

Electroanatomical Voltage Mapping Endomyocardial Biopsy-Guided Diagnosis and Therapy of Erythroparvovirus Myocarditis Presenting with Ventricular Arrhythmias: Case Series and Review of the Literature

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ABSTRACT

Background: Myocarditis of viral origin can be frequently missed due to its various manifestations and possible false negative results after a classical fluoroscopy-guided endomyocardial biopsy. The 3D-electroanatomic mapping (3D-EAM) -guided endomyocardial biopsy reduces the false negative results by targeting the tissue areas with abnormal electrical voltage while also reducing the radiation exposure for patients and operators.

Results: we report on two clinical cases of acute/subacute myocarditis with a first arrhythmic presentation, in which the endomyocardial biopsy guided by 3D-EAM system was fundamental in achieving the diagnosis and guiding the optimal medical therapy. As far as we know these are the two first published cases that show a documented link between Erythroparvovirus and sustained ventricular tachycardia and which moreover show the use of a developing technology such as 3DEAM-guided myocardial biopsy.

Conclusion: 3D-EAM-guided endomyocardial biopsy is promising not only in reducing radiation exposure for patients and operators during such procedures, but also in identifying the tissue areas that must be targeted in order to reduce the false negatives. We also demonstrated how the first manifestation of a myocarditis due to Erythroparvovirus can be a ventricular arrhythmia.

Abbreviations: EMB: Endomyocardial Biopsies; HHV6: Human Herpes Virus 6; COVID19: Coronavirus; 3D- EAM: 3 Dimensional Electroanatomical Mapping; VTs: Ventricular Tachycardias; c-MRI: Cardiac MRI; LV: Left Ventricle, RV: Right Ventricle; B19: Erythoparvovirus B19; RVOT: Right Ventricular Outflow Tract

Introduction

Myocarditis is an inflammation of the cardiac muscle caused by infiltration of immunogenic cells following different kinds of cardiac injury. It most commonly results from a viral illness; however, it can

also be due to non-infectious etiologies. Given its variable clinical presentation, the diagnosis is frequently missed, making it difficult to quantify the true incidence of acute myocarditis. Infectious causes

include a large number of viruses, as well as bacteria, protozoa and fungi; among these pathogens viruses are the most frequent cause of the myocardial inflammatory process. The most common forms of cardiotropic viruses found in endomyocardial biopsies (EMB) are erythroparvovirus B19 (B19V) and human herpes virus 6 (HHV6) and most recently Coronavirus (COVID19) [1-4]. We present two cases of 3 Dimensional electroanatomical mapping (3D-EAM) guided endomyocardial biopsy for the diagnosis and therapy of B19V myocarditis presenting with ventricular arrhythmias.

Case 1

A 54-year-old woman presented to our emergency department with sustained monomorphic ventricular tachycardias (VTs) (inferior axis, RBBB, Figure 1), which, due to evolving haemodynamic instability, had to be cardioverted externally. She had no other known diseases except for a MTHFR mutation without

clinical relevance and did not take any medications. On her arrival and after the external cardioversion she had no complaints. She had a normal blood work with no signs of an active infection and only a slightly elevated Troponin without elevation of CK as well as CKMB. Her ECG in sinus rhythm showed a minimal diffuse ST-elevation and relatively low voltages in the praecordial leads. The patient underwent a coronary-angiography, with no signs of coronary disease, an echocardiography which showed a normal left ventricular function with a slightly enlarged and dyskinetic right ventricle and finally a cardiac MRI (c-MRI) with evidence of preserved LV function and a RV dyskinesia as well as multiple RV aneurysms and areas of edema and multisegmental transmural late gadolinium enhancement on both ventricles, setting a differential diagnosis between sarcoidosis and myocarditis.

