



Kasuistika | Case report

Electrical storm due to myocarditis in post-infarct patient: When two diseases meet

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ARTICLE INFO

Article history:

Received: 1. 2. 2015

Received in revised form: 7. 5. 2015

Accepted: 8. 5. 2015

Available online: 3. 6. 2015

Klíčová slova:

Aneurysma

Arytmická bouře

Autoprotilátky proti β_1 -adrenergnímu receptoru

Komorová tachykardie

Myokarditida

Radiofrekvenční katetrizační ablace

Keywords:

Aneurysm

Autoantibodies to beta1-adrenergic receptor

Electrical storm

Myocarditis

Ventricular tachycardia

Radiofrequency catheter ablation

SOUHRN

V této kasuistice popisujeme epizodu arytmiické (elektrické) bouře (AB) na podkladě myokarditidy u pacienta po infarktu myokardu. Arytmická bouře byla přerušena aneurysmektomií a dodatečnou izolací ložisek komorové tachykardie pomocí radiofrekvenční katetrizační ablace. Histologické vyšetření aneurysmatické tkáně prokázalo akutní myokarditidu. Hlavními nálezy ukazujícími na akutní zánět myokardu byly zvýšené hodnoty biomarkeru zánětu IL-6 v periférii a autoprotilátek proti β_1 -adrenergnímu receptoru (β_1 -AABs). Gatovaná SPECT s analýzou fázových obrazů se ukázala být vhodnou strategií pro zobrazování potenciálně reverzibilních příčin komorových arytmí, např. myokarditidy. Naše nálezy by tak mohly přidat nové poznatky o patogenezi a faktorech predisponujících ke vzniku komorových arytmí, zvláště u pacientů s arytmiickou bouří.

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ABSTRACT

This case presents an episode of electrical storm (ES) in post-myocardial infarction patient results from myocarditis. ES was interrupted by aneurysmectomy and additional isolation of VT origins by radiofrequency catheter ablation. The histological evaluation of aneurysm material proved acute myocarditis. The key findings indicating acute inflammation in myocardium was an increased level of peripheral inflammatory biomarker IL6 and autoantibodies to beta1-adrenergic receptor (β_1 -AABs). Gated SPECT with phase images analysis turned out to be appropriate imaging strategy in visualizing potentially reversible causes of ventricular arrhythmias such as myocarditis. Taking together our findings might add some information on the pathogenesis and predisposing factors of ventricular arrhythmias especially in the cases of electrical storm.

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DOI: 10.1016/j.crvasa.2015.05.006

Introduction

Electrical storm (ES) is a life-threatening syndrome that is defined by three or more episodes of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) or appropriate shocks from implantable cardioverter-defibrillator (ICD) within 24 h. The incidence of ES varies from 4% to 28% in different studied populations. According to the MADIT-II substudy, patients who experienced ES showed a 7.4-fold higher risk of death compared with those without [1]. It is evident that ES is associated with worse patient's outcome, however it is still unclear whether their poor prognosis is a direct consequence of ES or it is simply an epiphenomenon of advanced structural heart disease [2].

A lot of attempts have been made in order to identify the possible predictors of ES. Undoubtedly that it is strongly associated with progressive heart failure (HF) [2]. Streitner et al. showed that episodes of ES in patients with HF could be predicted by elevated serum concentrations of inflammatory biomarkers such as hs-CRP, NT-pro BNP and IL-6 [3]. On the other hand the deterioration of HF itself can be accompanied by elevation of inflammatory biomarkers as well as anticardiac antibodies [4,5]. At the same time increased cytokine level and persistence of autoantibodies to beta1-adrenergic receptor (β 1-AAbs) is usually observed in the serum of patients with inflammatory cardiac pathology [5]. These biomarkers can directly or indirectly worsen left ventricular (LV) function and so trigger VTs [5,6] as well as reflect the ongoing inflammation in myocardium.

One of clinical manifestations of myocarditis is new-onset ventricular arrhythmias. Such arrhythmias are often related to myocardial damage caused by toxic or viral as well as autoimmune injury. Moreover inflammatory affection of myocardium can additionally trigger arrhythmias also in patients with pre-existing arrhythmogenic focuses as we observed in presented case.

