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Cardiac Sarcoidosis: A Contemporary Concept of Forgotten Granulomatosis

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Review Article

Abstract

Sarcoidosis is a complex multisystem inflammatory granulomatous disease that can affect any organ, with a wide range of clinical presentations. A significant number of patients with systemic sarcoidosis may also have cardiac involvement. Clinical manifestations of cardiac sarcoidosis can include various rhythm and conduction disturbances, as well as heart failure.

The structure of sarcoid granulomas is similar to that of tuberculous granulomas, but in contrast, they lack caseous necrosis. Tissue changes in sarcoidosis tissues depend on the stage of development of the disease, progressing from pathological process: macrophage-lymphocytic infiltration to epithelioid cell granuloma formation, and fibrosis. Granulomas can be found in any part of the myocardium, with the most common locations being the free wall of the left ventricle, the basal part of the interventricular septum, and the interatrial septum.

Advancements in diagnostic imaging techniques, such as computer tomography and magnetic resonance imaging, have facilitated the verification of cardiac sarcoidosis. This article presents an analysis of updated information on cardiac sarcoidosis by a multidisciplinary working group.

Keywords: Sarcoidosis, Heart, Myocardium, Biopsy, Heart failure

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Introduction

Sarcoidosis was a neglected problem in modern medicine and the healthcare system [1] The incidence of this disease is increasing around the world. Sarcoidosis has left the infectious units , increasingly debuting with cardiological, rheumatic, neurological, and other diseases, and therefore, the examination of patients must be mandatory in multidisciplinary clinics and comprehensive. The lung is no longer a monopoly organ of sarcoid granulomatosis [2].

There are two general terms: cardiac sarcoidosis and isolated cardiac sarcoidosis. In the context of the presented review, the authors will discuss only updated international issues of cardiac sarcoidosis.

Every new piece of information is of great interest because sarcoidosis is attracting the attention of an increasing number of clinicians and scientists [3]. A chronic maladaptive immune response linking genetic susceptibility and specific infectious factors together with environmental factors is thought to be the causes of sarcoidosis [4-6]. The infection factor in sarcoidosis is considered a trigger one since, in genetically predisposed patients, prolonged antigenic stimulation can lead to dysregulation of cytokine production, which is identified with an inadequate immune response.

Infectious agents that cause sarcoidosis are non-tuberculous mycobacteria, Chlamydia pneumonias - the causative agent of pneumonia, Borrelia burgdorferi - the causative agent of Lyme disease, Propionibacterium acnes - bacteria, commensals of the skin and intestines of a healthy person, and certain species of viruses: Epstein-Barr virus, hepatitis C virus, cytomegalovirus, type VI herpes virus, JC virus (John Cunningham), and HTLV1 (Human T-lymphotropic virus type 1) [3,7].

At the present stage, the concept of identifying the initiation of sarcoid granulomatosis is following that sarcoidosis cannot be a disease with a specific pathogen, while some researchers argue that an as-of-yet unidentified microorganism can be the causative agent of sarcoidosis [8]. It is not solely caused by a single microorganism, and it is highly likely that multiple factors are involved [9].

In the overwhelming majority of cases, the target of lesion in cardiac sarcoidosis is the myocardium, which is clinically manifested as multiple arrhythmias and conduction disorders (from extrasystole to asystole), disorders of myocardial vascularization (from stable angina pectoris to postinfarction cardiosclerosis), as well as heart failure [10]. These manifestations result from myocardial infiltration with granulomas and correlate with the degree of granuloma-associated disorganisation of the micro- and macro-picture of the intramyocardial parenchyma and stroma. Diffuse granulomatous alteration of the myocardium leads to a decrease in systolic function of the heart, however, if this indicator does not fall below 35%, then with timely maintenance therapy (pharmacological, hardware) and timely treatment of the underlying disease, normalization of the ejection fraction index can be achieved [8].

Ventricular arrhythmias and sudden cardiac death are the main causes of death in patients with sarcoidosis. As a rule, arrhythmogenic lesions of the myocardium are associated with granulomatous infiltration in the areas of the cardiac conduction system's structural and functional components [9,10]. With infiltration around the sinoatrial (SA) node, the SA node weakness pathognomonic syndrome occurs up to its complete shutdown, along with the characteristic clinical and electrophysiological manifestations [11]. The excitability, as well as the automatism, are disturbed, which is clinically identified with episodic syncope. When conducting daily ECG monitoring, one can often encounter a syndrome of migrating tachycardia and bradycardia [12-14].The complete atrioventricular (AV) block may occur, followed by asynchronous contraction with interference. The mechanisms of the development of sarcoid granulomatosis are potentially involved in arrhythmogenesis through the development and progression of myocardial remodeling, ischemia, fibrosis, neurohumoral deactivation, electrolyte imbalance, and various

channelopathies. In sarcoidosis, a complex of molecular, metabolic, and ultrastructural changes in cardiomyocytes and the extracellular matrix occur, causing an impairment of electrophysiological properties, which leads to structural changes in the myocardium [3]. This is clinically manifested by a syndrome of electrophysiologically unstable myocardium. Changes in the electrical and contractile properties of the atrial myocardium lead to a change in the volume and composition of the extracellular matrix and, as a result, to the development of myocardial fibrosis, which, in turn, contributes to the onset and maintenance of arrhythmia by a decrease in the elastic properties of the myocardium, in contractile function and pattern of coronary vasculature, which ultimately leads to the heart failure formation [14].

