Updates in diagnosis and treatment of acute pericarditis

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Abstract

Background: Acute pericarditis is inflammation of the pericardium that begins suddenly, is often painful, and causes fluid and blood components to enter the pericardial space. Acute pericarditis has numerous causes. However, in developed countries, roughly 80 to 90% of cases are idiopathic; that is, no specific cause is identified after routine evaluation. It is assumed that these cases are viral. The remaining 10 to 20% of cases are most commonly associated with post–cardiac injury syndromes, connective-tissue diseases, or cancer [1]. The true incidence of the disease is unknown, it is estimated that it accounts for 5% of emergency department visits for chest pain in the absence of myocardial infarction [2]. New diagnostic strategies have been proposed for the triage of patients with pericarditis and when additional diagnostic investigations are required to perform [3]. Major advances have occurred in therapy with the first multicentre randomized clinical trials.Colchicine has been demonstrated as a first-line drug to be added to conventional antiinflammatory therapies in patients with a first episode of pericarditis or recurrences [3,4]. The information presented here, also contains a clinical case of a patient admited to the cardiology clinic with pericardial effusion in acute pericarditis.
Conclusions: In the field of pericardial diseases there are a limited number of randomized controlled trials. Significant new data have become available since 2004, and the new version of recent guidelines published in 2015 have a great impact for clinical practice.
Key words: acute pericarditis, pericardial effusion, cardiac tamponade, cholchicine.

Introduction

Pericardial diseases may be either isolated disease or part of a systemic disease [4]. The main pericardial syndromes that are encountered in clinical practice include pericarditis (acute, subacute, chronic and recurrent), pericardial effusion, cardiac tamponade, constrictive pericarditis and pericardial masses (tab. 1, 2) [3]. In table 1 is presented a partial list of diseases that can involve the pericardium.

Acute pericarditis, defined as symptoms and/or signs resulting from pericardial inflammation of no more than 1 to 2 weeks duration, can occur in a variety of these diseases (denoted by asterisks), but most cases are considered idiopathic. The term idiopathic denotes acute pericarditis for which no specific cause can be found with routine diagnostic testing [5]. But majority of cases includes an immune-mediated process that is probably triggered by a viral infection in many cases, testing for specific viruses is not routine [6]. The etiology that can be found in a specific setting depends on the epidemiological background. Tuberculosis is the leading cause of pericardial diseases as well as pericarditis all over the world, being the most important etiology in developing countries where tuberculosis is endemic and often associated with HIV infection. On the contrary, tuberculosis is reported in <5% of cases in Western Europe and North America [7].

The true incidence and prevalence of the disease are unknown and there are a large number of undiagnosed cases. However, it may account for up to 5% of presentations to emergency departments for chest pain and up to 0.1% of hospital admissions. In an observational study from an urban area in Northen Italy the incidence of acute pericarditis was 27,7 cases per 100,000 persons per year [8]. A Swedish registry study found an incidence rate of 18,0 per 100 000 for pericarditis in the general population, in retired US military personnel, the incidence rate of pericarditis is 7,4 per 100 000 [9]. Many studies have reported conflicting results on the effect of sex on the risk of pericarditis. A recent randomized trial found 65% of 1361 patients to be male. Furthermore, the incidence rate of acute pericarditis in the general adult population was 2- fold among men compared with women [10]. Reasons for sex differences in pericardial inflammation are unknown, but experimental viral studies of myocardial inflammation have suggested that although genetic differences have some effect, sex hormones are major contributors for sex predisposition. Exogenous testosterone increases viral replication and inflammation in the heart and gonadectomy inhibits cardiac inflammation in experimental viral myocarditis. The in-hospital mortality rate for acute pericarditis is estimated at 1.10%. Female sex is associated with increased mortality in univariate analysis but was not an independent predictor of death in the multivariate model [11].

Case report

A 50 year old female patient M. was admitted to the Cardiologic Clinic on 08.02.2016 with difficulty of breath at low/medium physical effort, dull pericardial chest pain which was relieved by anterior thoracic bending, periodic cardiac palpitations, marked fatigue and light knee pain.