Case report

A 65-year old woman admitted to Intensive Care Unit of our Hospital in February 2013 because of recurrent VT episodes and multiple ICD shocks during the last three days.

The patient's history indicates that she survived from acute anterior myocardial infarction (MI) in 2001 and was clinically stable until the year 2012 on standard therapy. In July 2012 the patient suffered from recurrent anterior MI, which was complicated by sustained VT. That time the patient underwent coronary angiography followed by implantation of two stents in the left anterior descending artery. Two months later the patient suffered from several episodes of palpitations and presyncope, that were documented on ECG as VTs. Clinical examination showed symptoms relevant to NYHA class II of heart failure. The echocardiography revealed a large anterior-septal hypokinesis with an apical aneurysm and significantly decreased left ventricular ejection fraction (LVEF) (27%). Patient underwent ICD implantation for secondary prevention of SCD and was stable until February 2013. It should be noted, that about two weeks before the onset of ES the patient had an episode of acute respiratory infection.

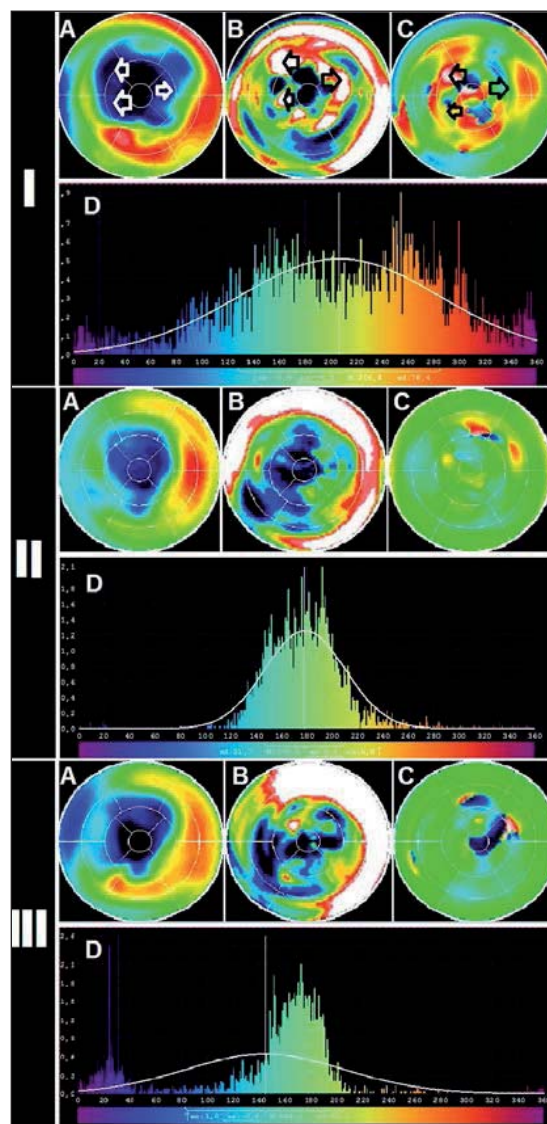


Fig. 1 – Dynamic changes of gated SPECT images on follow-up. I – study performed on admission to the hospital; II – study performed after aneurysm resection; III – the last study performed 5 months after additional catheter ablation of the VT origin. A – end diastolic perfusion images, B – wall motion images, C – phase images, D – histogram of phase images.

For study I: A – transmurial decreasing of perfusion at the anterior-apical segments of left ventricle, at the aneurysm; B – dissociated foci of pathological active wall motion inside the aneurysm (indicated by arrows); C – dissociated foci of pathological asynchrony which topographically corresponded to foci of active wall motion. For study II: Dissociated foci of wall motion at the aneurysm zone disappeared with only two focuses of pathological asynchrony at the borders of former aneurysm at the antero-lateral wall left (C). For study III: two left foci of pathological asynchrony (C) preserved their topography but changed their temporal characteristics, that indicates on changes of their pathological activity.

