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Infectious-immune pericarditis: clinical assessment, diagnostics, and differentiated baseline therapy with hydroxychloroquine

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Aim. To study the clinical spectrum of infectious-immune pericarditis, the potential for their invasive and non-invasive diagnosis, as well as long-term treatment with hydroxychloroquine (in comparison with other baseline therapy options).
Material and methods. The study included 44 patients with infectious-immune pericarditis (28 women and 16 men aged 49,4±13,3 years). Patients with transudate and specific types of pericarditis were excluded. Levels of C-reactive protein and anticardiac antibodies were determined Multislice computed tomography of the lung (n=23) and heart (n=16), cardiac magnetic resistance tomography (n=9), scintigraphy (n=14), and if necessary — immunoelectrophoresis, DNA testing, Diaskin-test. Pericardio- and thoracentesis were performed in 3/3 patients, thoracoscopic pericardial biopsy — 1, endomyocardial biopsy — 7. The follow-up period was 14,5 [3; 39,5] months.
Results. Isolated pericarditis was diagnosed in 10 patients (22,7%), myopericarditis — in 34 (77,3%). In 38 patients, pericarditis was exudative: in 24 (63,2%) with a small effusion (⩽10 mm), in 10 (26,3%) — with a moderate (11-20 mm), in 4 (10,5%) — with a large (⩾20 mm). Fibrin was detected in 18,2% of patients. Pericardial effusion was assessed as acute in 4, subacute — in 8, chronic — in 26 patients. The connection between the disease onset and infection was found in 56,8% of patents, and inflammatory blood changes — in 59,1%. In 80%, the punctate was lymphocytic; endomyocardial biopsy confirmed active/borderline (5/2) lymphocytic myocarditis (virus-positive — in 3 patients). Anticardiac antibody titers were increased in 88,2%. Baseline therapy included NSAIDs (34,1%), colchicine (27,3%), hydroxychloroquine (43,2%), methylprednisolone (56,8%, 16 [16; 21] mg/day), azathioprine (20,5%). The treatment scheme was selected individually. In most cases, combined therapy was carried out. The results of treatment were assessed in 36 patients: an excellent effect was noted in 16 (44,4%) patients, stable effect — in 13 (36,1%), no stable effect — in 7 (19,4%). There were no cases of constrictive pericarditis, acute relapses, cardiac tamponade. Mortality of 6,8% was associated with myocardial injury.
Conclusion. Criteria for the diagnosis of infectious-immune pericarditis were proposed. An increase in the titer of anticardiac antibodies was noted in all types of the disease. Prescription of corticosteroids is justified in many cases, including in combination with colchicine, cytostatics, hydroxychloroquine. Hydroxychloroquine monotherapy is effective for subacute/chronic pericarditis with moderate effusion.

Key words: infectious-immune pericarditis, myocarditis, anticardiac antibodies, endomyocardial biopsy, corticosteroids, hydroxychloroquine.

Relationships and Activities: none.

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Pericarditis is a very heterogeneous group of diseases, the differential diagnosis of which is very difficult and does not always lead to a definite result. Difficulties begin already at the differentiation of exudate from transudate. Some pericarditis occurs without effusion (dry, constrictive) and can mimic myocardial infarction, restrictive cardiomyopathy, liver cirrhosis and other diseases. But the most difficult are the search for the etiology of effusive pericarditis and the determination of the optimal treatment strategy. According to the 2015 ESC Guidelines for the diagnosis and management of pericardial diseases, in about half of cases, the etiology of pericarditis cannot be established [1]. At the same time, the ideologist of previous guidelines Maisch B from Marburg considers this percentage to be unjustifiably high and refers to his own unique experience in pericardioscopy and pericardial biopsy, which make it possible to establish diagnosis and carry out proper treatment in almost 100% of cases [2]. According to European experts and Maisch B and Ristic A group, the proportion of the established etiological factors are very close (bacteria, cancer, etc.), while 50% of European "idiopathic" types correspond to 12% of viral and 35% of the so-called autoreactive (lymphocytic) pericarditis [3].

Obviously, in both cases the issue is the most numerous groups of pericarditis, but without pericardial biopsy, pericardioscopy and even pericardiocentesis, cases of viral and lymphocytic pericarditis remain undiagnosed and considers as idiopathic. It seems to us justified to call this group "infectious-immune pericarditis", since even in the absence of a viral genome, it is highly probable that the starting role of infection in the development of autoreactive (lymphocytic) pericarditis can be assumed.

Therefore, a special study of infectious-immune pericarditis seems relevant, the results of which are presented in this work.

The aim was to study the infectious-immune pericarditis, potential of its invasive and non-invasive diagnosis, as well as long-term hydroxychloroquine therapy in comparison with other approaches.

Material and methods

Study sample. The study included 44 patients with infectious-immune pericarditis from 20 to 69 years (mean age, 49,4±13,3 years; 28 women and 16 men (53,2±10,3 and 42,9±15,4 years, respectively, $p<0,05$)). Inclusion criteria were the presence of inflammatory pericardial effusion or diagnostic criteria for dry pericarditis, as well as additional original criteria for infectious-immune pericarditis (see the Results section) with any disease duration. Patients with postpericardiotomy syndrome, purulent, tuberculous, post-traumatic pericarditis, cancer-related pericarditis (including after radiation and chemotherapy), systemic connective tissue diseases, vasculitis, amyloidosis, and sarcoidosis were excluded. The exclusion criteria were congestive pericardial effusion and hypothyroid effusion (i.e., hydropericardium).

