can be made when two of the four following criteria are met: chest pain (85–90% of cases, typically sharp and pleuritic; it is alleviated by sitting up and leaning forward; sometimes pain may radiate to the neck, the left shoulder, and the jaw; also, the pain in the back and shoulders may be present due to phrenic nerve involvement which innervates the trapezius muscles (7)), pericardial friction rub (≤33% of cases, a superficial scratchy or squeaking sound best heard over the left sternal border), typical of pericarditis ECG changes (up to 60% of cases, a new widespread ST elevation or a PR depression in the acute phase), and pericardial effusion (up to 60% of cases, generally

Table 1. Etiology of pericardial diseases (6)

Infectious causes
Viral (common): enteroviruses (coxsackieviruses, echoviruses), herpes viruses (Epstein-Barr virus, cytomegalovirus), adenoviruses, parvovirus B19
Bacterial (rare): *Mycobacterium tuberculosis* (common), *Coxiella burnetii, Borrelia burgdorferi*, gram-positive cocci, gram-negative cocci, *Chlamydia* spp., *Mycoplasma* spp., *Listeria* spp., *Legionella* spp., *Leptospira* spp., *Providencia stuartii*
Fungal (very rare): *Histoplasma* spp. (more likely in immunocompetent patients), *Aspergillus* spp., *Blastomyces* spp., *Candida* spp. (more likely in immunocompromised host)
Parasitic (very rare): *Echinococcus* spp., *Toxoplasma* spp.
Non-infectious causes
Autoimmune (common): systemic autoimmune and auto-inflammatory diseases, systemic vasculitides, sarcoidosis, familial Mediterranean fever, inflammatory bowel diseases, Still disease
Neoplastic: primary tumours (rare, above all pericardial mesothelioma), secondary metastatic tumours (common, above all – lung and breast cancer, lymphoma)
Metabolic: uraemia, myxoedema, anorexia nervosa
Traumatic and iatrogenic: early onset (rare) – direct injury (penetrating thoracic injury, esophageal perforation), indirect injury (non-penetrating thoracic injury, radiation injury); delayed onset – pericardial injury syndromes (postmyocardial infarction syndrome, postpericardiotomy syndrome, posttraumatic)
Drug-related (rare): lupus-like syndrome (procainamide, methyldopa, hydralazine, isoniazid, phenytoin), antineoplastic drugs, amiodarone, mesalazine, clozapine, streptokinase, cyclosporine and other
Other (common): amyloidosis, aortic dissection, pulmonary arterial hypertension, chronic heart failure
Other (uncommon): congenital partial and complete absence of the pericardium

mild) (6). Our patient complained of the chest pain typical of acute pericarditis; ECG changes and pericardial effusion were observed on admission to hospital.

The clinical presentation of pericardial effusion can include non-specific symptoms such as cough, weakness, fatigue, anorexia, and palpitations observed in this particular clinical case. These symptoms reflect the compressive effect of the pericardial fluid on contiguous anatomic structures of the heart and reduced blood pressure, and secondary sinus tachycardia is observed as well (8, 9). Findings of physical examination may be absolutely normal in patients without hemodynamic compromise. A rise in the markers of inflammation (CRP, erythrocyte sedimentation rate – ESR) and of the white blood cell count is a common and supportive finding in patients with acute or recurrent pericarditis and may be helpful for monitoring the activity of the disease and efficacy of therapy (8). Chest X-ray is recommended in all patients with suspected acute pericarditis to rule out bacterial etiology if pulmonary infiltration is not present. TTE is the first-line imaging test in patients with suspected pericardial disease, because it accurately detects pericardial effusion and cardiac tamponade, as well as ventricular dysfunction due to myocardial involvement (9). TTE is recommended in all patients with suspected acute pericarditis or other pericardial disease. Clinically, two-dimensional echocardiography with Doppler provides the most cost-effective way of diagnosing pericardial effusion and assessing its hemodynamic significance (6).

CT and cardiac magnetic resonance (CMR) are helpful in establishing diagnosis and, most importantly, in evaluating complications of pericardial diseases. On a CT scan, pericardial thickness of over 2 mm suggests acute pericarditis (11). In patients with recurrent pericarditis, signs of oedema of the inflamed pericardial layers and contrast accumulation can be observed, as in our clinical case (6, 11). Compared with CT, CMR has the advantage of providing information with regard to the hemodynamic consequences of the non-compliant pericardium on cardiac filling and has the potential of showing fibrotic fusion of pericardial layers (11, 12).

Cardiac catheterization is not routinely used for the diagnosis of the pericardial disease. In presence of non-invasive techniques which are usually sufficient in establishing the diagnosis of heart disease involving the pericardium, right heart catheterization may be useful in certain circumstances, such as differentiation between constrictive pericarditis and restrictive cardiomyopathy (6). To sum it up, a modern approach to the management of pericardial diseases should integrate different imaging modalities in order to improve the diagnostic accuracy and clinical management of patients.