On present admission to the hospital the patient was hemodynamically stable. She was on treatment with bisoprolol 5 mg/daily, amiodarone 200 mg/daily, clopidogrel, statins, aspirin, angiotensin converting enzyme (ACE) inhibitors and diuretics in appropriate doses. The ICD interrogation revealed multiple episodes of monomorphic VT with different QRS morphologies and maximal heart rate

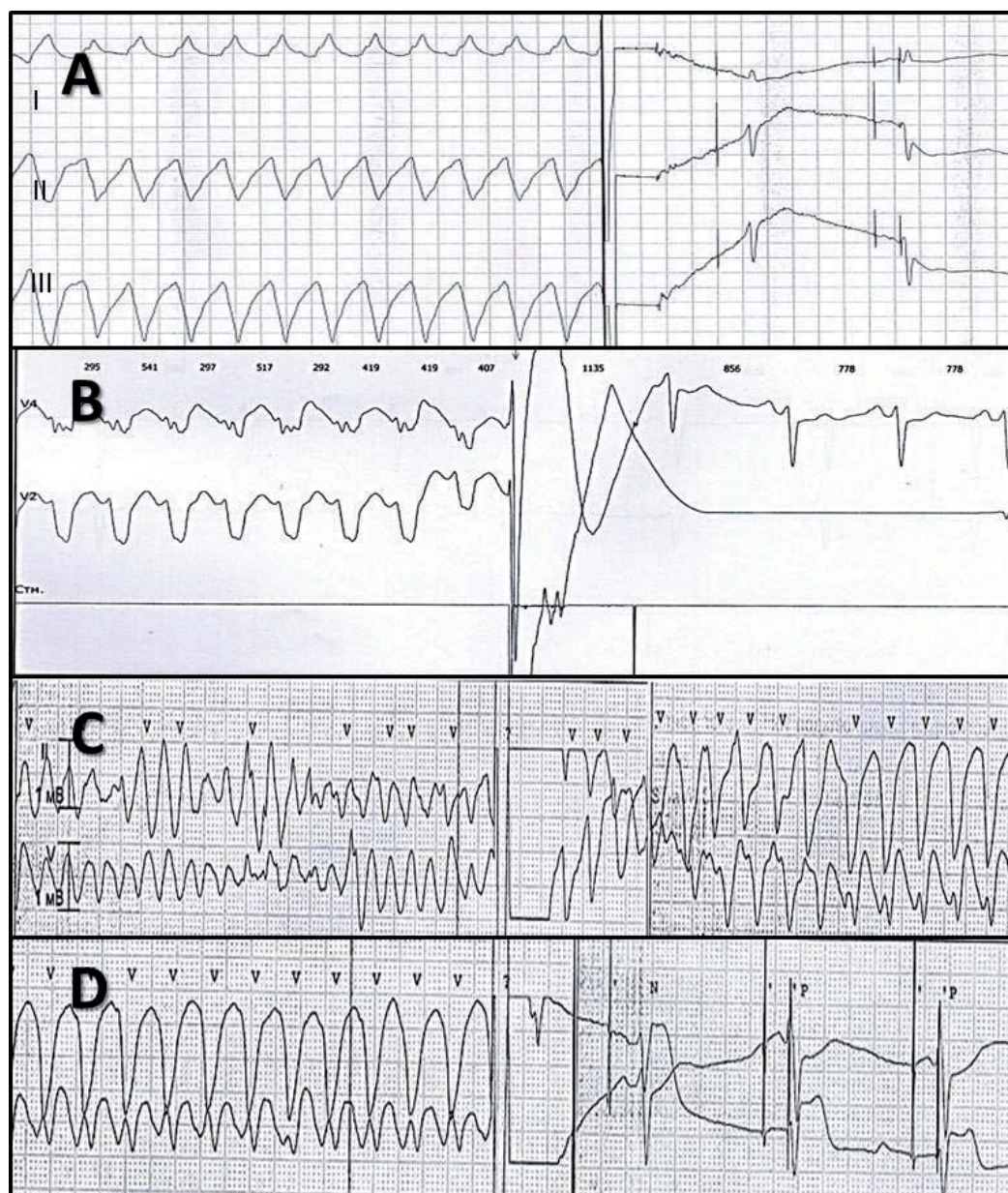


Fig. 2 – The ECG with episodes of monomorphic ventricular tachycardia (VT). (A, B) examples of successful treatment of VT with ICD shock. (C, D) continuous recording: ICD shock transforms VF into ventricular flutter (C), terminated by ICD shock (D).

of 220 b.p.m. and a single episode of VF. Ventricular arrhythmias were successfully terminated by ICD.