Notably, patients with sarcoid heart disease have an increased risk of developing arrhythmogenic cardiomyopathy (dysplasia) of the myocardium, both left and right ventricles[3,15].

The course of cardiac sarcoidosis does not correspond to the process phases in the lungs. About a third of patients have heart damage in the background of the mediastinal-pulmonary process. Cardiac sarcoidosis can manifest itself, masking other diseases, such as idiopathic cardiomyopathy, myocarditis, coronary artery disease, and coronary X syndrome, making it difficult to confirm the diagnosis without endomyocardial biopsy.

Diagnosis

Morphological pattern

Sarcoid granulomas, as a rule, have no necrosis area, which is why they are called non-necrotic granulomas. However, some research groups provide some evidence that necrosis can be found, but it cannot be caseous. Also, it is critically vital to separate sarcoid reactions from sarcoid granulomas. Sarcoid granuloma characterized by cells of monocytic origin include macrophages, epithelioid, Pirogov-Langhans CD4+ T-lymphocytes, and fibroblasts. The Pirogov-Langhans cells are pathognomonic for sarcoid granuloma and have the form of crystals. Sometimes, it is possible to detect Schauman bodies with calcium and iron salts [16].

Radiation diagnostics

Sarcoidosis implies a fundamentally morphological approach to diagnosis, however, highly effective methods for diagnosing infiltrative myocardial lesions, such as magnetic resonance imaging (MRI), have now been proposed [17-19]. However, the effectiveness of MRI is based mainly on statistical indicators of sensitivity and specificity, while to substantiate the place of MRI in the diagnosis of sarcoidosis, a careful comparison with morphological data, and diagnostic data of other infiltrative myocardial diseases is necessary. Characteristics of cardiac sarcoidosis are: small- or large-focal accumulation of contrast in the delayed phase on T1-weighted images (detection of cell necrosis or fibrosis), more often in the basal parts of interventricular septum. There is an increase in signal intensity on T2-weighted images. The chances of detecting the above signs are reduced on the background of corticosteroid therapy [20].

When performing positron emission tomography (PET), focal (mosaic) uptake of 18F-fluorodeoxyglucose and a decrease in the accumulation of 13N-ammonium (reflecting the "pseudo-ischemic" type of metabolism in the foci of active inflammation) are characteristic of cardiac sarcoidosis [21]. The sensitivity of endomyocardial biopsy does not exceed 30%, the reasons for which are: 1) "mosaic" location of granulomas in the myocardium (low percentage of accurate hit); 2) low accessibility of the most frequently affected areas (LV in general and its lower wall) [22].

One of the most promising methods for detecting cardiac sarcoidosis is cardiac magnetic resonance (MRI). An advantage of magnetic resonance is the ability to observe different phases of the myocardium. However, MRI semiotics in cardiac sarcoidosis are not

specific and can be quite variable, as are the variants of the clinical pattern in the studied patients. Interpretation of symptoms requires sufficient qualifications of the MRI specialist and experience with this nosology. Because patients with cardiac sarcoidosis, for several reasons, do not often come to the attention of MRI specialists, such experience is limited, even though modern medical societies are discussing the possible justification of MRI and PET as the "gold" standard for diagnosing cardiac sarcoidosis.

The diagnosis of cardiac sarcoidosis must be considered excluded [3, 23]:

- Among young people with low cardiovascular risk, but with symptoms of heart failure;
- Cardiomyopathy and/or blockade of impulse conduction with a positive response to glucocorticosteroid and/or other immunosuppressive therapy;
- An inexplicable decrease in the LV ejection fraction of less than 40%;
- Unexplained sustained (spontaneous or induced) ventricular tachycardia
- Idiopathic atrioventricular block II or III grade;
- Mosaic capture of 18F-FDG during PET myocardium;
- Delayed accumulation of gadolinium on MRI of the heart;
- Intramyocardial accumulation of 67Ga;
- According to the recommendations of the Russian Society of Cardiology in 2019, the authors distinguish major and minor criteria[24].

Major Criteria

• AV blockade 2 or 3 grades in adults younger than 55 years, in combination with sustained monomorphic VT;
- Thinning of the basal segment of the interventricular septum;
- Increased absorption of the Ga67 isotope by the myocardium;
- Decrease in the EF index less than 50%.