Methods. All patients underwent chest X-ray, electrocardiography (ECG), echocardiography, 24-hour Holter monitoring, standard blood tests, determination of CRP and fibrinogen levels. Blood detection of cardiotropic viruses (Herpesviridae, Parvovirus B19), anti-cardiac antibody level by enzyme-linked immunosorbent assay, lung (n=23) and cardiac (n=16) multislice computed tomography (MSCT), cardiac magnetic resonance imaging (n=9), myocardial scintigraphy (n=14), coronary angiography (n=4). In order to rule out specific types of pericarditis, the blood was tested for antinuclear factor (ANF), rheumatoid factor (RF), complement, and, if necessary, anti-cyclic citrullinated peptide, antineutrophil cytoplasmic, anti-cardiolipin antibodies, extractable nuclear antigens. Blood and urine immunoelectrophoresis with determination of free light chains by immunofixation, genetic testing of the *MEFV* gene, Diaskin test and phthisiatrician examination, and cancer diagnostic tests were performed.

Diagnostic pericardiocentesis by a standard approach was performed by a cardiac surgeon in 3 patients, thoracentesis — in 3 patients. In one case, a thoracoscopic pericardial biopsy was performed, in 7 — right ventricular endomyocardial biopsy (EMB). Van Gieson's staining and polymerase chain reaction for viral infections (Herpesviridae, Parvovirus B19, Adenoviruses) were carried out. Three patients underwent a biopsy of subcutaneous fat with staining for amyloid (negative result).

Treatment and follow-up. Therapy for pericarditis will be described in the Results section. Therapy for heart failure and arrhythmias was carried out in accordance with European and Russian guidelines. Symptoms, laboratory parameters, and volume of pericardial effusion were monitored in 36 patients. The endpoints were the maintenance and recurrence of pericardial effusion, constriction and need for pericardial surgery, and all-cause mortality. The mean follow-up period was 14,5 [3; 39,5] months (maximum up to 10 years).

The study was approved by the local Ethics Committee.

Statistical processing was carried out using the SPSS Statistics 21 software. Quantitative characteristics are presented as M±δ (mean±one standard deviation) or as a median with 1st and 3rd quartiles. The distribution normality was assessed using the Kolmogorov-Smirnov test. The significance of dif-

ferences was assessed using the Student's test. Differences were considered significant at $p<0,05$.

Results

Clinical characteristics of patients (Table 1). Dry pericarditis (in all cases — acute or subacute) was made to 6 patients, while in other patients, pericarditis with effusion was diagnosed. In almost 2/3 of cases the effusion was minor (⩽10 mm), in 1/4 — moderate (11-20 mm) and only 1/10 — large (>20 mm). There was relatively infrequent detection of fibrin in pericardial effusion during echocardiography. In more than 2/3 of cases, pericarditis was chronic. General inflammatory changes in the blood were detected in almost 60% of patients, but leukocytosis — only in 6 patients; no one had leukopenia. In 20,5%, a relative blood lymphocytosis was detected.

The severity of symptoms and their clear connection with the previous infection was noted in more than half of the patients (n=25), while in 14 patients, there was definitely no such connection; in 5 more, it was possible. Fever was present at the disease onset in almost 1/3 of patients; in 11 of them, the body temperature reached 38° C. Sweat and cough were rare.

In addition to the association between the disease onset and respiratory infection, the infectious-immune nature of pericarditis was indicated:

1. The simultaneous presence of systemic immune manifestations and diseases that did not meet criteria for major immune diseases in 10 (22,7%) patients; these included the blood detection of elevated titers of ANF, RF, eosinophilia and an increase in eosinophilic cationic protein levels, arthritis/arthralgia, myasthenia, psoriasis, asthma. Signs of polyserositis were present in 3 patients.

2. High titers of anti-cardiac antibodies, which were detected in 88,2% of the examined patients (Figure 1). At the same time, there was also an increase in anti-endothelial cell and anti-conduction system antibodies, but also in anti-cardiomyocyte antibodies (1:160-1:320 in 8 patients), as well as antinuclear antibodies, which is normally absent, in 57,1% of patients (1:160-1:320 in 6 patients).

3. Clinical signs of myocardial involvement in the inflammatory process, which could be presented by arrhythmias, heart failure (HF) symptoms, as well as asymptomatic or oligosymptomatic ECG and imaging changes. In particular, HF was diagnosed in 21 patients (47,7%) in the absence of correlation with effusion volume, including stage I in 6 patients, stage IIA — in 16, stage IIB — in 7. Class 1 HF was registered in 6 patients, class 2 — in 14, and class 3 — in 9. In patients with stage IIB HF, pericardial effusion did not correlate with pleural and peritoneal effusion, did not respond to diuretic therapy, and could not be regarded as a manifestation of HF.

According to echocardiography, left ventricular (LV) mean end-diastolic dimension was 5,0 [4,6; 5,9] cm, LV end-diastolic volume — 98 [76; 124] ml, LV end-systolic volume — 41 [28,5; 70,5] ml, LV ejection fraction (EF) — 55 [41; 63]%, left atrial (LA) diameter — 4,2±0,9 cm, LA volume — 55,5 [37,75; 85,5] ml, right atrial volume — 47,3±18,6 ml, right ventricular dimension — 2,6±0,7 cm, pulmonary artery systolic pressure — 25 [20; 38] mm Hg. At the same time, LV dilatation was noted in 14 patients, LVEF decrease (range of 45-54%) in 4 patients, while in 13 patients, LVEF was <45%. Pulmonary hypertension was detected in 11 patients. There were no signs of cardiac tamponade in any case. Two patients had thickened pericardial layers without clear criteria for constriction.