History. The symptoms became evident 2 weeks before when the fatigue and dyspnea progressed and the pericardial thoracic dull pain appeared along with nagging knee pain. During the last year she had 3-4 flu episodes, being liable to oral herpes infection, as well. Moreover, the patient has 1st

Table 1

Etiology of pericardial diseases [3]

A. Infectious causes
Viral (common): Enteroviruses (coxsackieviruses, echoviruses), herpes viruses (EBV, CMV, HHV-6), adenoviruses, parvovirus B19 (possible overlap with etiologic viral agents of myocarditis).
Bacterial: Mycobacterium tuberculosis (common, other bacterial rare), Coxiella burnetii, Borrelia burgdorferi, rarely: Pneumococcus spp, Meningococcus spp, Gonococcus spp, Streptococcus spp, Staphylococcus spp, Haemophilus spp, Chlamydia spp, Mycoplasma spp, Legionella spp, Leptospira spp, Listeria 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
B. Non-infectious causes
Autoimmune (common): Systemic autoimmune and auto-inflammatory diseases (systemic lupus erythematosus, Sjögren syndrome, rheumatoid arthritis, scleroderma), systemic vasculitides (i.e. eosinophilic granulomatosis with polyangiitis or allergic granulomatosis, previously named Churg-Strauss syndrome, Horton disease, Takayasu disease, Behçet syndrome), sarcoidosis, familia 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, other rare.
Traumatic and Iatrogenic: Early onset (rare): • Direct injury (penetrating thoracic injury, an esophageal perforation). • Indirect injury (non-penetrating thoracic injury, radiation injury). Delayed onset: Pericardial injury syndromes (common) such as postmyocardial infarction syndrome, postpericardiotomy syndrome, posttraumatic, including forms after iatrogenic trauma (e.g. coronary percutaneous intervention, pacemaker lead insertion and radiofrequency ablation).
Drug-related (rare): Lupus-like syndrome (procainamide, hydralazine, methyldopa, isoniazid, phenytoin); antineoplastic drugs (often associated with a cardiomyopathy, may cause a pericardiopathy): doxorubicin, daunorubicin, cardiomyopathy, may cause a pericardiopathy): doxorubicin, daunorubicin, hypersensitivity pericarditis with eosinophilia; amiodarone, methysergide, mesalazine, clozapine, minoxidil, dantrolene, practolol, phenylbutazone, thiazides, streptomycin, thiouracils, streptokinase, p-aminosalicylic acid, sulfadrugs, cyclosporine, bromocriptine, several vaccines, GM-CSF, anti-TNF agents.
Other (common): Amyloidosis, aortic dissection, pulmonary arterial hypertension and chronic heart failure.
Other (uncommon): congenital partial and complete absence of the pericardium.

degree anemia for 5-6 years and periodically uses iron medication for short period courses.

Personal history – normal physical childhood development. Profile history – works as a nurse in the emergency healthcare (physical strain, reduced sleeping).

Clinical examination showed pale pink skin without peripheral edema, and absence of jugular veins turgor. Normal pulmonary clinical examination. The clinical examination of the cardiovascular system showed the increased right and left relative cardiac dullness limits. Rhythmic and clear cardiac sounds with the cardiac contractions frequency of 84 bpm, and a blood pressure of 150/90 mmHg. Well-developed musculoskeletal system with no pain in joint movement. Light hepatomegaly. The thyroid is not palpable.

Investigations. All biological data was in normal range except for the 1st degree anemia (Hemoglobin level 99 g/l, red blood cells (RBC) 3,3x10^12/l) with anisocytosis and hypochromic RBC (microcytes), with a normal serum iron level – 9,9 umol/L, thrombocytes – 412.5x10^9/l, leucocytes – 3.8x10^9/l, and the inflammatory markers: erythrocyte sedimentation rate (ESR) – 40 mm/h, C-reactive protein (CRP) – 24 mg, antistreptolysine O – 200, and a negative latex-test. Troponins – negative, creatine kinase- MB (CK-MB) – 8 U/l, total creatine kinase (CK) – 25 U/l and alkaline phosphatase – 227 U/l.

Electrocardiogram (fig. 1): Sinus rhythm with cardiac contractions frequency – 82 bpm, normal electrical axis of the heart. Flattening of the T waves in all leads.

Thoracic radiography (fig. 2): Pulmonary area with signs of venous stasis. Pulmonary hypertension. Left basal disk shaped atelectasis. Bilateral free costo-diaphragmatic sinuses. Transversally dilated heart.

Echocardiography (fig. 3): Ascending Aorta – 34 mm, left atrium – 44 mm, left ventricle (LV) – 57 mm, right ventricle (RV) – 23 mm, right atrium (RA) – 42 mm, *interventricular septum* (IVS) and *left ventricular posterior wall* (*LVPW*) – 8 mm. *Pulmonary artery pressure* (PAP) – 43 mmHg. Considerable amount of fluid in the pericardium: LVPW – 25 mm, lateral wall of left ventricle (LWLV) – 28 mm, RA basal – 22 mm, anterior wall of right ventricle (AWRV) – 10mm, apex -10 mm. Conclusion: Light dilation of LA, RA, LV. Signs of RA collapse. Mitral valve insufficiency I-II degree, tricuspid valve insufficiency II degree. Preserved cardiac pump function (Ejection fraction (EF) – 65%).

Taking into consideration the clinical data and the investigations there was established the diagnosis: Exudative acute pericarditis, considerable amount of pericardial effusion. Mitral valve insufficiency (II degree), tricuspid valve insufficiency (II degree). Heart failure NYHA II. Anemia of unknown etiology.