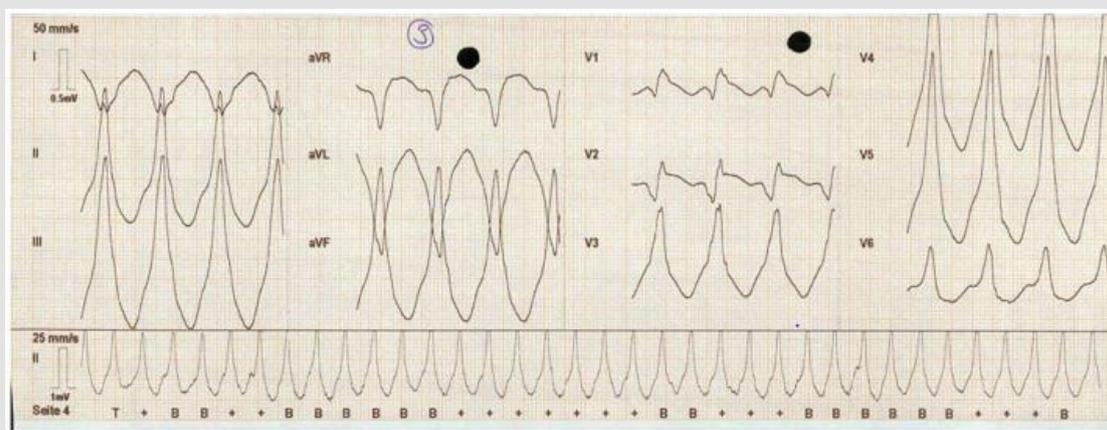


Figure 1: ECG: sustained monomorphic ventricular tachycardia with an inferior axis and a right bundle branch block, rhythm of presentation of the patient in upper case 1.

The patient underwent a PET-CT which ruled out the sarcoidosis. We performed a 3D-EAM-guided EMB to target areas of edema and fibrosis on the interventricular septum and avoid false negative results, which showed signs of an inflammatory cardiomyopathy with B19V with active replication (Table 1). The patient started on a therapy with interferon Beta which is a well-tolerated and safe treatment option, leading to effective virus clearance or reduction

of the virus load in patients with chronic viral cardiomyopathy [5]. After two months of therapy, we repeated a c-MRI which showed an almost complete resolution of the edema with persistence of late enhancement and scarred myocardial tissue. The patient underwent a secondary prophylactic implantation of an ICD and is stable ever since, without having experienced any new arrhythmias.

Table 1: Endomyocardial biopsy results.

	Patient 1	Patient 2
Immunohistology	Lymphocytes (CD3, LFA-1, CD45R0) and macropahges	Lymphocytes (LFA-1, CD45R0)
Morphology	Normal myocytes (18 mcm), normal desmosomal proteins	Enlarged myocytes (23 mcm)
PCR	Erythrovirus DNA and mRNA (active replication)	Erythrovirus DNA and mRNA (active replication)
Therapy	IFN-Beta to reduce the active replication of the virus (mRNA). No actual existing guidelines.	IFN-Beta to reduce the active replication of the virus (mRNA). No actual existing guidelines.

Case 2

A 66-year-old woman was sent to our cardiology department after a secondary prophylactic implantation of an ICD, due to sustained slow ventricular arrhythmias (LSB, inferior axis) after a probatory therapy with amiodarone as well as with sotalolol. The echocardiography showed a mildly reduced EF (41%) with a diffuse hypocontractility, more evident in the basal segments. There were no echocardiographic signs for a dilated cardiomyopathy or for a hypertrophic cardiomyopathy and a coronarography made in the first hospital had already ruled out any ischaemic cause of the reduced EF or the VTs. As the VTs were of incessant nature the patient underwent an emergency VT ablation of the RVOT-septal

focus. Even if the procedure had an acute success with termination of the ventricular arrhythmias, one day after the ablation the VTs started again, and the patient was put on Mexiletine.

Because of the unclear diagnosis of the origin of the ventricular arrhythmias, their persistence after ablation, and the impossibility to run a c-MRI because of the implanted ICD, we decided to perform a 3DEAM-guided EMB which showed an active B19V replication. (Figure 2). We then began an immunomodulating therapy with interferon-beta, under which a cessation of the ventricular arrhythmias was documented. At the follow-up, after six months of interferon-beta there were no sustained VTs anymore in the ICD-memory. No control MRI could be performed because of the device in situ.