Before considering the best treatment option for patients with acute pericarditis or a relapse of the disease, it is necessary to rule out specific final identifiable causes (non-viral non-idiopathic) of the pericardial disease (Table 1). Attention should be paid to possible high-risk features as these aspects of patients' condition can require specific therapeutic approaches and be associated with poor prognosis as well as an increased risk of complications during the follow-up (tamponade, recurrences and constriction) (Table 2). Any clinical presentation that may suggest an underlying aetiology or patients with at least one predictor of a poor prognosis (major or minor risk factors) warrants hospital admission and an aetiology search (6, 13).

Table 2. Predictors of a poor prognosis (6)

Major
fever >38°C
subacute onset
large pericardial effusion
cardiac tamponade
lack of response to aspirin or NSAID after at least 1 week of therapy
Minor
myopericarditis
immunosuppression
trauma
oral anticoagulant therapy

In this particular case, the patient had signs of a systemic inflammation (fever over 38°C), his medical history suggested a subacute onset of the disease – major predictors of a poor prognosis – therefore a decision was made to hospitalize this patient which was the right choice for

such a case. Patients without these symptoms of a poor prognosis can be managed as outpatients with empiric anti-inflammatories and short-term follow-up after one week to assess the response to treatment (13).

Both pharmacological and non-pharmacological treatment methods can be applied to patients with pericarditis. The main non-pharmacological recommendation is to restrict physical activity beyond ordinary sedentary life until resolution of symptoms and normalization of CRP, ECG, and echocardiogram (6). Pharmacological therapy remains an issue to be clarified as no drug has been registered until now for a specific pericardial indication. Aspirin or NSAIDs providing gastroprotection are drugs used as first-line therapy for acute pericarditis. Colchicine is recommended as adjunct for first-line therapy at low, weight-adjusted doses to improve the response to medical therapy and to prevent recurrences in patients with both acute and recurrent pericarditis (5, 6). Colchicine was introduced in 1987 for the treatment of recurrent pericarditis (14) but its use is not yet a common practice in Lithuania. However, colchicine together with other drugs used for the treatment of pericardial diseases has no registered specific pericardial indication.

Based on the data of systematic reviews and meta-analyses, colchicine is useful in reducing the incidence of primary pericarditis (OR: 0.38, 95% CI: 0.22–0.65) as well as recurrent pericarditis (OR: 0.31, 95% CI: 0.22–0.44) (15, 16). The most common side-effects are related to the gastrointestinal system (according to the literature, gastrointestinal side effects occur in up to 10% of cases) and no severe adverse events were observed in clinical trials of the drug (2, 15, 16). Gastrointestinal side effects are mild and may resolve with dose reduction (2). The use of colchicine should be avoided in patients with severe renal or hepatic dysfunction (colchicine undergoes extensive hepatic metabolism by cytochrome P450 (CYP) 3A4), previous allergic reaction to colchicine, in pregnant or lactating women, in patients with leukopenia and thrombocytopenia, and in patients with anaemia (2, 15). Careful monitoring of the full blood count, liver function and renal function is strongly recommended. Colchicine is given 0.5 mg daily (for patients weighing 70 kg or less) or 0.5 mg twice daily (for patients weighing 70 kg or more). The initial dose should be maintained until the resolution of symptoms and normalization of CRP, then tapering should be considered (6).

Corticosteroids should be considered as a second option in patients with acute or recurrent pericarditis and used only if infection is excluded or the autoimmune process is present, also in patients with contraindications and failure of aspirin or NSAIDs. In this case they are used with colchicine at low to moderate doses (5, 6). In the cases of incomplete response to aspirin or NSAIDs and colchicine, corticosteroids may be used, but they should be added at low to moderate doses to aspirin or NSAIDs and colchicine as triple therapy. Tapering should be attempted only if symptoms are absent and CRP is normal (6). As a last resort, pericardiectomy may be considered, but only after a thorough trial of unsuccessful medical therapy (5). Our patient received treatment with NSAIDs and empiric antimicrobial therapy was administered (after ruling out viral aetiology of the disease and symptoms of a systemic inflammation being present). Corticosteroids were not prescribed for our patient (infection could not be excluded and there was no evidence of an autoimmune process). Colchicine was not administered as its use was not widespread in Lithuania at that time.