Question No 1: What are the diagnostic criteria of acute pericarditis and which one of them is seen in the presented patient?

The classic presentation of acute pericarditis, regardless of its etiology, is a patient with chest pain that is sharp, pleuritic in nature, retrosternal or left-sided in location, that is present in more than 85-90% of cases [3]. The pain is often exacerbated by lying down and is relieved by sitting up or leaning forward. The pain may radiate to the neck, arms, or left shoulder, making it difficult to differentiate from the pain of myocardial infarction. However, pain that radiates to one or both trapezius muscle ridges suggests pericarditis because the phrenic nerve innervates these muscles and crosses the pericardium as well [12]. Acute chest pain may or may not occur in patients with uremic pericarditis or pericarditis associated with rheumatologic disorders, although pleuritic chest pain may be the initial presentation of systemic lupus erythematosus. A pericardial friction rub, which is highly

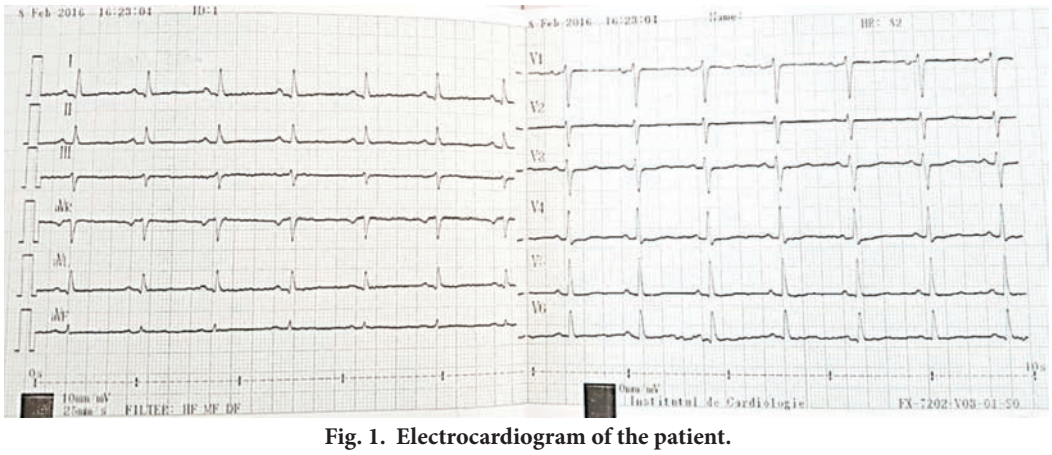

Fig. 1. Electrocardiogram of the patient.

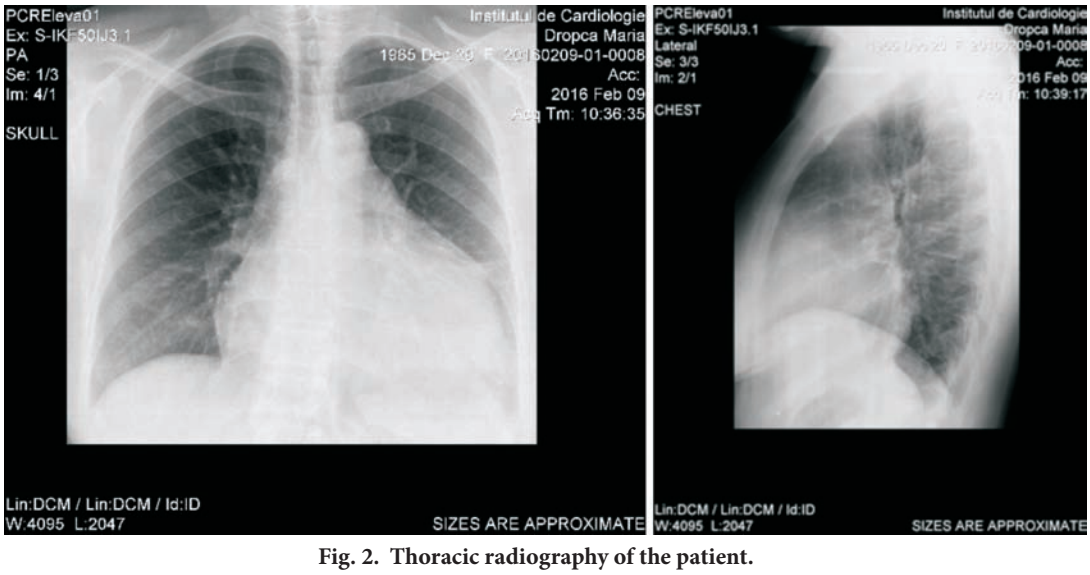

Fig. 2. Thoracic radiography of the patient.

specific and pathognomonic for acute pericarditis, occurs in up to 33% of patients, but its absence does not exclude the diagnosis [3]. According to the European Society of Cardiology, 2015 (ESC), the diagnosis of acute pericarditis is established by the presence of at least 2 of the 4 criteria presented in Table 2 with/ without additional signs.