Cardiac arrhythmias were represented mainly by ventricular premature contractions and unstable ventricular tachycardia, supraventricular premature contractions and atrial fibrillation, as well as atrial flutter, unstable supraventricular tachycardia (Table 1), first-degree atrioventricular block (n=5, 11,4%). One patient each had a complete left and right bundle branch blocks, sick sinus syndrome. The most characteristic ECG changes were a flattened or inverted T wave (n=16, 36,4%), transient ST segment depression or elevation (n=9, 20,5%), as well as signs of LV hypertrophy (n=8, 18,2%) and a QRS voltage decrease (n=5, 11,4%).

According to ^{99m}Tc scintigraphy, diffuse uneven impairment of myocardial perfusion in 6 patients (42,9%) was noted, as well as its combination with focal perfusion disorders in two more (14,3%). Intramyocardial, subepicardial delayed accumulation and their combination in 44,4% of MRI performances, signs of active contrast accumulation by the pericardium was revealed in one patient. Intramural, subepicardial and transmural delayed contrast accumulation in the myocardium according to MSCT (43,8%). Various types of lung fibrosis were detected in 55% of MSCT images, hilar lymphadenopathy — only in 3 patients.

4. The results of morphological and virological tests of the myocardium, which were obtained using EMB in 7 patients with suspicion of myocarditis, fully confirmed this diagnosis (Figure 2): active (according to Dallas criteria) lymphocytic myocarditis was detected in 5 cases, and borderline — in 2 cases. The viral genome in the myocardium was detected in 3 patients (in 2 — parvovirus B19, in 1 — the Epstein-Barr virus); the Epstein-Barr virus in the blood — in other 7 patients. The common pathogenesis of pericarditis in virus-positive and virus-negative patients was proved by an increase in

Table 1

Clinical characteristics and therapy in patients with various types of infectious-immune pericarditis

Parameter	All patients	Isolated pericarditis	Myoperi-/perimyocarditis
n	44	10	34
Age, years	49,4±13,3	54,1±14,7	47,9±12,7
Female/male	28/16	5/5	23/11
Acute /subacute/chronic	4/12/28	2/3/5	2/9/23
Dry/effusive	6/38	2/8	4/30
Minor/moderate/large effusion	24/10/4	3/3/2	21/7/2
Mean effusion volume, ml	200 [150; 450]	375 [200; 875]	200 [150; 450]
Onset association with infection	25 (56,8%)	5 (50%)	20 (58,8%)
Fever on the onset	14 (31,8%)	6 (60%)	8 (23,5%)
Sweat	4 (9,1%)	3 (30%)	1 (2,9%)
Cough	11 (25,0%)	4 (40%)	7 (20,6%)
Cardialgia	21 (47,7%)	5 (50%)	16 (47,1%)
HF	21 (47,7%)	7 (70%)	14 (41,2%)
PVC/unstable VT	18/5 (40,9/11,4%)	2/1 (20/10%)	16/4 (47,1/11,8%)
PSVC/SVT	14/9 (31,8/20,5%)	2/2 (20/20%)	12/7 (35,3/20,6%)
AF/AFL	10/6 (22,7/13,6%)	2/1 (20/10%)	8/5 (23,5/14,7%)
General inflammatory abnormalities	26 (59,1%)	10 (100%)	18 (52,9%)
Systemic immune manifestations	10 (22,7%)	4 (40%)	6 (17,6%)

Abbreviations: HF — heart failure, PVC — premature ventricular contractions, VT — ventricular tachycardia, PSVC — premature supraventricular contractions, SVT — supraventricular tachycardia, AF — atrial fibrillation, AFL — atrial flutter.