Severe complications are uncommon in patients with idiopathic recurrent pericarditis. Complication rates are related to the aetiology of the disease and not to the number of recurrences (5, 6). Constrictive pericarditis (CP) is one possible serious complication in clinical practice and needs additional attention. The true prevalence of CP is unknown but it is observed in 0.2–0.4% of patients who have undergone cardiac surgery or have had a pericardial trauma or an inflammation due to a variety of aetiologies in their medical history (1). In 20–30% of cases, constriction evolves in patients treated for bacterial pericarditis, especially if purulent pericarditis was present (6). If patient develops CP, the heart is constricted to a limited diastolic filling by the inflamed and/or scarred pericardium. The mainstay of treatment is surgery. Pharmacological therapy is available in some cases. Medical therapy (generally based on anti-inflammatory drugs) may solve the transient constriction occurring in 10–20% of cases as a temporary phenomenon during the resolution of pericarditis. Medical therapy is also supportive

and aimed at controlling symptoms of congestion in advanced cases and when surgery is contraindicated or at high risk. Drugs can also be administered if a patient is diagnosed with tuberculosis constrictive pericarditis (6).

Despite that the use of colchicine gave satisfying results in the treatment of pericardial diseases, constant search for new, more effective and individualized therapies is in process. The latest developments in the field of pharmacological therapy are currently focused on the search for the treatment of refractory recurrent pericarditis. Recently, azathioprine (immunosuppressive therapy), intravenous immunoglobulin (IVIG – immunomodulatory but also anti-viral), and anakinra (a recombinant IL-1b receptor antagonist) may be considered in the cases of proven infection-negative, corticosteroid-dependent, recurrent pericarditis not responsive to colchicine (17). These relatively new therapeutic options need to be approved by further trials on efficacy and safety of these agents. A number of issues regarding the choice of drugs and the duration of the treatment need to be clarified, additional data is required on long-term outcomes and patient observations after first and subsequent episodes of pericarditis in order to optimize treatment of pericardial diseases and to achieve better treatment results.

CONCLUSIONS

Clinical manifestation of pericarditis can vary depending especially on the aetiology of the disease. Although it is not mandatory to search for the aetiology of pericarditis in all clinical cases, specific therapy is indicated considering the epidemiological background in patients identified with a cause other than viral infection. Despite available diagnostic tests, the aetiology of pericarditis is often not identified and for both acute and recurrent pericarditis empirical treatment is given by carefully observing patients' clinical response to prescribed treatment. No drug has been registered yet for a specific pericardial indication. Colchicine has been demonstrated as a first-line drug to be added to conventional anti-inflammatory therapies as it has shown an effective reduction of symptoms and prevention of recurrence in observational trials. Constant search for new and individualized therapies is in process. Attention is being paid to the treatment of refractory recurrent pericarditis. Despite the progress in the diagnostic and treatment of pericarditis, a number of issues, such as hospital admission criteria (currently in-patient treatment is required when major or minor predictors of a poor prognosis are present), the best treatment duration for patients with pericardial diseases, best timing for surgical therapies, and possible long-term outcomes need to be better characterized to optimize the treatment of pericardial diseases.

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RECIDYVUOJANTIS PERIKARDITAS: KLINIKINIO ATVEJO PRISTATYMAS IR LITERATŪROS APŽVALGA

Santrauka

Tikslas. Iš ūmiu perikarditu persirgusiųjų apie 30 % pacientų (nuo 20 iki 50 %) 18 mėn. laikotarpiu po pirminio ligos epizodo nustatomas recidyvas, lemiantis kartotines hospitalizacijas. Esant dideliems pacientų, hospitalizuotų dėl pirmo ligos epizodo ar pasireiškusio recidyvo, gydymo kaštams, būtina optimizuoti tiek ūmaus, tiek kartotinio perikardito gydymą.

Medžiaga ir metodai. Pateikiame recidyvuojančio perikardito atvejį. Pirmas perikardito epizodas pacientui diagnozuotas 2006 m. Po 3 mėn. pacientas hospitalizuotas pasireiškus recidyvuojančio perikardito klinikai. Praėjus 10 metų nuo pradinio ligos epizodo pacientas pakartotinai gydomas stacionare dėl perikardito recidyvo. Nesėkmingai ieškota galimos susirgimo etiologijos, taikytas standartinis gydymas nesteroidiniais vaistais nuo uždegimo ir skirta empirinė antibakterinė terapija.

Rezultatai ir išvados. Ūmus perikarditas – klinikinėje praktikoje dažniausiai sutinkama perikardo patologija. Pastaruoju metu simptomams palengvinti ir išvengti ūmaus perikardito recidyvų efektyviu vaistu laikomas kolchicinas, skiriant jį kartu su standartine perikardito terapija. Reikalingos tolimesnės vaistų, skirtų perikardo ligoms gydyti, paieškos, gydymo trukmės, pacientų ligos stebėjimo optimizavimas siekiant sutrumpinti stacionarinio gydymo laiką ir išvengti ūmaus perikardito recidyvų pasireiškimo.

Raktažodžiai: ūmus perikarditas, recidyvuojantis perikarditas, transtorakalinė echokardioskopija, karščiavimas, leukocitozė