The electrocardiogram (ECG) is the most important tool in the diagnosis of pericarditis. Typical ECG changes have been reported in up to 60% of cases [13]. It may show sinus tachycardia and widespread ST-segment elevation which has been considered the hallmark of acute pericarditis [14]. The ST segment is usually coved upward and lead involvement in acute pericarditis is more extensive than reciprocal ST-segment depression in ischemia. Another recent criteria to differentiate acute ST segment elevation myocardial infarction (STEMI) from acute pericarditis is the prolongation of the QRS complex and shortening of the QT interval in ECG leads with ST segment elevation which are not the case in patients

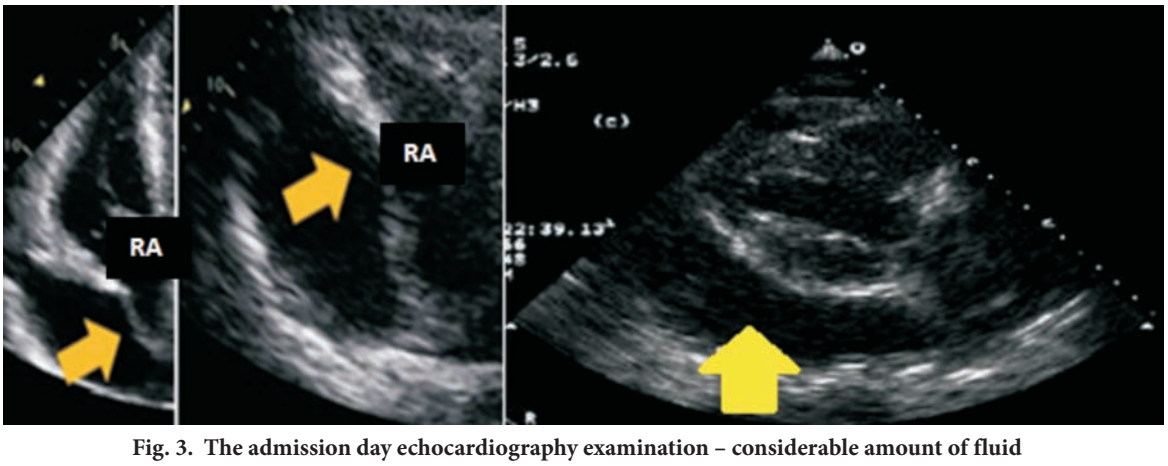

Fig. 3. The admission day echocardiography examination – considerable amount of fluid in the pericardium and signs of RA collapse.

with pericarditis [15]. PR-depression is another feature in the ECG of the patient with pericarditis. According to a study by Porela et al. the most common location for PR depression was lead II (55.9%), while this ECG finding least likely appeared in lead aVL (2.9%). PR depression in any lead had a high sensitivity (88.2%), but fairly low specificity (78.3%) for miopericarditis. The combination of PR depressions in both precordial and limb leads had the most favorable predictive power to differentiate miopericarditis from STEMI (positive 96.7% and negative power 90%) [16]. A useful data suggests how to distinguish by ECG acute pericarditis and benign early repolarization as both conditions are associated with concave ST elevation. Thus, the vertical height of the ST segment elevation (from the end of the PR segment to the J point) is measured and compared to the amplitude of the T wave in V6. A ratio of > 0.25 suggests pericarditis and ratio of < 0.25 suggests benign early repolarization [17].

Other mandatory checks besides auscultation and ECG according to the latest European guidelines on pericardial diseases are echocardiography to rule out effusion concomitant heart disease or signs of myocarditis. Transthoracic echocardiogram (TTE) is the first-line imaging test to detect pericardial effusion and tamponade physiology. Although many patients with acute pericarditis may appear to have normal echocardiographic results, the presence of an effusion is consistent with acute pericarditis [18]. Other findings may include increased pericardial brightness, pericardial thickening, and abnormal septal bounce, suggesting early constriction. A pericardial effusion can be trivial to large and localized, loculated, or circumferential. Importantly, tamponade physiology can be seen in 3% of patients. Intrapericardial fibrinous strands suggest either an inflammatory etiology or clotted blood. TTE may also help differentiate acute pericarditis from myocardial ischemia or injury by excluding wall motion abnormalities, even though a small percentage of patients with acute pericarditis (5%) will demonstrate segmental wall motion abnormalities. If the results of TTE are negative or equivocal in a patient suspected to have acute pericarditis with poor prognostic signs, or evidence of hemodynamic compromise, the most sensitive subsequent test is CMR, which shows edema and inflammation as well as features of constrictive physiology. The choice of CT or CMR should be based on the specific clinical question according to the strength of these modalities. The following are scenarios in which additional imaging with CT or CMR may be considered:

- Inconclusive echocardiographic findings and ongoing clinical concern;
- Failure to respond promptly to anti-inflammatory therapy;
- Atypical clinical presentation;
- Search for a specific cause (i.e., malignancy or tuberculosis);
- Suspicion of constrictive pericarditis or effusive constrictive pericarditis;
- Associated trauma (penetrating injury, chest injury); and
- Acute pericarditis in the setting of acute myocardial infarction, neoplasm, lung or chest infection, or pancreatitis [19].

A chest X-ray is generally normal in patients with acute pericarditis since an increased cardiothoracic ratio only occurs with pericardial effusions exceeding 300 ml [20].

Elevation of markers of inflammation (i.e. CRP and ESR), as well as elevation of the white blood cell count) is a common and supportive finding in patients with acute pericarditis and may be helpful for monitoring the activity of the disease and efficacy of therapy. Patients with concomitant myocarditis may present with an elevation of markers of myocardial injury (i.e., CK, troponin) [21].

Our patient presented 2 of those 4 mentioned criteria: pericardial type pain and pericardial effusion (on TTE and thoracic radiography) and the additional signs found were the inflammatory markers – elevated ESR and CRP levels. Electrocardiogram didn't show typical signs, only flattening of the T waves in all leads.

Table 2

Definitions and diagnostic criteria for pericarditis [3]

Pericarditis	Definition and diagnostic criteria
Acute	Inflammatory pericardial syndrome to be diagnosed with at least 2 of the 4 following criteria: (1) pericarditic chest pain (> 85- 90% of cases) (2) pericardial rubs (≤33% of cases) (3) new widespread ST-elevation or PR depression on ECG (60% of cases) (4) pericardial effusion (new or worsening) (60% of cases) Additional supporting findings: - Elevation of markers of inflammation (i.e. C-reactive protein, erythrocyte sedimentation rate, and white blood cell count); - Evidence of pericardial inflammation by an imaging technique (CT, CMR).
Incesant	Pericarditis lasting for > 4-6 weeks but <3 months without remission.
Recurrent	Recurrence of pericarditis after a documented first episode of acute pericarditis and a symptom-free interval of 4–6 weeks or longer (usually within 18-24 months).
Chronic	Pericarditis lasting for >3 months.

Question No 2: What is the possible etiology of pericarditis in this patient?

In this patient there were evaluated the following possible causes of acute pericarditis:

- Pericarditis in the context of autoimmune diseases (System Lupus Erythematosus, Rheumatoid arthritis, Spondyloarthropathy, etc.), because the patient had joint pain when moving and resting.
- Myxedematous pericarditis
- Viral pericarditis

Pericarditis in the context of systemic diseases was excluded through the evaluation of systemic autoimmune markers, which happened to be negative (tab. 3).

Myxedematous pericarditis was excluded through the evaluation of thyroid hormones, which happened to be in normal range and the thyroid ultrasound examination did not find any pathological changes.

Table 3

Systemic autoimmune markers

Parameter	Results
Anti-ANA, IgG	Negative
dsDNA	Negative
Nucleosomes	Negative
Histones	Negative
SmD1	Negative
PCNA	Negative
PO	Negative
SS-A/Ro60kD	Negative
SS-A/Ro52kD	Negative
SS-B/La	Negative
CENP-B	Negative
Scl-70	Negative
1 snRNP	Negative
AMA M2	Negative
Jo-1	Negative
Pm-Scl	Negative
Ku	Negative
Mi-2	Negative

Frequently, the cause of pericarditis cannot be found, the idiopathic pericarditis having an estimated incidence of 85 – 90 % [22], but many of these cases are probably viral, viral pericarditis being the most frequent cause of infectious pericarditis. Most likely, in the presented case report, the cause of acute pericarditis remains to be viral, as the patient had episodes of flu in the previous period of time, that went through with catarrhal signs (persistent rhinorrhea, viral conjunctivitis) and had a rapid regression. Moreover, denoting that the patient is liable to oral herpes infection.

Question No 3: Is pericardiocentesis a treatment option?

In correspondence with the management algorithm of pericardial effusion mentioned in the ESC 2015 guide for pericarditis, pericardiocentesis or cardiac surgery is a 1C class indication in case of cardiac tamponade, or in case of symptomatic moderate – large pericardial effusion which does not respond to medication or in case of unknown bacterial or neoplastic etiology suspecting (fig. 4). In this case there are no indications for pericardiocentesis, because the patient was hemodynamically stable, without paradox pulse, besides the echocardiographic signs of RA collapse. The diagnosis of cardiac tamponade is a more clinical one and in the absence of hypotension, paradox pulse cannot be established, as well as, during the clinical examination and from the history there was not appreciated the coexistence of a neoplastic process. An eventual pericardiocentesis was difficult to perform because of the possible complications and the technique – since the pericardial fluid was located in the posterior, hard to access space.