Minor Criteria

- ECG: ventricular arrhythmias (VT, polyfocal or frequent PVCs), complete right bundle branch block, diffuse ST depression and/or ST elevation (up to 0.2).
- Echocardiography: focal disorders of wall contractility or structural changes in the myocardium (aneurysm, thickening or thinning of the left ventricle wall).
- Perfusion defect in myocardial scintigraphy with thallium201 or technetium99m isotopes.
- Presence of structural changes in the wall of the left ventricle and interatrial septum during MRI examination.
- Interstitial fibrosis or moderate infiltration on endomyocardial biopsy.

Heart involvement in sarcoidosis can be identified based on the following clinical features:
- If there are 2 or more major signs;
- If there is 1 major criterion and 2 or more minor criteria;
- If there are 3 or more minor signs.

Differential diagnosis is carried out with coronary artery disease, non-compact myocardium, idiopathic variant of dilated cardiomyopathy, toxic and infectious lesions of the myocardium, arrhythmogenic right ventricular dysplasia, etc.

Laboratory diagnostics

For an approximate assessment of the rheology of a sarcoid lesion, it is customary to use the following markers: soluble interleukin-2 receptor, neopterin, β2-microglobulin, chitotriosidase. An additional assessment can be given by the study of angiotensin-converting enzyme (ACE), C-reactive protein (CRP), as well as the concentration of calcium ions in the blood and urine [3].

The soluble interleukin-2 receptor (sIL-2R) is a fragment of a low-specific subunit of the membrane interleukin-2 receptor [25]. Upon activation of T-lymphocytes and macrophages, sIL-2R is cleaved from the cell membrane. This marker may also be elevated in certain

infections and autoinflammatory conditions (particularly periodic disease like mediterranean fever). Recently, this biomarker has been correlated with the degree of development of sarcoid granulomatosis. It is noted that a persistent decrease in the concentration of this biomarker is determined after the start of glucocorticosteroids (GCS) therapy and during the period of achieving remission. When comparing sIL-2R with CRP and ACE activity, sIL-2R alone predicts the severity of sarcoidosis [26].

There is also some evidence regarding neopterin. Among patients diagnosed with sarcoidosis, neopterin is found at higher levels and decreases as the disease resolves. The combined increase in the concentration of neopterin and sIL-2R is associated with an unfavorable prognosis and requires more aggressive corticosteroid therapy.

It is also necessary to mention that a study shows that among 123 patients with acute sarcoidosis and erythema nodosum with elevated levels of β2-microglobulin, an increase in ACE activity was recorded in only 43 patients [27].

Chitotriosidase is a macrophage activation biomarker that can be elevated in various lysosomal and non-lysosomal diseases, including Gaucher disease, Niemann-Pick disease, galactosialidosis, glycogenosis, malaria, thalassemia, and fungal infections, and serum levels serve as an indicator of the severity of sarcoidosis.

It should be noted that an increase in chitotriosidase is also observed in the development of sarcoid granulomatosis. The information content of this marker was 3 times higher than the values of ACE activity.

An increase in the IL-4/IL-2 index and a decrease in the level of IFN-γ serve as predictors of an unfavorable progressive course of the disease [3, 28].

Cardiac Sarcoidosis: Treatment

The goal of sarcoidosis treatment is to prevent or control organ damage as much as possible, as well as to alleviate organ-dependent symptoms and improve the patient's quality of life. Regardless of the form of manifestation of the disease, all patients are strongly recommended to conduct a comprehensive study, followed by a dynamic observation by the attending physician (immunologist, pulmonologist, rheumatologist, cardiologist, therapist, etc.). It should be considered that spontaneous remission (30-45%) is possible in sarcoidosis, but most often this phenomenon is observed in the acute variant of the course with an isolated lesion of the intrathoracic lymph nodes. There is no etiotropic therapy for sarcoidosis. In all cases, it is recommended to compare the need for treatment with the severity of the consequences from the use of corticosteroid, cytostatic or biological ("targeted") therapy administration.

The treatment of cardiac sarcoidosis should be initiated as soon as the diagnosis is confirmed by a council or advisory committee in the heart failure unit. The treatment approach for cardiac sarcoidosis or cardiac involvement in systemic sarcoid granulomatosis is similar [29, 30].

Glucocorticosteroids (GCS) are the first-line drugs. In the absence of contraindications, all patients with an established diagnosis of cardiac sarcoidosis are recommended to take corticosteroids. Managing patients with cardiac sarcoidosis is an arduous task with many unknowns, the solution of which requires great responsibility, careful monitoring of the dynamics of clinical manifestations and the processing process activity, as well as the efficacy and safety of prescribed drugs. Oral corticosteroids in most patients reduce systemic inflammation, thereby slowing down, stopping and sometimes even preventing organ alteration. GCS can be prescribed as monotherapy or in combination with other drugs.

