Brugada syndrome—Malignant phenotype associated with acute cardiac inflammation?

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Introduction

Since the publication of the seminal case series in 1992 of right bundle branch block and persistent ST elevation in the right precordial leads associated with sudden death, there remain significant gaps in our knowledge surrounding Brugada syndrome.[1] In particular, debate continues regarding its pathogenesis and has in part contributed to the difficulties in risk stratification of sudden death.

We present interesting observations in 2 well-characterized Brugada syndrome patients who had acute inflammation seen on fluorodeoxyglucose (FDG)–positron emission tomography (PET) / computed tomography (CT) in association with frequent ventricular fibrillation episodes.

Case report
Case 1

A 52-year-old Caucasian man was transferred from an outside hospital for management of ventricular fibrillation (VF) storm with multiple implantable cardioverter-defibrillator (ICD) shocks. He had presented 3 years previously following a resuscitated cardiac arrest and was diagnosed with Brugada syndrome based on a type 1 pattern electrocardiogram (ECG), after which he underwent ICD implantation. He had a history of hypertension, hemophilia, cerebrovascular accident, chronic obstructive pulmonary disease, obstructive sleep apnea, and a remote diagnosis of histoplasmosis. There was no family history of sudden cardiac death. He had a normal echocardiogram and normal coronary angiogram. Genetic testing for *SCN5a* was negative.

After transfer, he underwent cardiac magnetic resonance imaging (MRI) with his ICD in situ, which showed no late gadolinium enhancement and normal biventricular function. An FDG-PET scan demonstrated decreased perfusion to the basal mid inferolateral left ventricle (LV) with increased FDG uptake and no extra cardiac activity, suggestive of isolated cardiac inflammation. Serum angiotensin converting enzyme was normal and autoimmune screen negative. He was taken to the electrophysiology laboratory, where a procainamide provocation test induced a type 1 Brugada pattern. Endocardial and epicardial mapping demonstrated no endocardial right ventricular (RV)/right ventricular outflow tract (RVOT) scar. However, fractionated and delayed activity was seen at the RVOT epicardium down to the RV free wall (Figure 1). Programmed stimulation did not induce sustained arrhythmia. Premature ventricular contractions (PVCs) were seen and mapped to the RVOT anteroseptum endocardially. Endocardial ablation to target the PVCs and substrate modification of the epicardial RVOT was performed. During follow-up, a spontaneous type 1 pattern was noted on ECG.

Repeat PET 3 weeks later showed a similar pattern of FDG uptake. Five ICD shocks were experienced over the next 2 months and empiric treatment with prednisolone and hydroxychloroquine was commenced. Endomyocardial RV septal biopsy at that point showed no giant cells or granulomas. Serial PET showed reducing FDG uptake, suggesting response to treatment. The patient remained free of ICD shocks for 1 year. In the interim, family screening identified Brugada syndrome in his sister. He was then diagnosed with thyroid carcinoma and had his immunosuppression withdrawn after a year of treatment and experienced an increase in shock frequency thereafter. Over his treatment course, amiodarone, mexiletine, and quinidine were tried and were either ineffective or not tolerated. Owing to failure of medical therapy, he underwent repeat ablation, targeting an RVOT PVC endocardially and substrate modification at the RVOT epicardium. Over the next year, he experienced a further 2 ICD shocks.

Case 2

A 35-year-old Caucasian man was referred to clinic from an outside hospital with 8 shocks over the preceding 6 months; the shocks were exclusively nocturnal and due to PVC-triggered VF. He presented 3 years previously following a

resuscitated VF arrest. He had no prior medical history of note. Investigations at that time showed normal coronary angiography and normal biventricular function, with no evidence of scar on cardiac MRI. He was diagnosed with idiopathic VF and had an ICD implanted.