Laboratory tests showed normal serum levels of thyroid hormones, potassium, magnesium, hs-CRP. The troponin test was negative. Polymerase chain reaction (PCR) revealed absent of herpes simplex 1–2 virus, human herpes 6 virus, Epstein-Barr virus, cytomegalovirus and parvovirus B19. The additional evaluation of inflammatory biomarkers found negative concentration of tumor necrosis factor alpha while the level of interleukin 6 (IL6) exceeded reference ranges and was 14.8 pg/ml. We also performed the evaluation of β 1-AAbs in serum by enzyme-linked immunosorbent assay. The level of β 1-AAbs was increased up to 7.2 (the normal values were considered to be less than 1), indicating possible autoimmune component of heart injury process.

Instrumental testing: The chest X-ray showed left ventricle enlargement, no signs of pulmonary edema. Dual-chamber ICD and electrodes were in normal position. Transthoracic echocardiography showed dilated left ventricle (end diastolic diameter [EDD] 6.7 cm, end diastolic volume [EDV] 268 ml) with extensive anterior-septal hypokinesia, huge apical aneurysm, accompanied by decreased LVEF (30%), moderate mitral regurgitation and mild lung pulmonary hypertension (pulmonary artery systolic pressure [PASP] 40 mmHg). Urgent coronary angiography did not show any coronary artery lesions including no evidence of restenosis in previously implanted stents.

Gated SPECT (MIBI) myocardial perfusion revealed significantly dilated left ventricle (EDV = 290 ml) with a clear non-perfused apical and anterior zones. Additional akinesis at non-perfused regions confirmed the diagnosis of anterior