The drug of choice is prednisolone. The recommended daily dose is 0.3-0.5 mg/kg (15-

40 mg) per doses daily, for 1-3 months, for at least 9-12 months. When a positive effect is achieved, the prednisolone dose is reduced by 5 mg per month to a maintenance dose of 5–15 mg per day, for another 6–9 months until complete canceling [31-33].

Methotrexate is especially recommended for cardiac sarcoidosis orally at a dose of 2.5-15 mg 1 per week. In the cases of resistance, the dose can be elevated to 25 mg 1 per week[34, 35]. Subcutaneous administration is more recommended during doses above 15 mg 1 per week. Monitoring of liver and kidney function every 1–3 months is highly recommended[36]. If serum creatinine > 1.5 mg/dl (GFR < 50 ml/min), dosage adjustment or an alternative drug may be required for individuals with renal insufficiency.

Treatment with methotrexate should be interrupted when AST and ALT levels rise by more than 3 times, with subsequent resumption at a lower dose after laboratory parameters normalization. In each case, it is worth raising the question of the possible use of hepatoprotectors (low evidence). The use of methotrexate is contraindicated in women who are planning pregnancy, since methotrexate induces ovum necrosis. To minimize the side effects that occur during treatment with methotrexate, it is mandatory to take folic acid (5-10 mg/week), which should be prescribed no earlier than 24 hours after methotrexate intake.

According to the recommendations of the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) expert commission, methotrexate in the treatment of sarcoidosis is considered as [37]:

1. Second line drug with refractory to corticosteroids, with adverse reactions caused by steroids, and also to reduce the dose of a steroid;
2. A first-line drug as mono- or combined therapy with steroids (bridge therapy).

TNF-alpha inhibitors have been shown to be effective in reducing the symptoms of systemic sarcoidosis with cardiac involvement [31, 38-40].

Dosage modes:

- Infliximab – as an intravenous infusion, starts at 3-5 mg/kg, with loading doses at weeks «zero» (first injection), then second and six weeks, after which patients receive an infusion for 4-8 weeks.
- Adalimumab – preferably in the mode of "intermittent loading" of 120 mg in the first week and 80 mg in the second week. After this, switch to a dose of 40 mg per week.

Other treatment strategies: Due to cyclophosphamide toxicity, it is usually indicated for the treatment of patients with severe sarcoidosis not controlled with corticosteroids, methotrexate, or in the case of limitations of TNF inhibitors administration. Studies have demonstrated that cyclophosphamide is effective in some patients with refractory manifestations of cardiac sarcoidosis [41].

Tofacitinib is a selective inhibitor of the Janus kinase (JAK) family and an activator of the STAT protein. Studies have shown this drug's effectiveness in treating refractory forms of permanent ventricular tachycardia [42].

In certain situations, individuals with cardiac sarcoidosis may require a cardiac defibrillator to prevent sudden cardiac arrest or manage heart rhythm abnormalities. Healthcare professionals evaluate various factors to determine the risk of life-threatening arrhythmias, such as the presence of heart tissue scarring or abnormal electrical conductance. They also consider the patient's medical history, symptoms, and the severity of the cardiac sarcoidosis. If the risk of sudden cardiac arrest is high, a cardiac defibrillator may be recommended to protect against sudden death. In some cases, cardiac sarcoidosis can cause issues with the heart's conduction system, necessitating both pacing and defibrillation capabilities in a defibrillator. The decision to insert a cardiac defibrillator is based on a thorough assessment of individual circumstances and the risk of life-threatening arrhythmias. Collaboration between cardiologists, electrophysiologists, and other specialists is crucial to tailor the treatment approach to the specific needs of each patient.

A cardioverter-defibrillator is recommended for patients with life-threatening ventricular arrhythmias. Notably, systemic corticosteroid therapy normalizes myocardial conduction and excitability, however, in some patients, ectopic foci remain active for up to 6 months from the start of successful treatment of sarcoidosis. Therefore, the risk of destabilization of the rhythm and conduction of the heart also remains and increases whenever the dose of the administered drug is reduced [43-48].

Patients with severe heart failure should be considered for a heart transplant. However, cases of recurrent sarcoidosis have been reported.

Prognosis

Cardiovascular risk must be calculated using the SCORE2 scale [49, 50]. All patients must be assessed regarding possible comorbidities, for example, diabetes-related cardiovascular injury [51-55], history of chemotherapy intake [56], thyroid gland pathology [57], oral cavity inflammation [58], helicobacter pylori infection [59], human immunodeficiency viruses [60] and other viruses related inflammation [61]. The level of high sensitive troponin [62] and apolipoprotein(a) [63], Nt-pro-BNP [64] can provide supplementary information regarding the state of cardiovascular health in cardiac sarcoidosis patients. Independent predictors of a poor prognosis are heart failure III-IV functional class by NYHA classification, as well as critical increase in the LV end-diastolic size, and resistant ventricular tachycardia [3, 30, 31].