A PET/CT was undertaken and showed increased heterogeneous FDG activity throughout the LV with more focal uptake in the basal septum and inferolateral LV. No extracardiac activity was seen. Serum angiotensin converting enzyme was normal. He was taken electively to the electrophysiology laboratory, where a procainamide challenge induced a type 1 Brugada pattern. Voltage mapping showed no RV/RVOT endocardial scar. Epicardial mapping showed abnormal fractionated and delayed electrograms at the RVOT epicardium and significant low voltage over the epicardial RV free wall and epicardial basal inferolateral LV (Figure 2). Endomyocardial biopsy undertaken at the time of the procedure was negative for giant cells and granuloma. Ablation was deferred for a trial of immunosuppressive therapy, which was not tolerated owing to side effects and discontinued after 7 months. Genetic testing was negative for SCN5A mutation. A further 4 ICD therapies were experienced over the next 3 months. Repeat PET showed decreased uptake compared to the previous scan but with residual FDG uptake in the basal inferolateral LV. A year after his initial procedure, he underwent mapping and extensive substrate ablation of the epicardial RVOT. He remained free of arrhythmia for 10 months until he experienced 3 shocks for VF while asleep. Quinidine was started and he is currently being seen in follow-up.

Discussion

We describe 2 well-characterized patients with Brugada syndrome and a malignant arrhythmia course associated with cardiac inflammation on FDG-PET. To our knowledge, this is the first report of this association. Possible explanations for this include Brugada syndrome as the primary condition with inflammation acting as a modulating factor; a coincidental cardiac inflammatory cardiomyopathy, such as isolated cardiac sarcoidosis and Brugada syndrome; or a cardiac inflammatory cardiomyopathy acting as a Brugada phenocopy. Although we made every effort to exclude isolated cardiac sarcoidosis as a cause, including endomyocardial RV septal biopsy, it was not possible to definitively exclude owing to sampling error. However, the low probability of the occurrence of 2 rare conditions in the same patient and the presence of a family history of Brugada syndrome in a first-degree relative in 1 patient would favor Brugada syndrome as the primary condition. Furthermore, our findings on electroanatomical mapping are consistent with a Brugada syndrome substrate, as described in other ablation reports.[2] Criteria for the diagnosis of a Brugada phenocopy have been proposed and include, among other distinguishing features, negative drug provocation testing with sodium channel blockade.[3] Therefore, the presence of a phenocopy should not be invoked according to these criteria. This terminology is, however, debated in the literature, with some considering a phenocopy to be an acquired form of the syndrome.

Brugada syndrome has been traditionally thought of as a condition present in normal hearts. There is, however, mounting evidence that structural abnormalities may contribute to its pathogenesis. Furthermore, there are increasing reports of more widespread structural abnormalities outside of the RVOT. Gross structural changes that have been identified include RV dilatation and regional wall motion abnormalities in the RV and RVOT on MRI,[4] microaneurysms in the LV by angiography,[5] and, more recently, late gadolinium enhancement in the left ventricle.[6] Histologic evidence of fibrosis, myocarditis with positive polymerase chain reactions for viral genomes, and inflammatory infiltrates have also been found after endomyocardial biopsy from both ventricles in high-risk Brugada syndrome patients presenting with ventricular tachycardia/VF and syncope.[5] The finding of uptake in the LV but not the RVOT on PET/CT may reflect a limitation of this imaging modality in that region. In both cases, endocardial LV mapping was not performed. Although PET/CT has also been shown to highlight areas in the lateral LV in normal individuals, epicardial LV mapping revealed low-voltage areas matched to areas of uptake, suggesting these are true positive results. The sensitivity, specificity, and predictive values of PET/CT in diagnosing inflammation are uncertain owing to the sampling error of the current gold standard of biopsy. Further, systematic regional evaluation is most well characterized for the LV and currently lacks validation for other regions.[7]