Question No 4: What would be the appropriate treatment in this patient?

The medication choice has to deal with the patients' history (contraindications, anterior efficacy or medication

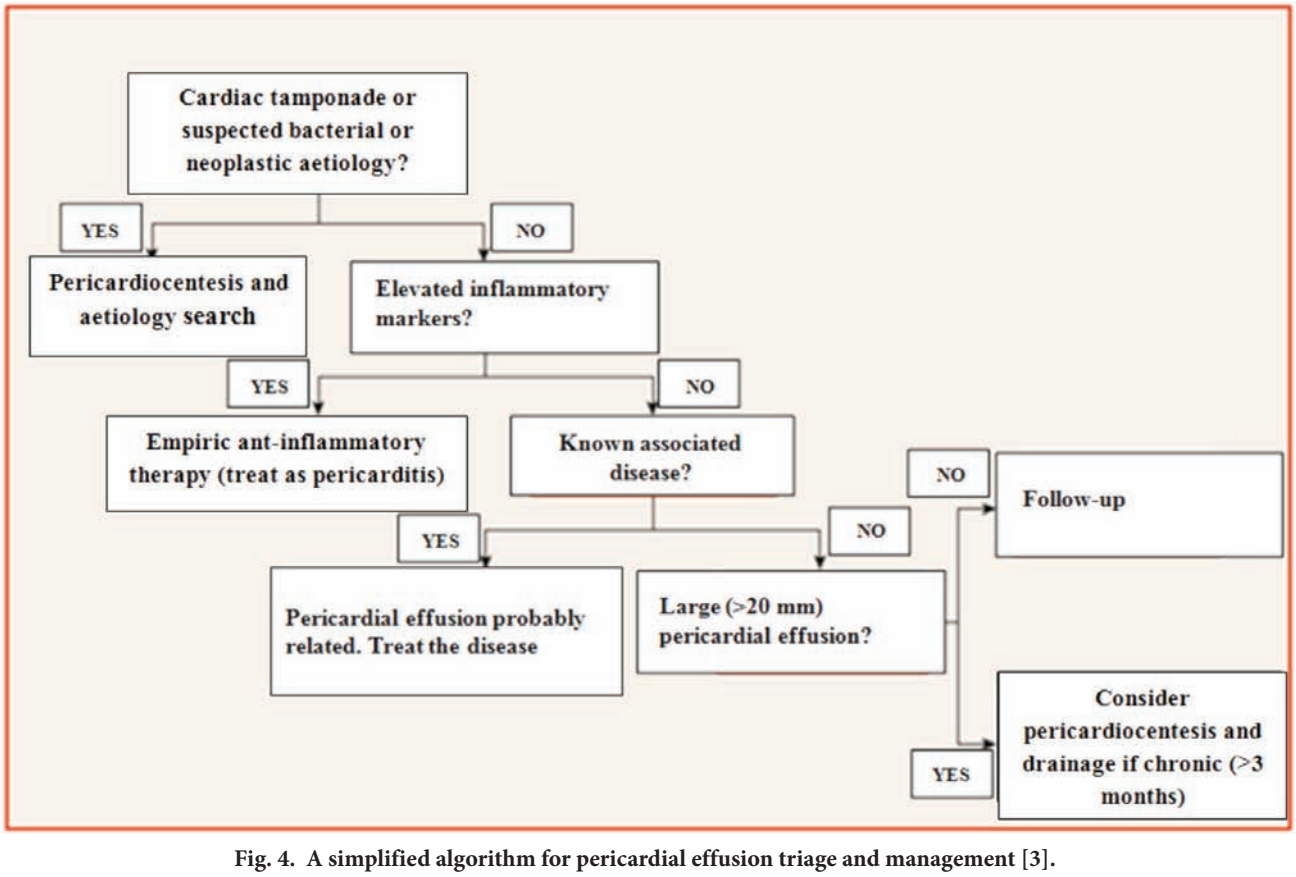

Fig. 4. A simplified algorithm for pericardial effusion triage and management [3].