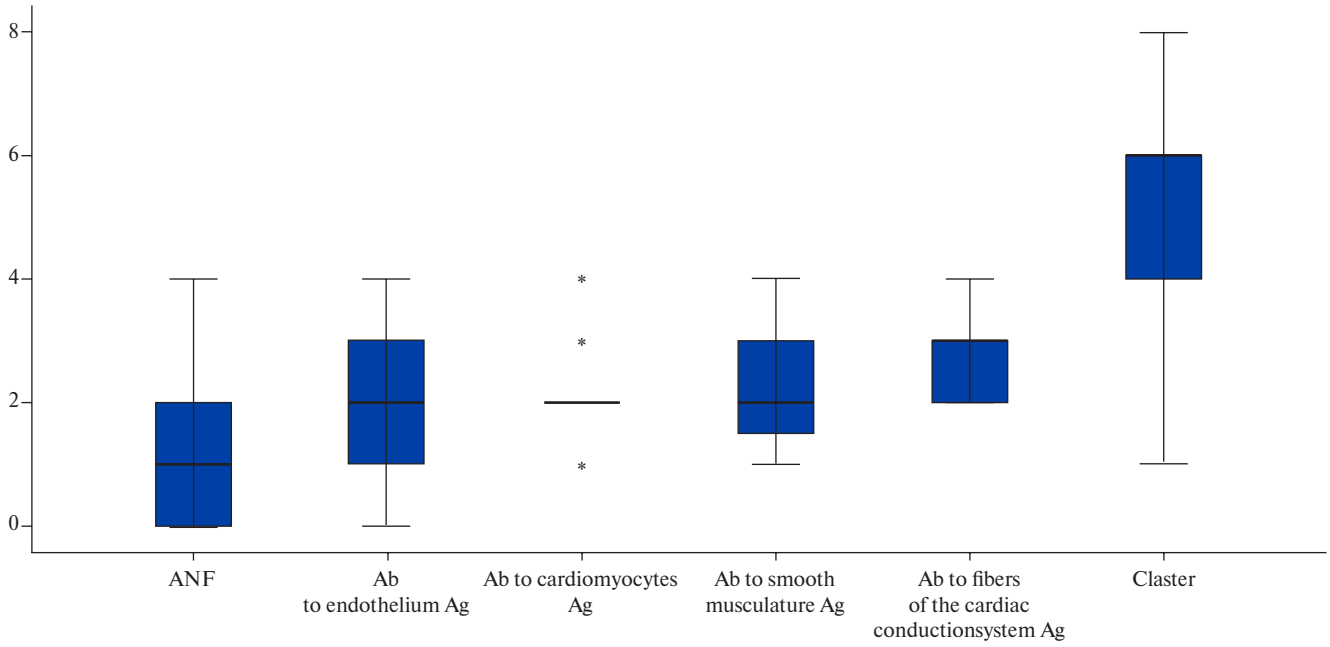


Figure 1. Concentration of various anticardiac antibodies in patients with infectious-immune pericarditis.
Note: ordinate is the level of titer increase (relative to the normal range).
Abbreviations: ANF — antinuclear factor, Ab — antibodies, Ag — antigens.

titers anticardiac antibodies and the simultaneous presence of myocarditis.

5. The results of a cytological examination of pericardial/pleural effusions, which were performed in patients with a sufficient fluid volume. In addition to confirming the inflammatory effusion nature (exudate in all cases), showed a significant (from 80 to 97%) prevalence of lymphocytes in 80% of tests. The viral genome was never detected. Due to the small number of examinations, the level of anticar-

diac antibodies in pericardial effusion was not analyzed.

6. The results of a pericardial biopsy, which was performed in a single case and showed a picture of active eukocytoclastic vasculitis (Figure 3).

Clinical types of infectious-immune pericarditis. Two main clinical types that were observed in patients of this group can be distinguished.

1. Isolated infectious-immune pericarditis. This type was diagnosed in a minority of patients (n=10, 22,7%). It was distinguished by acuity (in 70%), pronounced general inflammatory manifestations in all patients, as well as a significant volume of pericardial effusion (on average 375 [200; 875] ml, up to 1000 ml, with the exception of two cases of acute dry pericarditis), the presence of fibrin and resistance to treatment (which in half of the patients required the appointment of corticosteroids, see below). Fever was noted in 6 patients (>38° C). In 40% of cases, there were some systemic immune manifestations, including polyserositis (n=3).

Despite the absence of obvious signs of myocardial injury, a normal status of anticardiac antibodies was noted in only one patient, while in other cases, their increase was revealed (including ANF in 3 patients). The viral genome in the blood was not detected. An example is a 64-year-old, male patient (Figure 4), an Armenian, with an acute disease onset (fever >39° C), pericardial effusion up to 36 mm, neutrophilic leukocytosis up to 22 thousand, hyperfibrinogenemia, CRP of 168 mg/l, RF of 32 IU/ml, an increase in titers of specific ANP, anti-endothelial cell and anti-conduction system antibodies to 1:160, cardiolipin antibody IgM to 26,6 IU/ml. Pericardiocentesis removed 1,6 liters of serous fluid (neutrophils, 80%; lymphocytes, 20%). Immunoelectrophoresis revealed inflammatory dysproteinemia. No *MEFV* gene mutations in exon 10 were detected. Treatment with corticosteroids and colchicine was effective.

2. Pericarditis with simultaneous myocardial involvement (perimyo-/myopericarditis). This type was diagnosed in 34 (77,3%) patients: in 10 of them (29,4%), signs of myocarditis prevailed, in 17 (50%) — pericarditis; in 7 (20,6%), myo- and pericarditis had the same degree of severity. In a significant part of the patients, the symptoms were determined by myocarditis, which manifested itself not only in HF with EF decrease (44,1% of patients), arrhythmias, but also microvascular ischemia, an infarct-like signs (Figure 3). As noted earlier, in 7 cases the diagnosis of myocarditis was confirmed using EMB. Myocardium/blood of three-seven patients were virus-positive.

Pericarditis was exudative in 30 (88,2%) patients, in 2 cases was regarded as acute, in 9 as subacute and in 23 (67,6%) as chronic, mainly with small

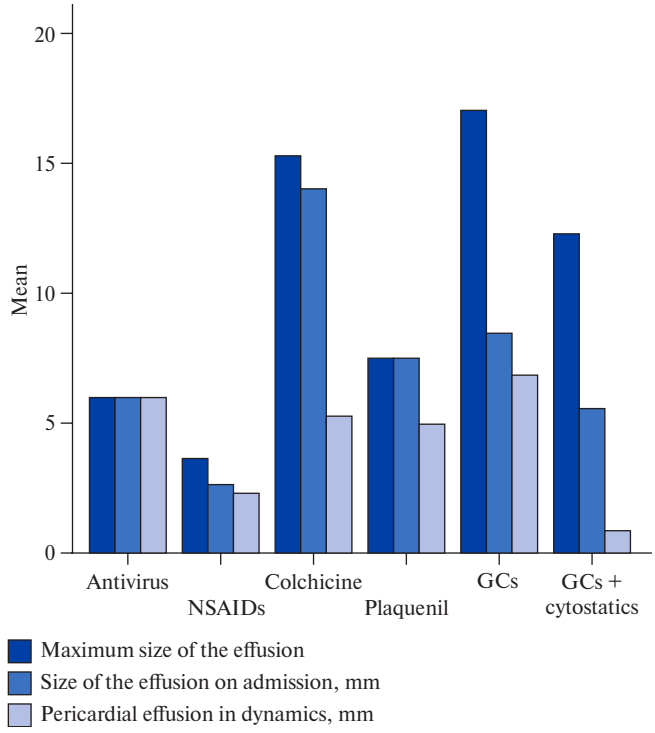


Figure 2. Changes in pericardial effusion volume depending on the type of initial therapy.
Abbreviations: GCs — glucocorticosteroids, NSAIDs — non-steroidal anti-inflammatory drugs.

effusion volume (on average 200 [140; 450] ml), general inflammatory blood abnormalities in 52,9% patients, systemic immune manifestations in 17,6%, fever at the onset in 23,5%, the absence of fibrin according to echocardiography in 86,7% of effusion pericarditis (Table 1). In general, it was less full-blown than isolated infectious-immune pericarditis.