Conclusion

Summarizing the above facts, the authors can draw the following conclusions:

- Sarcoidosis has transformed into multiorgan, multisystem granulomatosis with an unpredictable course;
- To screen the potential involvement of the heart in the continuum of sarcoid granulomatosis, all patients with sarcoidosis are recommended to conduct ECG and echocardiography studies;
- The importance of creating a donor base, its improvement and increase in availability is noted, since with refractory current forms of cardiac sarcoidosis, heart transplantation is, although radical, but an effective method of treatment despite the long postoperative and recovery period.

References

1. Alba AC, Takaya Y, Nakamura K, Nishii N, Ito H. Clinical outcomes of patients with isolated cardiac sarcoidosis confirmed by clinical diagnostic criteria. Int J Cardiol 2021; 345: 49-53. https://doi.org/10.1016/j.ijcard.2021.10.150

2. Lehtonen J, Uusitalo V, Pöyhönen P, Mäyränpää MI, Kupari M. Cardiac sarcoidosis: phenotypes, diagnosis, treatment, and prognosis. Eur Heart J 2023; 44(17): 1495-1510. https://doi.org/10.1093/eurheartj/ehad067

3. Avagimyan A, Mrochek A. Sarcoidosis textbooks for clinicians. Yerevan-Minsk. Yerevan, Republic of Armenia; 2021 ISBN 9789939031750.

4. Spagnolo P, Bernardinello N. Sarcoidosis. Immunol Allergy Clin North Am 2023; 43(2): 259-272. https://doi.org/10.1016/j.iac.2023.01.008

5. Evlampieva LG, Yaroslavskaya EI. Sarcoidosis in Actual Clinical Practice. Sib J Clin Exp Med 2018; 33(3): 17-21. https://doi.org/10.29001/2073-8552-2018-33-3-17-21

6. Voronkova OO, Tsvetkova OA, Avdeev SN, Rogova EF, Abdullaeva GB. Sarcoidosis with Cardiac

Involvement and Monoclonal Gammopathy. Kardiologiia 2020;60(4):151-6. https://doi.org/10.18087/cardio.2020.4.n712

7. Sama C, Fongwen NT, Chobufo MD, Hamirani YS, Mills JD, Roberts M, et al. A systematic review and meta-analysis of the prevalence, incidence, and predictors of atrial fibrillation in cardiac sarcoidosis. Int J Cardiol 2023; 391: 131285. https://doi.org/10.1016/j.ijcard.2023.131285

8. Sohn DW, Park JB. Cardiac sarcoidosis. Heart 2023; 109(15): 1132-1138. https://doi.org/10.1136/heartjnl-2022-321379

9. Piriou N, Bruneval P. Cardiac sarcoidosis: A multimodal approach to reach the diagnosis. Int J Cardiol 2021; 323: 264-266. https://doi.org/10.1016/j.ijcard.2020.10.047

10. Dabir D, Luetkens J, Kuetting D, Nadal J, Schild HH, Thomas D. Myocardial Mapping in Systemic Sarcoidosis: A Comparison of Two Measurement Approaches. Rofo 2021;193(1):68-76. https://doi.org/10.1055/a-1174-0537

11. Schindler TH, Derenoncourt P, Leucker TM. Cardiac sarcoidosis and prediction of sudden death: An ongoing clinical dilemma?. Int J Cardiol 2021; 329: 177-178. https://doi.org/10.1016/j.ijcard.2020.12.035

12. Franke KB, Marshall H, Kennewell P, Pham HD, Tully PJ, Rattanakosit T, et al. Risk and predictors of sudden death in cardiac sarcoidosis: A systematic review and meta-analysis. Int J Cardiol 2021; 328: 130-140. https://doi.org/10.1016/j.ijcard.2020.11.044

13. Koyanagawa K, Naya M, Aikawa T, Manabe O, Kuzume M, Ohira H, et al. Prognostic value of phase analysis on gated single photon emission computed tomography in patients with cardiac sarcoidosis. J Nucl Cardiol 2021; 28(1): 128-136. https://doi.org/10.1007/s12350-019-01660-9

14. Kouranos V, Sharma R. Cardiac sarcoidosis: state-of-the-art review. Heart 2021;107(19):1591-9. https://doi.org/10.1136/heartjnl-2019-316442

15. Pelzer T, Jung P. Pulmonary and Cardiac Sarcoidosis - Diagnosis and Therapy. Dtsch Med Wochenschr 2021; 146(5): 335-343. https://doi.org/10.1055/a-1239-4492

16. Palchikova IA, Denisova OA, Chernyavskaya GM, Purlik IL, Kalacheva TP, Naumov AO, et al. Clinical and morphological phenotypes in intrathoracic sarcoidosis. Bull Sib Med 2021; 20(4): 18-24. https://doi.org/10.20538/1682-0363-2021-4-18-24