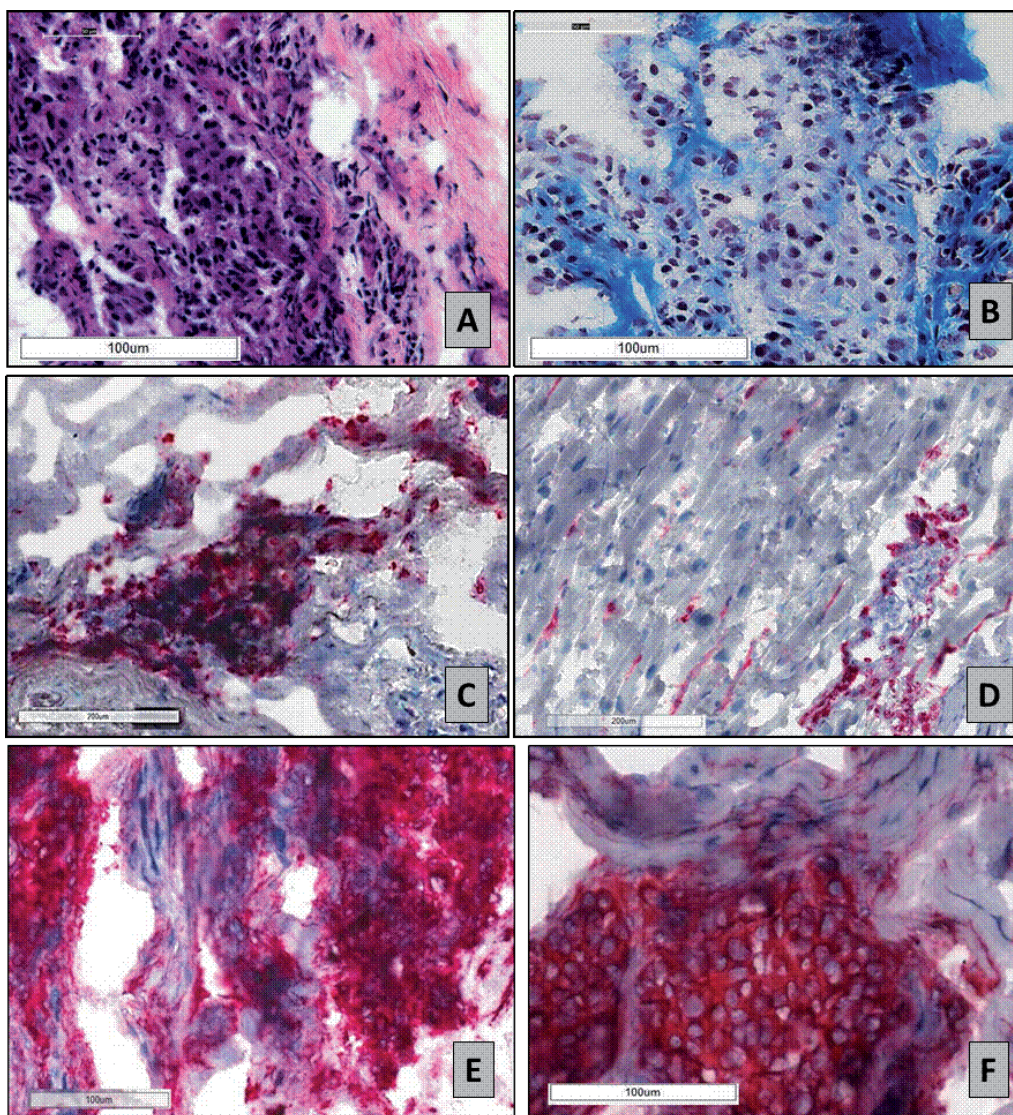


Fig. 3 – Histological evaluation of the rejected aneurysm. Light microscopy.

(A) – hematoxyline-eosine staining. The large infiltrate of lymphocytes and macrophages is detected among the fields of connective tissue. (B) – Masson's trichrome staining. Among collagen fibers the same infiltrate could be seen. (C, D, E, F) - immunohistochemistry alkaline phosphatase staining for CD4+ (C), CD8+ (D), CD68+ (E) and CD3+ (F) inflammatory cells, the cellular nuclei are additionally stained with hematoxyline.

or-apical aneurysm. The only lateral and posterior left ventricular walls were functionally preserved being resulted in LVEF of 24%, the summed *rest* score (SRS) of 49 and high volume of affected myocardium (up to 61%). The additional left ventricular perfusion protocols matching the wall motion abnormalities and phase images detected several dissociated foci of pathological asynchrony and active wall motion inside the aneurysm. The heterogeneous features of these foci makes possible to consider them as probable origins of ventricular arrhythmias (Fig. 1, study I).

According to 24-h Holter ECG almost all spontaneous VT episodes were preceded by bradycardia and have been usually triggered by R-on-T premature ventricular beats. Therefore as the first line of treatment strategy the baseline pacing frequency of ICD was increased from 55 to 70 b.p.m., the dose of bisoprolol was increased to 7.5 mg/daily. Additional continuous infusion of amiodarone (600–900 mg/daily) was started but that produced only temporary

effect. Based on previous history of acute respiratory infection, above mentioned laboratory findings and gated SPECT (MIBI) hypothesis of ES in our patient have been suggested. This made us to start glucocorticosteroid therapy (prednisolon 1 mg/kg daily per os). However, despite of all efforts the patient continued to suffer from frequent VT/VF episodes that required repeated ICD shocks (up to 10 shocks daily) (Fig. 2). Absolute resistance of ES to pharmacological therapy, urged us to the surgical management.