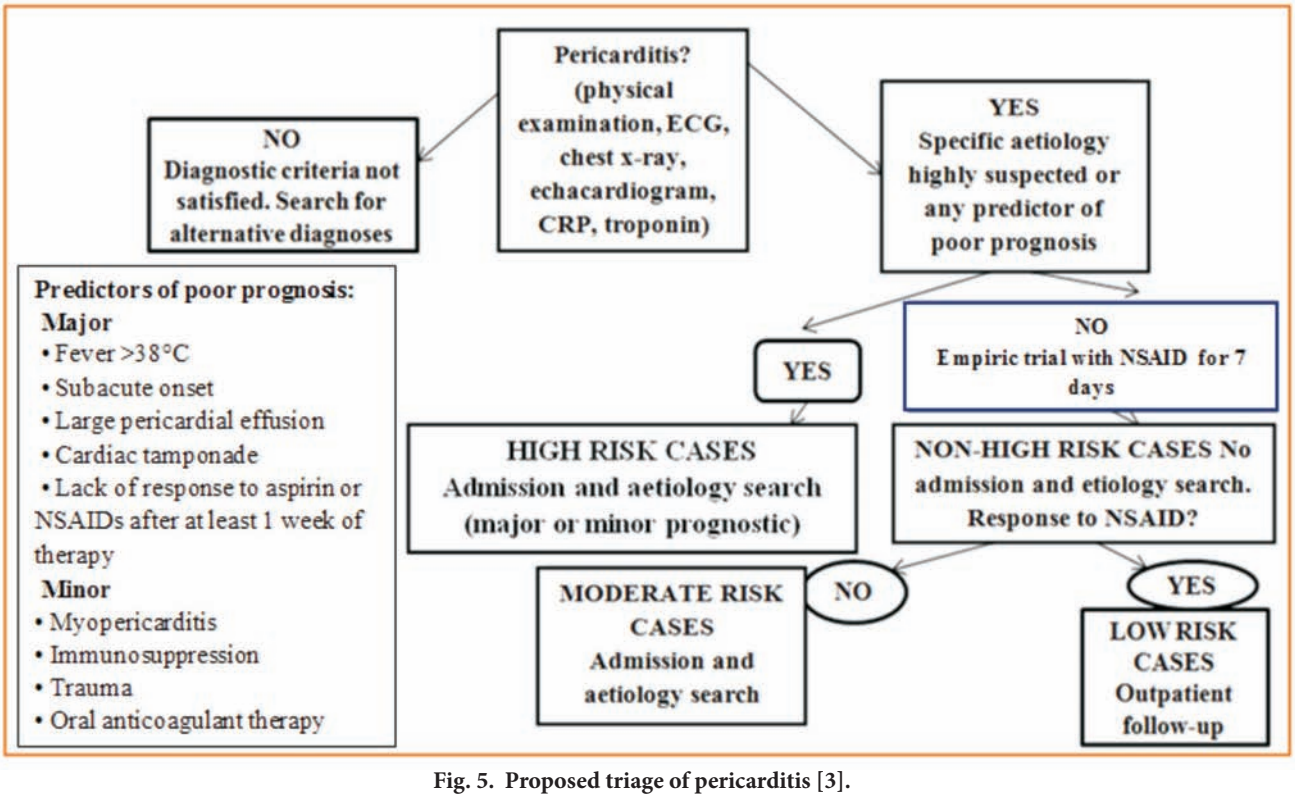

Fig. 5. Proposed triage of pericarditis [3].

side effects), the accompanying diseases [23]. The first non-pharmacologic precaution is avoiding physical effort until stabilization of CRP and the symptoms. Acute idiopathic pericarditis is a self-limited disease with a recurrence rate after an initial episode from 15 to 30% [24]. Because of its excellent safety profile, is preferred ibuprofen (600 mg every 8h). Acetylsalicylic acid (ASA), 750–1000 mg every 8h daily in divided doses, is an alternative and often preferable in patients who require ASA for other indications, as in patients with pericarditis after myocardial infarction because other NSAIDs have delayed infarct healing in animal models and are associated with an increased risk of future coronary events in this population In either case, gastric protection in the form of a proton pump inhibitor should be provided [25]. Colchicine is recommended at low, weight-adjusted doses (0.5 mg once (<70 kg) or 0.5 mg b.i.d. (≥70 kg)) to improve the response to medical therapy and significantly reduced the rate of subsequent recurrences of pericarditis in patients with multiple recurrences. Taken together with results from other randomized controlled trials, colchicine should be probably regarded as a first-line treatment for either acute or recurrent pericarditis in the absence of contraindications or specific indications [26]. Corticosteroids should be considered as a second option in patients with contraindications and failure of aspirin or NSAIDs because of the risk of favoring the chronic evolution of the disease and promoting drug dependence [27].

Thus, in this patient was started empiric treatment (according to the algorithm in fig. 5) with ibuprofen – 1600 mg/day divided in 4 doses and colchicine – 1 mg, ½ tablet x 2/24h, beta – blockers and diuretics. At the 7th day from admission the echocardiography examination was repeated (Fig. 6) to evaluate the pericardial effusion dynamics, where there was found an essential reduction of the pericardial effusion: LVPW – 9 mm, LWLV – 8 mm, RA basal – 3 mm, AWRV – 3mm, apex – 3mm. As well, the inflammatory markers reduced: ESR – 20 mm/h, CRP – 6 mg.