17. Jabbari P, Sadeghalvad M, Rezaei N. An inflammatory triangle in Sarcoidosis: PPAR-γ, immune microenvironment, and inflammation. Expert Opin Biol Ther 2021;21(11):1451-9. https://doi.org/10.1080/14712598.2021.1913118

18. Hauer RNW. Cardiac sarcoidosis mimicking definite arrhythmogenic right ventricular cardiomyopathy. Heart Rhythm 2021; 18(2): 239-240. https://doi.org/10.1016/j.hrthm.2020.10.012

19. Locke AH, Gurin MI, Sabe M, Hauser TH, Zimetbaum P. Cardiol Rev 2021; 29(3): 131-142. https://doi.org/10.1097/CRD.0000000000000354

20. Lagan J, Naish JH, Simpson K, Zi M, Cartwright EJ, Foden P, et al. JACC Cardiov Imag 2021; 14(2): 365-376. https://doi.org/10.1016/j.jcmg.2020.02.001

21. Ribeiro Neto ML, Jellis CL, Joyce E, Callahan TD, Hachamovitch R, Culver DA. Update in Cardiac Sarcoidosis. Ann Am Thorac Soc 2019; 16(11): 1341-1350. https://doi.org/10.1513/AnnalsATS.201902-119CME

22. Kobayashi Y. Idiopathic Ventricular Premature Contraction and Ventricular Tachycardia: Distribution of the Origin, Diagnostic Algorithm, and Catheter Ablation. J Nippon Med Sch 2018; 85(2): 87-94. https://doi.org/10.1272/jnms.2018_85-14

23. Trisvetova E, Yudina O, Smolenskiy A, Cherstvyy E. Diagnostics of isolated heart sarcoidosis. Arkh Patol 2019; 81 (1): 57-64. https://doi.org/10.17116/patol20198101157

24. Rosenthal DG, Fang CD, Groh CA, Nah G, Vittinghoff E, Dewland TA, et al. Heart Failure, Atrioventricular Block, and Ventricular Tachycardia in Sarcoidosis. J

Am Heart Assoc 2021; 10(5): e017692. https://doi.org/10.1161/JAHA.120.017692

25. Fathima S, Roberts WC. Comparison of Clinical and Morphologic Findings in Patients With Cardiac Sarcoidosis Severe Enough to Warrant Heart Transplantation in Those With -vs- Those Without Non-Caseating Granulomas in the Explanted Heart (Burnt-Out Sarcoid). Am J Cardiol 2019; 124(4): 599-603. https://doi.org/10.1016/j.amjcard.2019.05.020

26. Markatis E, Afthinos A, Antonakis E, Papanikolaou IC. Cardiac sarcoidosis: diagnosis and management. Rev Cardiovasc Med 2020; 21(3): 321-338. https://doi.org/10.31083/j.rcm.2020.03.102

27. Stukalova OV, Meladze NV, Ivanova DA, Shvecz TM, Gaman SA, Butorova EA, et al. Magnetic resonance imaging of the heart in the diagnosis of sarcoidosis. Ter Arkh 2018; 90(12): 101-106. https://doi.org/10.26442/00403660.2018.12.000017

28. Komada T, Suzuki K, Ishiguchi H, Kawai H, Okumura T, Hirashiki A, et al. Magnetic resonance imaging of cardiac sarcoidosis: an evaluation of the cardiac segments and layers that exhibit late gadolinium enhancement. Nagoya J Med Sci 2016; 78(4): 437-446. https://doi.org/10.18999/nagjms.78.4.437

29. Popova EN, Strizhakov LA, Sholomova VI, Ponomarev AB, Moiseev SV, Brovko MU, et al. Clinical features of cardiac lesion in patients with generalized sarcoidosis. Ter Arkh. 2018;90(1):54-9. https://doi.org/10.26442/terarkh201890154-59

30. Shlyakhto E. Russian Society of Cardiology. National cardiology guidelines. 2019, 2nd edition, revised and supplemented, p.689-690. GEOTAR-Media. Moscow, RF.

31. Chuchalin AG, Avdeev SN, Aisanov ZR, Baranova OP, Borisov SE, Geppe NA, et al.Sarcoidosis: federal clinical guidelines for diagnosis and treatment. Pulmonologiia 2022; 32(6): 806-833. https://doi.org/10.18093/0869-0189-2022-32-6-806-833

32. Kouranos V, Wells AU, Sharma R. Treatment of cardiac sarcoidosis. Curr Opin Pulm Med 2019; 25(5): 519-525. https://doi.org/10.1097/MCP.0000000000000611

33. Mairina SV, Ryzhkova DV, Mitrofanova LB, Ryzhkov AV, Murtazalieva PM, Moiseeva OM.. Modern approaches to the diagnosis and treatment of cardiac sarcoidosis: results of a cohort study. Russ J Cardiol 2023; 28(5): 5301. https://doi.org/10.15829/1560-4071-2023-5301