Aneurysmectomy with endocardial resection and ultrasound destruction of endocardium have been performed under intra-aortic balloon pumping and continuous intravenous infusion of lidocaine and was accomplished by endoventricular patch plasty repair (Dor's operation). No intra- and post-operative complications have been noted. During histological evaluation of aneurysm material there were revealed massive subendocardial infiltration with different inflammatory cells (predominantly CD3+ and CD8+ T-cells and CD68+

macrophages, more than 80 cells per 1 mm²). Infiltrates were located among huge areas of connective tissue and sometimes related to necrotizing cardiomyocytes (Fig. 3). According to present quantitative immunohistological criteria the persistence of more than 14 inflammatory cells per 1 mm² is enough for histological diagnosis of active inflammation in myocardium [7]. So, these findings confirmed the diagnosis of acute myocarditis. The most probable cause of myocarditis in our patient seemed to be autoimmune since PCR analyses of aneurysm sample for herpes simplex 1-2 virus, human herpes 6 virus, Epstein-Barr virus, cytomegalovirus, adenovirus, coxsackie virus B3 and parvovirus B19 was negative. No additional therapy based on these findings has been prescribed because of previously unsuccessful experience of glucocorticoid therapy and lack of standardized treatment strategies for myocarditis according to present knowledge.

Post-operative echocardiography demonstrated LV reduction (EDD 6.0 cm, EDV 177 ml), an improvement of LVEF (33 %), with residual akinesia of apical segments due to patch plasty repair, mild-to-moderate mitral regurgitation and decrease of PSAP to 28 mmHg. According to repeated gated SPECT (MIBI) multiple dissociated foci of wall motion abnormalities inside the aneurysm disappeared. However, two foci of pathological asynchrony located in antero-lateral wall were still present (Fig. 1, study II).

The first month after surgery passed uncomplicated. A little later despite continued amiodarone therapy the new onset of ES consisted of 4 ICD shocks occurred. This prompted to perform radiofrequency catheter ablation (RFCA). The electrophysiological mapping of arrhythmogenic substrate revealed the area of delayed activation in anterior LV wall which matched topographically with foci of pathological asynchrony revealed by SPECT that followed by expanded RFCA.

During next five months no ICD interventions occurred and the patient was in stable sinus rhythm on standard HF therapy and amiodarone. Repeated gated SPECT (MIBI) showed that two previously observed focuses of pathological asynchrony in antero-lateral wall had the same topography but changed their temporal characteristics, what indicated changes of their pathological activity (Fig. 1, study III).

Discussion

The main finding in our case is that ES even in post-MI patient can be initiated by inflammatory affection of myocardium. The relation of ES to episode of viral infection in our patient and the elevated level of peripheral biomarkers (IL6 and β 1-AABs) made us to suspect myocarditis. The diagnosis of myocarditis is complex and practically based on both non-invasive and invasive approaches. Endomyocardial biopsy (EMB) is up to now the only "gold standard" in the verification of myocardial inflammation [6]. The clinical course of our patients (its relation to episode of viral infection) and the elevated level of peripheral biomarkers made us to suspect myocarditis. Among noninvasive strategies the cardiac MRI with late gadolinium enhancement is the most prominent nowadays method, which is well standardized for diagnosis of myocarditis [7]. However there is growing evidence that sensitivity and specificity of this method in cases of chronic myocarditis is not high enough [8], moreover it is impossible to use MRI in

patients with implanted pacemaker or ICD. These limitations of existent visualizing modalities for myocarditis detection led to searching for other imaging approaches. The chosen gated SPECT method has helped to solve many tasks: to determine the size and topography of both scar tissue [9] and viable myocardium [10]. Special evaluation of phase images which were previously reported to be useful in dyssynchrony assessment [11] was performed. Due to this analyses we detected pathological pre-contractility foci around the aneurysmatic fibrotic tissue indicated the viable myocardium with possible ectopic activity. In the aspect of heart rhythm disturbances this method turned out to be representative as it was noticed in previous publications [12]. The observed foci were inflammatory by their nature and supposed to be VT origins due to all other findings.