The finding of myocarditis and inflammatory infiltrates has implicated acute inflammation in the pathogenesis of Brugada syndrome. It is possible that repeated inflammation episodes may lay down substrate or act as triggers for malignant ventricular arrhythmias in the acute setting. Although PET/CT currently appears to be the most sensitive imaging modality to detect cardiac inflammation, serum biomarkers may play a role. Acute inflammation in Brugada syndrome has been systematically investigated in a single study where CRP levels >2 mg/L were found to be an independent
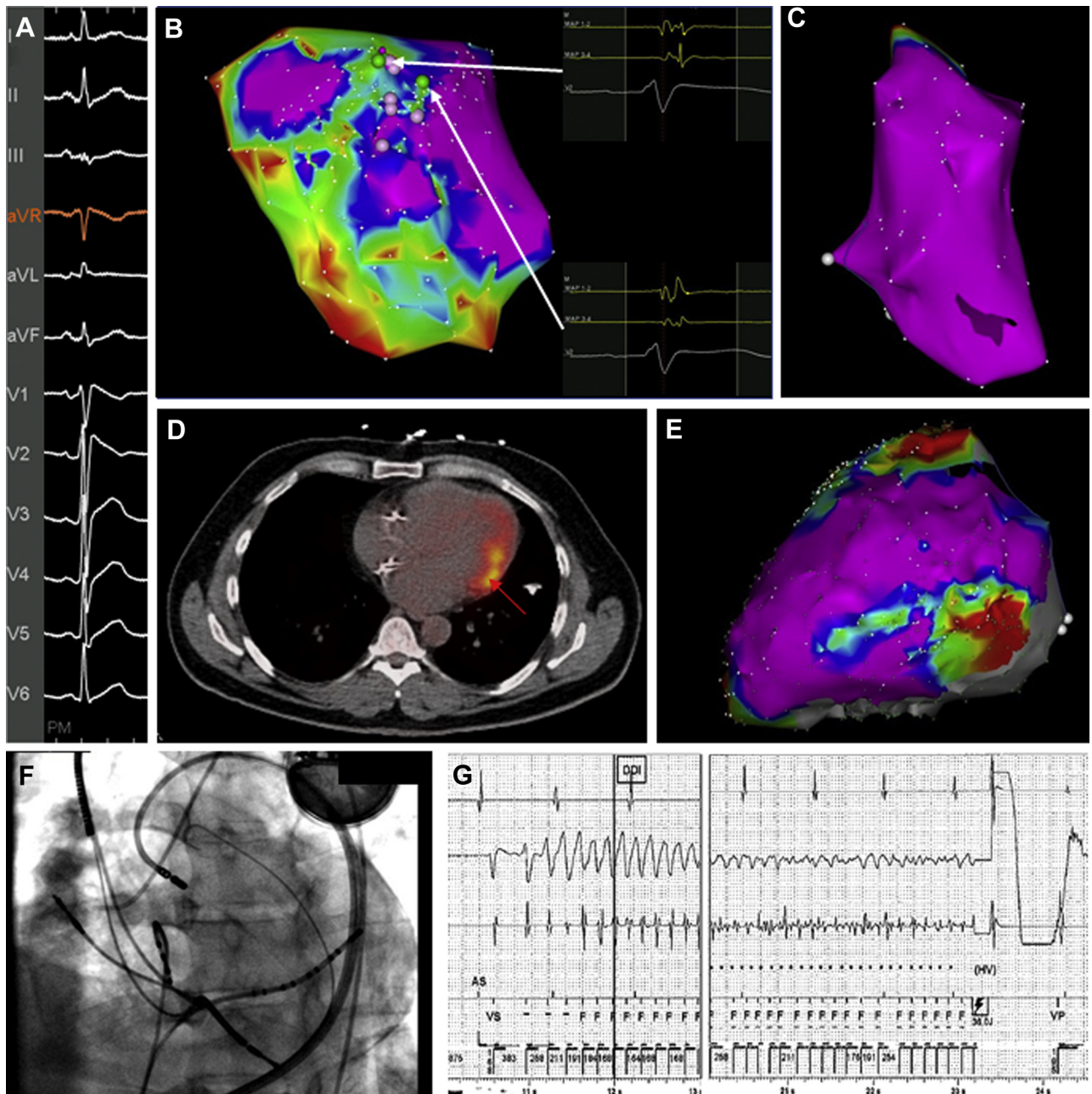
Figure 1 Images from case 1. **A:** A 12-lead electrocardiogram in a standard configuration during procainamide testing showing a type 1 Brugada syndrome pattern in leads V1 and V2. **B:** Epicardial right ventricular/right ventricular outflow tract (RVOT) voltage map with low-voltage, fractionated electrograms tagged (*green and pink dots*). Typical electrogram appearances are shown at their locations (*white arrows*). **C:** Normal endocardial RVOT voltage. **D:** Positron emission tomography–computed tomography (PET/CT) showing posterior wall fluorodeoxyglucose uptake (*red arrow*). **E:** Epicardial left ventricle map showing area of low voltage (*red*) corresponding to area of uptake on PET/CT. **F:** Fluoroscopic anteroposterior view of ablation catheter in the epicardium overlying the RVOT. **G:** Implantable defibrillator traces showing onset of ventricular fibrillation and termination by a single 36 J shock.