34. Kengo K,Kazuhiro S. Diagnosis and treatment of cardiac sarcoidosis. Heart 2016; 102(3): 184-190. https://doi.org/10.1136/heartjnl-2015-307877

35. Nagai S, Yokomatsu T, Tanizawa K, Ikezoe K, Handa T, Ito Y, et al. Treatment with methotrexate and low-dose corticosteroids in sarcoidosis patients with cardiac lesions. Intern Med 2014; 53(5): 427-33. https://doi.org/10.2169/internalmedicine.53.0794

36. Shabalin V, Grinshteyn Yu. Cardiac sarcoidosis: modern diagnostics and therapy. Russ J Cardiol 2020; 25(11): 4052. https://doi.org/10.15829/29/1560-4071-2020-4052

37. Cremers JP, Drent M, Bast A, Shigemitsu H, Baughman RP, Valeyre D, et al. Multinational evidence-based World Association of Sarcoidosis and Other Granulomatous Disorders recommendations for the use of methotrexate in sarcoidosis: integrating systematic literature research and expert opinion of sarcoidologists worldwide. Curr Opin Pulm Med 2013; 19(5): 545-561. https://doi.org/10.1097/MCP.0b013e3283642a7a

38. Baker MC, Sheth K, Witteles R, Genovese MC, Shoor S, Simard JF. TNF-alpha inhibition for the treatment of cardiac sarcoidosis. Semin Arthritis Rheum 2020; 50(3): 546-552. https://doi.org/10.1016/j.semarthrit.2019.11.004

39. Bakker AL, Mathijssen H, Azzahhafi J, Swaans MJ, Veltkamp M, Keijsers RG, et al. Effectiveness and safety of infliximab in cardiac Sarcoidosis. Int J Cardiol 2021; 330: 179-185. https://doi.org/10.1016/j.ijcard.2021.02.022

40. Papanikolaou IC, Antonakis E, Pandi A. State-of-the-Art Treatments for Sarcoidosis. Methodist Debakey Cardiovasc J 2022; 18(2): 94-105. https://doi.org/10.14797/mdcvj.1068

41. Schulze AB, Evers G, Kümmel A, Rosenow F, Sackarnd J, Hering JP, et al. Cyclophosphamide pulse therapy as treatment for severe interstitial lung diseases. Sarcoidosis Vasc Diffuse Lung Dis 2019; 36(2): 157-166. https//doi: 10.36141/svdld.v36i2.7636.

42. Damsky W, Wang A, Kim DJ, Young BD, Singh K, Murphy MJ, et al. Inhibition of type 1 immunity with tofacitinib is associated with marked improvement in longstanding sarcoidosis. Nat Commun 2022; 13(1): 3140. https://doi.org/10.1038/s41467-022-30615-x

43. Hussain B, Markson F, Mamas MA, Alraies C, Aggarwal V, Kumar G, et al. Effects of Valvular Heart Disease on Clinical Outcomes in Sarcoidosis. Curr Probl Cardiol 2023; 48(10): 101866. https://doi.org/10.1016/j.cpcardiol.2023.101866

44. daSilva-deAbreu A, Mandras SA. Sarcoidosis-Associated Pulmonary Hypertension: An Updated Review and Discussion of the Clinical Conundrum. Curr Probl Cardiol 2021; 46(3): 100506. https://doi.org/10.1016/j.cpcardiol.2019.100506

45. Mkoko P, Rajoo ST, Chin A. Causes of Heart Block in Young and Middle-Aged South Africans. Curr Probl Cardiol 2023; 48(8): 101247. https://doi.org/10.1016/j.cpcardiol.2022.101247

46. Alba AC, Gupta S, Kugathasan L, Ha A, Ochoa A, Balter M, et al. Council of Myocardiopathies of the Inter-American Society of Cardiology. Cardiac Sarcoidosis: A Clinical Overview. Curr Probl Cardiol 2021; 46(10): 100936. https://doi.org/10.1016/j.cpcardiol.2021.100936

47. Thakker RA, Abdelmaseih R, Hasan SM. Sarcoidosis and Aortic Stenosis: A Role for Transcatheter Aortic Valve Replacement?. Curr Probl Cardiol 2021; 46(12): 100858. https://doi.org/10.1016/j.cpcardiol.2021.100858

48. DaSilva-deAbreu A, daSilva-deAbreu A, Bracamonte-Baran W, Condado JF, Babaliaros V, Tafur-Soto J, Mandras SA. Characteristics and Outcomes of Pulmonary Angioplasty With or Without Stenting for Sarcoidosis-Associated Pulmonary Hypertension: Systematic Review and Individual Participant Data Meta-Analysis. Curr Probl Cardiol. 2021;46(3):100616. https://doi.org/10.1016/j.cpcardiol.2020.100616

49. Boytsov SA, Pogosova NV, Ansheles AA, Badtieva VA, Balakhonova TV, Barbarash OL, et al. Cardiovascular prevention 2022. Russian national guidelines. Russ J Cardiol 2023; 28(5): 5452. https://doi.org/10.15829/1560-4071-2023-545250.