Myocarditis may cause arrhythmias both in acute phase due to inflammatory infiltration and necrosis of the myocytes, and in its chronic phase due to immune reaction, fibrosis and ventricular electrical remodeling. Our patient was known to have large electrically neutral scar zone as the result of recurrent myocardial infarctions. The so called "borderline zone" located at the frontier between scar and viable myocardium is supposed to be the arrhythmogenic substrate of ventricular arrhythmias in most post-MI patients [13]. According to modern concept the onset of major VT/VF episodes is the consequence of activation of "sleeping" arrhythmogenic substrate in ventricular myocardium under the influence of specific triggers and modulating factors. Such a factor in the present case turned out to be inflammation. Our hypothesis was confirmed by results of histological evaluation of aneurysm: we found inflammatory infiltrates in borderline zone of rejected aneurysmatic sac, which served as a *locus minoris resistentiae* predominantly affected during myocarditis.

The existent etiopathogenic strategies of myocarditis treatment are not well established. There were only few attempts aimed to develop specific therapeutic schemes in myocarditis treatment. One of them was randomized, double-blind, placebo-controlled study (TIMIC) reported by Frustaci (2009) suggested prednisolone 1 mg kg⁻¹ day⁻¹ for 4 weeks followed by 0.33 mg kg⁻¹ day⁻¹ for 5 months and azathioprine 2 mg kg⁻¹ day⁻¹ for 6 months in EMB positive myocarditis and chronic (> 6 months) heart failure unresponsive to conventional therapy. Combined therapy (prednisolone and azathioprine) is not recommended until histological confirmation of myocarditis and virus persistence exclusion because virus persistence can result in ineffectiveness of immunosuppressive therapy [15]. In our case the relation of ES to episode of viral infection and the elevated level of peripheral biomarkers (IL6 and β 1-AABs) made us to suspect myocarditis. Together with maximal antiarrhythmic therapy we performed unsuccessful attempt to abort the ongoing inflammation in myocardium by using prednisolone relying on importance of autoimmune injury (high titer of autoantibodies to β 1-AABs). It should be added that patients with ventricular arrhythmias were not included in TIMIC trial so there is no data that such therapy can abort ES. Moreover another one trial (A clinical trial of immunosuppressive therapy for myocarditis: the Myocarditis Treatment Trial Investigators) published by Mason et al. at NEMH in 1995 contradicts TIMIC trial. Its results do not support routine treatment of myocarditis with immunosuppressive drugs [16].

Due to the lack of effectiveness of immunosuppressive treatment no other options were performed to stop inflammation. That's why we turned to surgical methods of VT treatment. Left ventricular aneurysm is a serious complication of acute myocardial infarction (MI) associated with congestive heart failure and ventricular tachycardia (VT). It represents an independent predictor of late sudden cardiac death after acute MI [17]. Moreover recent study performed by Russo (2012) have clearly demonstrated that in a cases of persisting drug-refractory VTs after a biopsy-proven myocarditis RFCA is feasible, safe and effective [18]. Resection of aneurysm with a portion of inflamed myocardium and subsequent RFCA of residuary inflammatory foci interrupted VT recurrence.

Conclusion

ES in post-MI patients at least in some cases may result from inflammatory affection of myocardium. The increased level of peripheral inflammatory biomarkers such as IL6 and β 1-AAbs if observed in patients with ES may reflect the current myocardial inflammation. Gated SPECT with phase images analysis turned out to be a good visualizing method in detection of pathologic ventricular activity and also for diagnosis of the potentially reversible causes of ventricular arrhythmias such as myocarditis.

Taking together our findings might add some information on the pathogenesis and predisposing factors of ventricular arrhythmias especially in the cases of electrical storm. Future investigations should be performed in order to develop strategies for myocarditis treatment which additionally to surgical methods can help to interrupt inflammatory related VTs.

Conflict of interest

All authors have declared no conflict of interest.

Funding body

Financial support for preparation this clinical case was provided by Russian Ministry of Education and Science Agreement No 14.604.21.00.68 from 27.06.2014.

Ethical statement

This document stated that the clinical case was written according to ethical standards. It doesn't contain any patient identifying information. It is completely original.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images (it is written and signed in Russian). A copy of the written informed consent is available for review by the editors of this journal and would be provided immediately if needed.

Author's contributions

All listed authors were involved in drafting the manuscript. They have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data.

All authors have read and approved the final manuscript.

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