As a special type, one should probably talk about the development of infectious-immune perimyocarditis in patients with primary cardiomyopathies. Thus, in one patient, perimyocarditis (with a predominance of pericarditis) developed against the background of severe obstructive hypertrophic cardiomyopathy, in the second — myopericarditis against the background of noncompact cardiomyopathy, and in the third — against the background of sarcomeric cardiomyopathy (MyBPC3 gene mutation). In two more patients, myopericarditis developed with arrhythmogenic right ventricular dysplasia (Figure 3). Two out of five patients were virus-positive (myocardium), which may indicate the viral tropism to genetically defective myocardium and its triggering role in pericarditis development.

Therapy of infectious-immune pericarditis, short-term and long-term outcomes. Therapy is presented in Table 2.

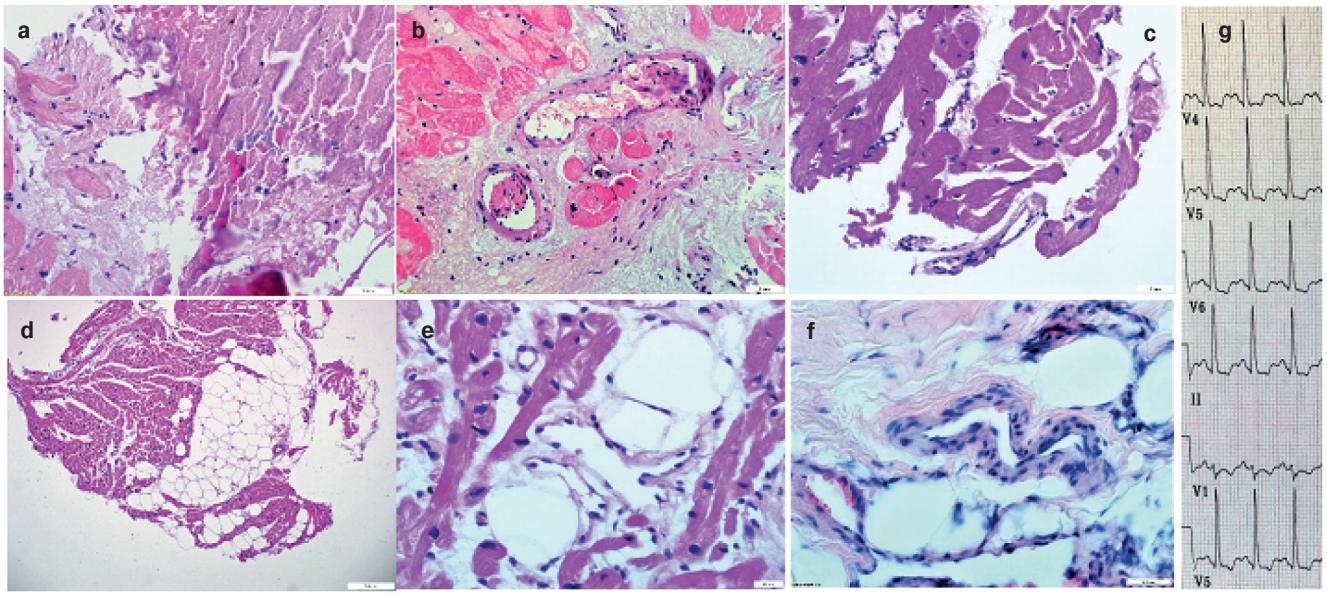


Figure 3. Results of biopsy of myocardium and pericardium in patients with infectious-immune myopericarditis (with ECG).
Note: a-e — right ventricular myocardial biopsy, **f** — pericardial biopsy, **a**, **d** — low-power magnification, **b**, **c**, **e**, **f** — high-power magnification; hematoxylin and eosin staining; dystrophy and necrosis of cardiomyocytes (**a**, **b**), interstitial (**a**, **d**, **e**) and perivascular (**b**, **c**) lymphohistiocytic infiltration, fatty myocardial replacement in a patient with arrhythmogenic right ventricular dysplasia (**d**, **e**), leucoclastic vasculitis (**f**); **g** — ECG during treadmill test, paper speed 25 mm/s (microvascular ischemia in a patient with vasculitis).

Antibiotic therapy was carried out mainly due to respiratory infections that developed at the onset of pericarditis or during treatment, much more often, with isolated pericarditis with a full-blown onset and general inflammatory changes. Antiviral drugs (acyclovir, ganciclovir) were prescribed only to virus-positive patients with myopericarditis. The relatively low percentage of NSAID use (mainly ibuprofen 1200-1600 mg/day for 1-2 months) is due to a small proportion of acute types of pericarditis. Colchicine was prescribed mainly for acute/subacute isolated pericarditis, while in the presence of myocarditis, preference was given to the immunosuppressive therapy.