Question No 5: How long does the treatment take?

The ibuprofen recommended treatment duration is 1 – 2 weeks (the patient administered ibuprofen being in the hospital for 8 days, and at discharge she was recommended to continue administering it 6 more days)

Question No 6: Why is the prolonged colchicine treatment necessary?

According to the recent data the simultaneous administration of colchicine for 3 months favors a rapid regression of the symptoms and with fewer recurrences in comparison with patients which administered only NSAIDs and/or colchicine less time [28]. The recurrence rate after an initial episode of pericarditis may increase to 50% after a first recurrence of acute pericarditis in patients not treated with colchicine [29].

Question No 7: What is the prognosis in acute pericarditis?

The prognosis for acute pericarditis is usually good. Although mortality in idiopathic/viral pericarditis is low, purulent pericarditis is always fatal if untreated and carries a mortality of approximately 40% even when treated [29]. In the acute pericarditis it is important to consider the high risk factors for development of complications during the pathologic evolution (cardiac tamponade, recurrence and constriction) [30]. The risk factors associated with a negative prognosis

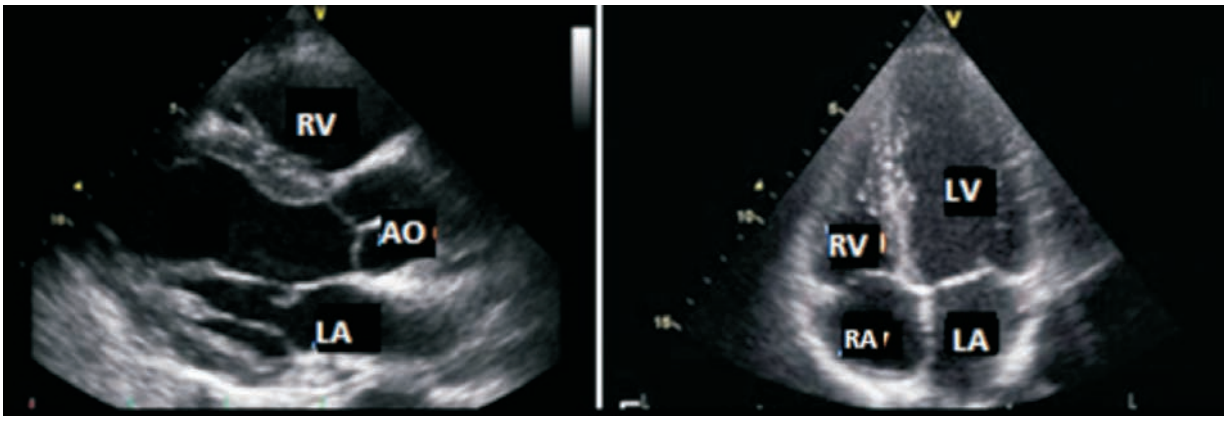

Fig. 6 The echocardiography examination at the 7th day from admission.

are: severe fever (>38°C), subacute evolution, evidence of pericardial fluid in significant amount (> 20 mm), cardiac tamponade, the treatment response absence during a 7 day NSAIDs course, or other minor risk factors as: pericarditis in association with myocarditis, immunosuppression, trauma or oral anticoagulation treatment. Perhaps 15% to 30% of patients with apparent idiopathic acute pericarditis who respond satisfactorily to treatment suffer a relapse. Genetic disorders of the immune system underlie some cases of recurrent pericarditis. A recent study found that 8 of 131 (6.1%) patients thought to have recurrent idiopathic pericarditis had mutations of the TNFRSF1A gene that causes tumor necrosis factor receptor-1–associated periodic syndrome (TRAPS), 25 a monogenic disorder resulting in dysfunction of the innate immune system with periodic fever, rash, abdominal pain, periorbital edema, and polyserositis with pericarditis. Patients with TRAPS respond to corticosteroids but not to colchicine [31]. In another report, 4 of 30 patients with recurrent pericarditis refractory to colchicine were found to have TNFRSF1A mutations. A report that human leukocyte antigen allel patterns are associated with recurrent pericarditis also supports a role of genetic variation in innate immunity as an underlying determinant. The extent to which TRAPS and other innate immune disorders are responsible for recurrent pericarditis merits additional research [32].

In the presented patient there was found a single risk factor – significant amount of pericardial fluid which had a good response to the administered treatment. The majority of patients with acute pericarditis have a long term favorable prognosis. Constrictive pericarditis can appear in < 1% of acute idiopathic pericarditis cases, in about 2 – 5 % of autoimmune pericarditis and about 20 – 30 % of the bacterial ones, especially tuberculous [33].

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