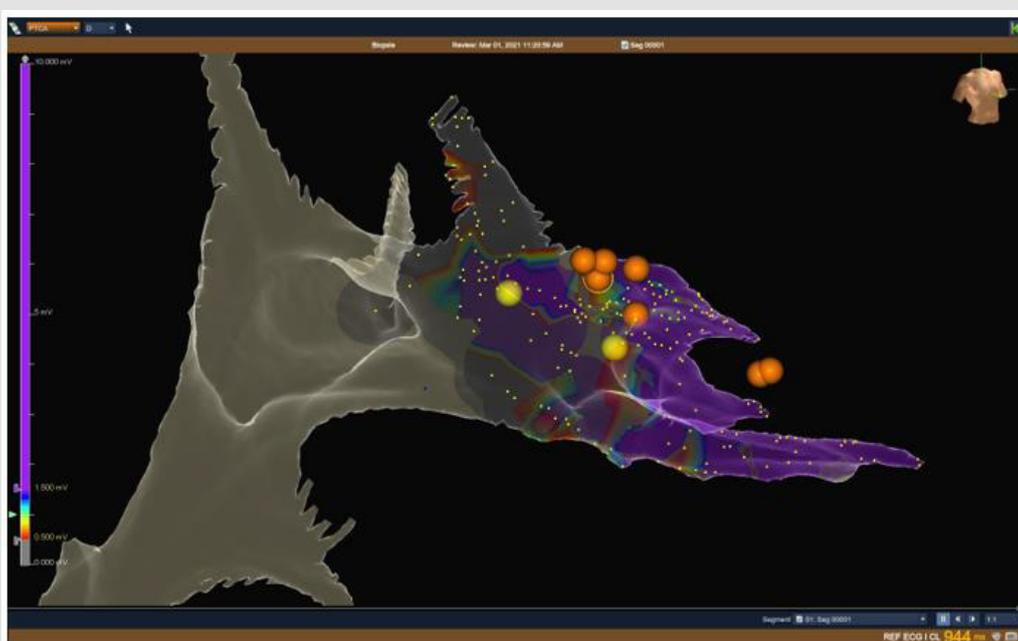


Figure 2: NavX Ensight Precision™ Image : bipolar voltage mapping of the right ventricle showing healthy ventricular tissue in purple (bipolar voltage > 1,5 mV) and scar ventricular tissue (grey, < 0,5 mV) with pathological area identified with the color coded scale. Right anterior oblique view with NavX Ensight Precision™ system. The yellow dots show the His Bundle and the right fascicle.

While the orange dots show the site in which the endomyocardial biopsy has been made, targeting the fibrotic or edematous tissue on the septal right ventricular wall.

Discussion

Even though for many years the medical research has failed to show a causative role of B19V in the genesis of heart failure confirming only an association [5-7], some more recent works have reported that chronic viral infections of the heart can be one antecedent event leading to progressive dysfunction of the myocardium, often with an impaired prognosis due to a virus- or immune-mediated myocardial injury [6]. Moreover, even if it is known that myocarditis can lead to cardiac dysfunction and to

ventricular arrhythmias through the development of scars and therefore reentry circuits [8] no direct association between B19V persistence and those clinical pictures has been described.

As the diagnosis of viral myocarditis can be problematic and the presentation can mimic other diseases such as sarcoidosis, arrhythmogenic cardiomyopathy as well as an evolution in dilated cardiomyopathy, the gold standard for the diagnosis and guide of the therapy is the EMB, an invasive but safe diagnostic tool that allows the quantification and identification of immune cell

infiltrates, the quantification of viral loads and confirmation of virus subtypes via sequencing [9-14]. Historically, the EMB was performed under fluoroscopy guidance and was associated with potentially critical complications such as a cardiac tamponade. In the last years, there has been an evolving and promising use of EMB guided by 3D-electroanatomic voltage mapping, which could confere a higher specificity and sensitivity in targeting the involved tissue and in reducing false negative result. Moreover, it could reduce the radiation exposure of patients and operators in such procedures and present a higher safety profile compared with the mono-dimensional fluoroscopy images [15].

We described how two patients presenting with ventricular tachycardias of unknown cause could be successfully managed after a diagnostic 3D-EAM guided EMB after ruling out the most common causes of ventricular tachycardia. In our patients a subacute viral myocarditis caused by persistent erythroparvovirus, having sustained ventricular tachycardias as clinical presentation and demonstrating active replication of the virus, an immunomodulating therapy with interferon Beta was able to stabilize and resolve the ventricular arrhythmias. The 3D EAM guided EMB either combined with cMRI or not, can help to improve specificity and sensitivity in targeting the involved myocardial tissue and avoid false negative results, without increasing risks for the patients, as already shown in the literature [15,16].

Conclusion

To our knowledge this is the first case series described in the literature of B19V presenting with ventricular arrhythmias. Even if we will need a greater number of patients to confirm our observations, we hypothesize that B19V active replication could have a pivotal role in some forms of myocarditis which show an arrhythmogenic clinical presentation and that diagnosing and treating B19V in patients with a subacute myocarditis and ventricular arrhythmias could be determinant in solving the arrhythmias as well as the myocardial inflammation, although is not curative of the areas where the myocarditis has already produced a myocardial scar. We also described the emerging role of 3DEAM-guided endomyocardial biopsy targeting the involved myocardial tissue and reducing complications and false negative results.

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