marker for being symptomatic.[8] In our cases, the setting of acute electrical storm and multiple ICD therapies would make it challenging to interpret and distinguish any rise in serum biomarkers of inflammation or myocyte injury as being attributable to a primary cardiac cause or secondary to ICD therapy. Granulomatous diseases are causes of acute cardiac inflammation. Of these conditions, only chagasic cardiomyopathy has been seen in association with a type 1

ECG pattern in case reports, suggesting that it may act as a phenocopy.[9]

Taken as a whole, the above observations lend weight to the hypothesis that acute inflammation may play a role in modulating the phenotype of Brugada syndrome. In our case, the apparent reduction in ICD therapies owing to VF with a limited course of glucocorticoid therapy may also suggest a role for inflammation acting as the primary driver
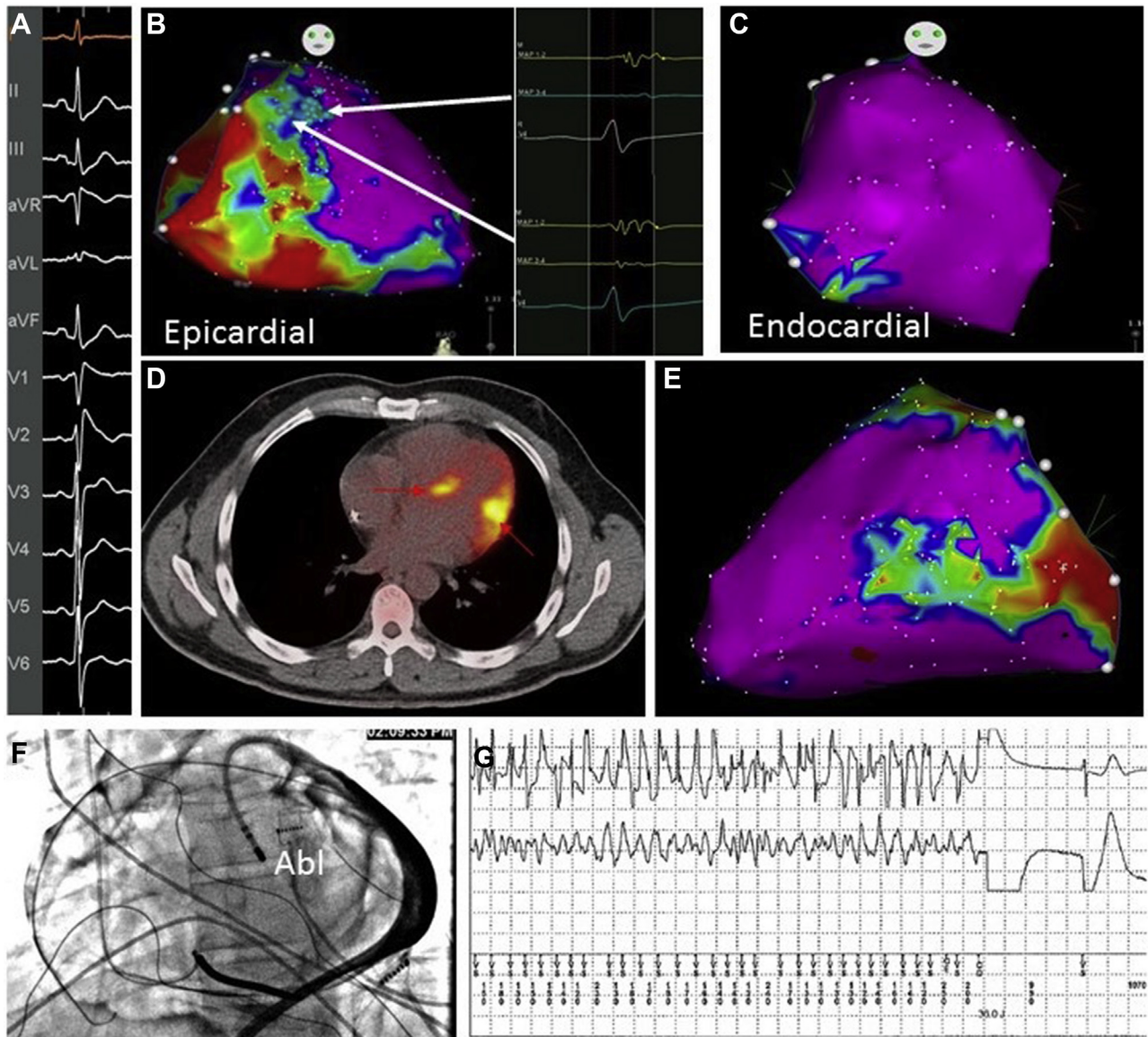
Figure 2 Images from case 2. **A:** A 12-lead electrocardiogram in a standard configuration during procainamide testing showing a type 1 Brugada syndrome pattern in leads V1 and V2. **B:** Epicardial right ventricular/right ventricular outflow tract (RVOT) voltage map with low-voltage, fractionated electrograms tagged (*green dots*). Typical electrogram appearances are shown at their locations (*white arrows*). **C:** Normal endocardial RVOT voltage. **D:** Positron emission tomography–computed tomography (PET/CT) showing posterior left ventricle (LV) wall and basal septum uptake (*red arrows*). **E:** Epicardial LV map showing area