Steroids was the basis of treatment in about half of cases of both isolated pericarditis and myopericarditis. The mean dose was low and corresponded to the standards of treatment of pericarditis rather than myocarditis. In the case of combined types, a cytostatic drug was added to the treatment (mainly azathioprine at a dose of 100-150 mg/day; in one case, mycophenolate mofetil 2 g/day). The combination of steroids with colchicine was prescribed to 6 patients, with hydroxychloroquine — 7; in 12 cases, monotherapy with hydroxychloroquine 200 mg/day was carried out. The choice of therapy was individual and depended on the clinical type of pericarditis, severity, effusion volume, previous treatment experience, the presence of contraindications or intolerance.

The effectiveness of pericarditis treatment was controlled primarily by changes of pericardial effusion volume. In patients with concomitant myocarditis, the goals of treatment were also relief of HF and arrhythmia symptoms, restoration of myocardial contractility (increase in EF), and improvement of other structural and functional disorders. In addition, decrease in anticardiac antibody titers was monitored.

The dynamics of pericardial effusion depending on the initial therapy is shown in Figure 2. Monotherapy with antiviral drugs was used in few patients and did not have a clear response in relation to effusion. With initially small-volume effusions, which differed in a chronic course and were not prone to spontaneous disappearance, hydroxychloroquine (Plaquenil) had a positive effect. At the same time, effusions >1 cm often required more aggressive therapy — not colchicine (used as monotherapy in isolated cases), but rather corticosteroids. In a significant part of patients, they were used in combination with cytostatic agents, which was due to the presence of clinically significant myocarditis.

In general, differentiated selection with a change in therapy made it possible to achieve good control of pericarditis in most patients. All cases of dry pericarditis resulted in complete resolution of symptoms without effusion formation. In 36 patients, an excellent effect (no effusion, relapses and constriction) was noted in 16 (44,4%), a stable effect (preservation of a small effusion, no congestive HF) — in 13 (36,1%). Absence of stable effect (presence or

Table 2

Characteristics of therapy for infectious-immune pericarditis

Parameter	All patients	Isolated pericarditis	Myoperi-/perimyocarditis
n	44	10	34
Antibiotic therapy	12 (27,3%)	6 (60%)	6 (17,6%)
Antiviral therapy	11 (25,0%)	-	11 (32,4%)
NSAIDs	15 (34,1%)	6 (60%)	9 (20,5%)
Colchicine	12 (27,3%)	7 (70%)	5 (14,7%)
Hydroxychloroquine	19 (43,2%)	3 (30%)	16 (47,1%)
Corticosteroids	25 (56,8%)	5 (50%)	20 (58,8%)
Mean dose of methylprednisolone, mg/day	16 [16; 21]	16 [14; 20]	16 [16; 22]
Azathioprine	9 (20,5%)	-	9 (26,5%)
Mycophenolate mofetil	1 (2,3%)	-	1 (2,9%)
β-blockers	31 (70,5%)	9 (90%)	22 (64,7%)
ACE inhibitors	23 (52,3%)	6 (60%)	17 (50,0%)
Mineralocorticoid receptor blockers	17 (38,6%)	2 (20%)	15 (44,1%)

Abbreviations: ACE — angiotensin-converting enzyme, NSAIDs — non-steroidal anti-inflammatory drugs.

increase in effusion, HF) — in 7 (19,4%). There were no cases of constrictive pericarditis, and acute recurrence. The frequency of different types of response to treatment in general and depending on the clinical type is shown in Figure 5.

Three patients died during the follow-up period. In all cases, this was caused by myocardial injury with severe HF and its complications: two patients with hypertrophic cardiomyopathy died in the early postoperative period from multiple organ failure. A third one had a stroke as the cause of death.

Criteria for infectious immune pericarditis. At the end of our analysis, we formulated criteria to diagnose infectious-immune pericarditis mainly by non-invasive methods and prescribe therapy:

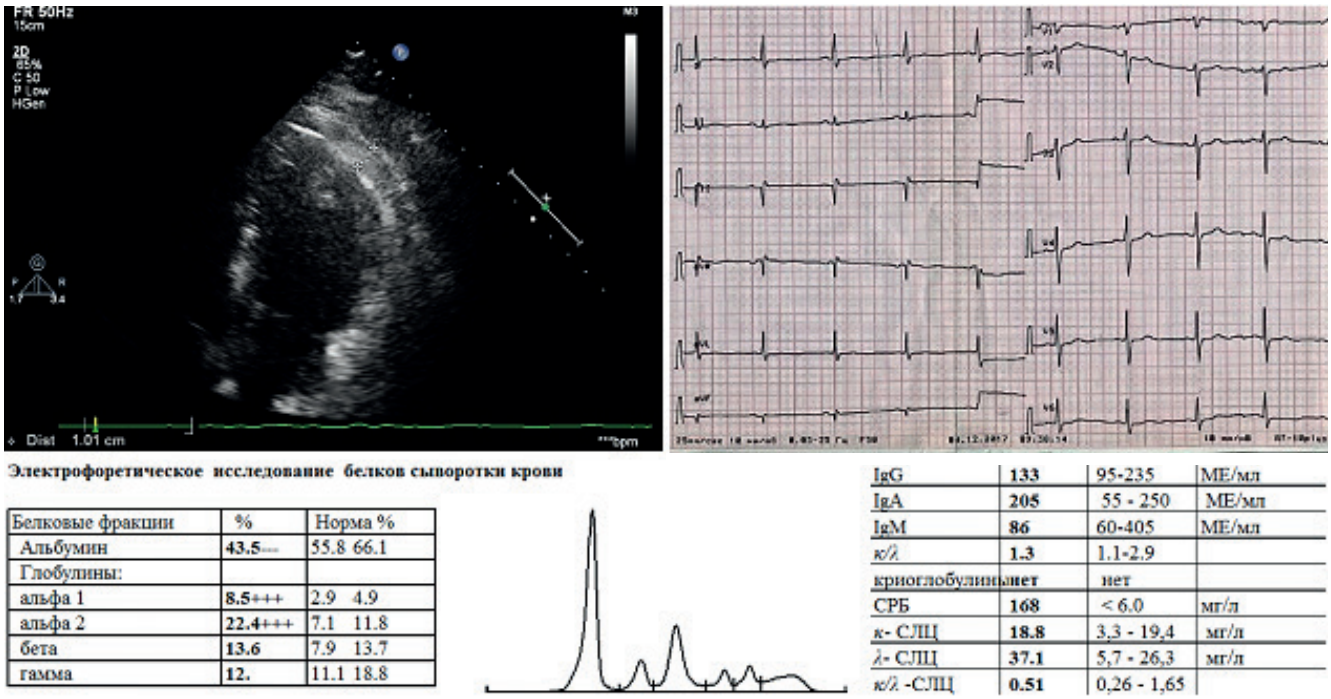
1. No prior cancer, tuberculosis, sarcoidosis, amyloidosis, systemic connective tissue diseases and vasculitis.
2. No history of radiation therapy, chemotherapy and any cardiac surgery less than six months old.
3. The relationship of disease onset with the previous infection (URTI, bronchitis, pneumonia, tonsillitis, etc.).
4. Concomitant myocarditis (including confirmed by EMB).
5. Three-four times increased titers of anticardiac antibodies in the blood (and, possibly, pericardial fluid).
6. Predominantly lymphocytic pericardial/pleural effusion.
7. Presence of the viral genome in the pericardial/pleural fluid/myocardium.
8. Small (up to 1 cm) or moderate (1-2 cm) volume of pericardial effusion.
9. Favorable course (without tamponade and constriction).
10. Positive effect of NSAID/colchicine/hydroxychloroquine/corticosteroid therapy during the first 3-6 months.

Discussion

One of the main aims of this study was to move away from the concept of idiopathic pericarditis. According to the Brucato A and Imazio M, up to 50-80% of patients with acute pericarditis remain without a definite diagnosis [5]. As these authors rightly point out, this is only due to lack of information. However, the first reason for the unjustifiably high proportion of idiopathic pericarditis is still underdiagnosis of tuberculosis, systemic diseases, cancer and other known causes of the disease.

Our experience shows that intensive diagnostics, including the repeated pericardiocentesis and invasive biopsy, is necessary in all cases of unclear pericarditis and gives results [6, 7]. It is interesting and quite natural that one of the few works on the diagnostic value of pericardioscopy and thoracoscopic biopsy of the pericardium in Russia was carried in tuberculosis institution, where it made it possible to diagnose tuberculous pericarditis in 44,4% of patients [8]. The present study included only those patients who had already undergone the necessary additional examination aimed at ruling out all known causes of pericarditis, and none of these causes was found.

As far as we know, the term “infectious-immune pericarditis” was not previously used, but there is nothing fundamentally novel. In the monograph



Электрофоретическое исследование белков сыворотки крови

Белковые фракции	%	Норма %
Альбумин	43.5---	55.8 66.1
Глобулины:		
альфа 1	8.5+++	2.9 4.9
альфа 2	22.4+++	7.1 11.8
бета	13.6	7.9 13.7
гамма	12.	11.1 18.8

IgG	133	95-235	МЕ/мл
IgA	205	55 - 250	МЕ/мл
IgM	86	60-405	МЕ/мл
κ/λ	1.3	1.1-2.9	
криоглобулины	нет	нет	
СРБ	168	< 6.0	мг/л
κ- СЛЦ	18.8	3,3 - 19,4	мг/л
λ- СЛЦ	37.1	5,7 - 26,3	мг/л
κ/λ -СЛЦ	0.51	0,26 - 1,65	

Figure 4. Diagnostic data on a patient with isolated infectious-immune pericarditis.

by Gogin RR (1979) the concepts of "infectious-allergic pericarditis", "acute benign or idiopathic pericarditis", "allergic pericarditis" were used [9]. The author discusses primarily the viral and allergic nature of acute benign pericarditis. The unifying features of this type include the absence of a microbial pathogen, a favorable outcome and a tendency to recurrence.

At present, two leading groups of European researchers offer similar, in our opinion, terms and consider idiopathic pericarditis in a similar way. The first group of authors (Maisch B and Ristic A, et al.) relies on their own unique experience of morphological and molecular diagnostics, which allows them, firstly, to distinguish a group of viral pericarditis and, secondly, to diagnose autoreactive (lymphocytic) viral-negative pericarditis [3]. The autoimmune nature of the latter is confirmed by the authors by detecting not only CD45-positive lymphocytes in the pericardium, but also anticardiac antibodies in the blood and pericardial fluid.

The second group of authors (Brucato A and Imazio M, et al.), without denying the role of viruses and even suggesting to term "presumed viral pericarditis", develops an interesting concept of "idiopathic" pericarditis as an autoinflammatory disease due to innate immune response [5]. Typical for autoinflammation is a recurrence, the onset in childhood, an acute inflammatory response with a high CRP level and subsequent regression of symptoms [10]. The key mediator of this response is interleukin-1, and the efficacy of anakinra in some patients with resistant pericarditis undoubtedly confirms the role of autoinflammation [11], as well as the proven anti-recurrent effect of colchicine, which modulates the innate immune response [4]. This concept is also supported by Russian authors [12].