50. Lobanova N, Chicherina E. Alternative risk factors and their importance in assessment of cardiovascular risk in asymptomatic patients. Bull Siber Med 2020; 19(2): 182-188. https://doi.org/10.20538/1682-0363-2020-2-182-188

51.Avagimyan A, Popov S, Shalnova S. The Pathophysiological Basis of Diabetic Cardiomyopathy Development. Curr Probl Cardiol 2022; 47(9): 101156. https://doi.org/10.1016/j.cpcardiol.2022.101156

52. Avagimyan A, Fogacci F, Pogosova N, Kakrurskiy L, Kogan E, Urazova O, et al. Diabetic Cardiomyopathy: 2023 Update by the International Multidisciplinary Board of Experts. Curr Probl Cardiol 2024;49(1 Pt A):102052. https://doi.org/10.1016/j.cpcardiol.2023.102052

53. Bespalova I, Romanov D, Denisova O,Bragina E, Koshchavtseva Y, Mitrichenko U, et al. Sarcoidosis as a disease associated with metabolic syndrome. Bull Siber Med 2023; 22(3): 80-87. https://doi.org/10.20538/1682-0363-2023-3-80-87

54. Avagimyan A, Sukiasyan L, Sahakyan K, Gevorgyan T, Aznauryan A. The molecular mechanism of diabetes mellitus - related impairment of cardiovascular homeostasis. Georgian Med News 2021; (315): 99-103.

55. Papadopoulos KI, Hallengren B. Multiple etiologies explain the association between sarcoidosis and diabetes mellitus. Expert Rev Respir Med 2022; 16(3): 367-368. https://doi.org/10.1080/17476348.2022.2035220

56. Avagimyan A, Kakturskiy L, Heshmat-Ghahdarijani K, Pogosova N, Sarrafzadegan N. Anthracycline Associated Disturbances of Cardiovascular

Homeostasis. Curr Probl Cardiol 2022; 47(5): 100909. https://doi.org/10.1016/j.cpcardiol.2021.100909

57. Avagimyan A, Gvianishvili T, Gogiashvili L, Kakturskiy L, Sarrafzadegan N, Aznauryan A.Chemotherapy, hypothyroidism and oral dysbiosis as a novel risk factor of cardiovascular pathology development. Curr Probl Cardiol 2023; 48(3): 101051. https://doi.org/10.1016/j.cpcardiol.2021.101051

58.Avagimyan A, Gvianishvili T, Gogiashvili L, Kakturskiy L, Sarrafzadegan N, Aznauryan A. The atherogenic impact of oral cavity disbiosis. Georgian Med News 2020; (304-305) : 69-74.

59. Avagimyan AA, Mkrtchyan LG, Navasardyan GA, Gevorkyan AA, Ananyan EA, Pashinyan NE, et al.The role of Helicobacter pylori in cardiovascular toxicity mechanisms. Russ J Cardiol 2019; (12): 169-174. https://doi.org/10.15829/1560-4071-2019-12-169-174

60. Avagimyan A, Pogosova N, Kakturskiy L, Sheibani M, Urazova O, Trofimenko A,et al.HIV-Related Atherosclerosis: State-of-the-Art-Review. Curr Probl Cardiol 2023; 48(9): 101783. https://doi.org/10.1016/j.cpcardiol.2023.101783

61. Avagimyan A, Aznauryan A, Chernova A. The Role of Viral Infection in the Mechanisms of Initiation of Atherogenesis and Destabilization of Atheroma. Cardiol Belarus 2019; 11(6): 947-953.

62. Bobbio E, Hjalmarsson C, Björkenstam M, Polte CL, Oldfors A, Lindström U, et al. Diagnosis, management, and outcome of cardiac sarcoidosis and giant cell myocarditis: a Swedish single center experience. BMC Cardiovasc Disord 2022; 22(1): 192. https://doi.org/10.1186/s12872-022-02639-0

63. Fogacci F, Di Micoli V, Avagimyan A, Giovannini M, Imbalzano E, Cicero AF. Assessment of Apolipoprotein(a) Isoform Size Using Phenotypic and Genotypic Methods. Int J Mol Sci 2023; 24(18): 13886. https://doi.org/10.3390/ijms241813886

64. Darlington P, Gabrielsen A, Cederlund K, Kullberg S, Grunewald J, Eklund A, et al., Diagnostic approach for cardiac involvement in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2019; 36(1): 11-17. https://doi.org/10.36141/svdld.v36i1.7132

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