of low voltage (*red*) corresponding to area of uptake on PET/CT. **F:** Fluoroscopic anteroposterior view of ablation catheter (Abl) in the epicardium overlying the RVOT. **G:** Implantable defibrillator traces showing termination of ventricular fibrillation by a single 36 J shock.

for VF. Whether or not acute cardiac inflammation is involved in the pathogenesis and/or acts as a trigger for ventricular arrhythmias of Brugada syndrome is unknown. Furthermore, it is unknown if all inflammatory cardiomyopathies can act as phenocopies. It may be possible that the type 1 ECG, diagnostic of the syndrome, is merely a marker of RV/RVOT pathology, of which there are a multitude of causes.

At our center, treatment for acute isolated cardiac inflammation is not protocol driven but is assessed on a case-by-case basis. Investigations including biopsy are directed at establishing an underlying cause and treated accordingly.

Our experience with acute inflammatory cardiomyopathy, where an underlying cause is uncertain, has suggested that it may be reasonable to start glucocorticoid therapy and assess the clinical and radiological response with interval PET scans prior to undertaking ablation.[10]

If, indeed, active cardiac inflammation reveals itself as a critical factor in the natural history of Brugada syndrome, it could represent a novel target for treatment. We propose that in cases of Brugada syndrome running a malignant course, PET/CT may be a useful investigation to guide further management.

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