Our data show that both concepts are true. Undoubtedly, isolated pericarditis with a supposed autoinflammatory nature is the most full-blown representative of this group of pericarditis. However, not all cases of infectious-immune pericarditis fit into this concept. It seems that the presence of concomitant myocarditis is a very clear indicator of a chronic autoimmune process, where viruses can be a trigger. Therefore, the algorithm proposed by Maisch B for the verification of myopericarditis with small effusion using EMB [3] looks very attractive, as we have seen from our own experience.

Concomitant detection of anticardiac antibodies in blood and pericardium makes it possible to use their determination in blood as a diagnostic marker of infectious-immune pericarditis. An increase in the titer of anticardiac anti-intercalated disk antibodies has already been shown in 67,5% of patients with recurrent pericarditis [13]. The results of our work indicate that the titers of antibodies to various cardiac structures were equally increased in patients with both isolated pericarditis and myopericarditis. This fact, as well as the association between the dis-

ease onset and prior respiratory infection in more than half of the patients, proves the common pathogenesis and the rationale of the concept of "infectious-immune pericarditis".

It also follows from our study that not all cases of infectious-immune pericarditis require therapy not only with anti-interleukin drugs, but also with colchicine. In most cases, more traditional treatment for immune diseases have been effective. First of all, this concerns chronic pericardial effusion, in which the effectiveness of colchicine (and, moreover, NSAIDs) has not been studied at all. The idea of the effect of colchicine on viral pericarditis remains controversial: after the catastrophic result of the experiment on mice with the treatment of Coxsackie-viral myocarditis (on the 3rd day of treatment, 50% of the mice died [14]), an opinion was expressed about too high doses used; the Tschöpe C group showed that colchicine improves the course of Coxsackie-viral myocarditis in mice by reducing the activity of inflammasomes [15]. In general, the presence of viruses in pericarditis is not given so much importance as in myocarditis.

On the other hand, there is evidence of greater efficacy of low doses of corticosteroids (0,2-0,5 mg/kg of prednisolone) in comparison with the standard for the treatment of myocarditis (1 mg/kg) [16]. The authors established long-term (86,7%) antirelapse efficacy of intrapericardial administration of triamcinolone (300 mg per 1 m^2 of body surface) for autoreactive pericarditis [3]. High efficacy of steroids in combination with azathioprine or mycophenolate mofetil in the treatment of idiopathic recurrent pericarditis has been shown [17]. We successfully used these regimens in patients with myopericarditis and achieved almost complete suppression of effusion (Figure 2), while in isolated pericarditis, the combination of corticosteroids with colchicine had the best effect. A similar regimen has been successfully used by other authors, who noted the insufficient effect of first-line drugs (NSAIDs and colchicine) in 62% of 276 patients [18].

Finally, the results of hydroxychloroquine use in our study deserve a separate analysis. We are not aware of special studies of this kind; there are only reports of its use for pericarditis in the framework of systemic diseases and rheumatism [19]. We have successfully used it to control pericardial effusion both in addition to maintenance doses of corticosteroids, and as monotherapy, at a minimum dose (200 mg/day). To date, hydroxychloroquine is used in patients with minor subacute and chronic effusions, which we attributed mainly to a slow onset of the effect. However, in the light of recent data on the

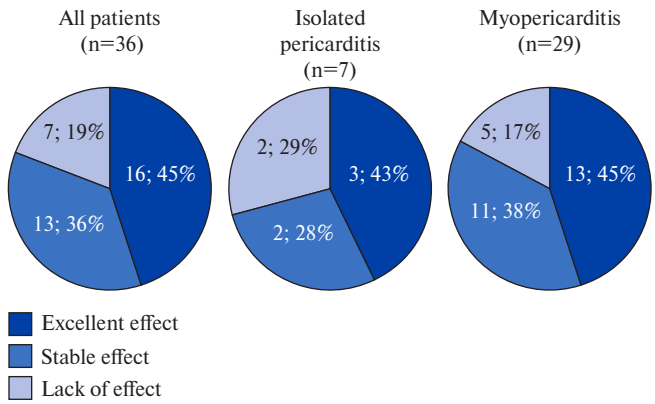


Figure 5. Results of treatment of infectious-immune pericarditis.

effectiveness of higher doses of hydroxychloroquine (800 mg/day with a switch to 400 mg/day) and its combinations with steroids and antiviral drugs in Coronavirus disease 2019, including leading to active myocarditis [20, 21], it is of particular interest to study its effectiveness in more acute and aggressive pericarditis types.

Conclusion

The concept of "infectious-immune pericarditis" and its clinical criteria were proposed. There are two main types of infectious-immune pericarditis (isolated pericarditis and myoperi-/perimyocarditis). It is analogous to autoreactive, lymphocytic pericarditis and underlies most cases of idiopathic pericarditis. Isolated pericarditis is more severe and characterize by more effusion. With myopericarditis, symptoms caused by myocardial injury may come to the fore. An increase in the titer of anticardiac antibodies is observed in all types of infectious-immune pericarditis and is a good marker of disease activity. Due to the relatively small volume of effusion, in most cases, pericardiocentesis is not possible and is not necessary for the diagnosis and choice of treatment. Anti-inflammatory/immunosuppressive therapy is determined by the severity, the volume of effusion, presence of concomitant myocardial injury, and the experience of previous treatment. The appointment of corticosteroids is justified in many cases of infectious-immune pericarditis, including in combination with colchicine in isolated pericarditis with significant effusion, with cytostatics — in myocarditis. The combination of steroids with hydroxychloroquine can be used for any option. Long-term monotherapy with hydroxychloroquine is quite effective in subacute/chronic pericarditis with moderate effusion. Further study of its effectiveness is necessary.

Relationships and Activities: none.

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