Patient 1:

A 48-year-old male presented for evaluation of recurrent ventricular tachycardia (VT) refractory to antiarrhythmic therapy and VT ablation. Two years prior he had developed complete heart block requiring pacemaker. Over the course of the subsequent two years he developed dilated cardiomyopathy (ejection fraction of 24%) and sustained VT for which his device was upgraded to a cardiac resynchronization therapy defibrillator (CRT-D). Due to recurrent shocks, he eventually underwent VT ablation. Following the ablation he continued to have symptomatic VT and he was scheduled for a repeat electrophysiologic (EP) study. To delineate between possible etiologies for his cardiomyopathy, he underwent electrogram-guided endomyocardial biopsy (EMB) during the EP study. Upon catheter insertion, he developed multiple different hemodynamically unstable VTs and an Impella (Abiomed, Danvers, MA) left ventricular (LV) assist device (Impella) was inserted. An electrogram map of the interventricular septum was created and an area with fragmented electrograms at the midseptal right ventricle (RV) was biopsied. After the biopsy, three morphologically distinct inducible VTs were successfully ablated.

Histopathology of one of the RV specimens demonstrated active myocarditis (lymphocytic type) with myocyte damage. Chronic mild myocyte hypertrophy and moderate interstitial fibrosis were also seen. A diagnosis of lymphocytic myocarditis was made and he was promptly commenced on immunosuppression with corticosteroids and mycophenolate mofetil. Over the next three years, he was continued on immunosuppression and amiodarone

and aside from experiencing two implantable cardioverter-defibrillator (ICD) shocks, he did well clinically.

Patient 2:

A 50-year-old female who had undergone pacemaker implantation 5 years prior for complete heart block presented to the emergency department with chest pain. Coronary angiography was unremarkable and transthoracic echocardiogram (TTE), which had been normal in the past, now demonstrated an ejection fraction of 28% with global hypokinesis and abnormal septal morphology and motion. Positron emission tomography (PET) myocardial perfusion and metabolism imaging demonstrated absent perfusion in areas of marked hypermetabolism at the basal septal and anterior segments and at the lateral apex. Due to the patchy nature of the echocardiographic and PET findings, electrogram-guided EMB was performed. Areas with low voltage, slowed conduction, and fractionated signal **(Figure 2)** were identified at the posteroseptal portion of the RV outflow tract and the RV septum near the RV base above the region of the right bundle branch. Biopsies were taken from both of these sites.

Histopathology of the biopsy specimens revealed the presence of both non-necrotizing granulomas with fibrosis as well as scattered eosinophilic infiltrates consistent with a mixed picture of cardiac sarcoidosis (CS) and giant cell myocarditis (GCM) **(Figure 2).** Her device was up-graded to an ICD and she was started on immunosuppressive therapy with high-dose corticosteroids and mycophenolate mofetil in addition to beta blocker and ACE-inhibitor therapy. Repeat PET imaging both two months and six months later demonstrated marked improvement in the perfusion-metabolism mismatch.

Patient 3:

A 44-year-old previously healthy male developed complete heart block requiring pacemaker implantation. LV ejection fraction was normal at time of implantation, but was found to be depressed (35%) on follow-up TTE six months later. He was started on carvedilol and irbesartan pharmacologic heart failure therapy. Due to frequent ventricular ectopy in the setting of systolic dysfunction, his pacemaker was upgraded to a CRT-D. Chest computed tomography scan revealed mediastinal lymphadenopathy with left apical stellate nodules. Biopsies of a lung nodule revealed benign endobronchial mucosa with acute and chronic inflammation but no evidence of granulomatous inflammation. Cardiac PET scan revealed areas at the basal septum and inferior wall which were nonperfused but had normal metabolism. These areas corresponded to the areas of delayed gadolinium enhancement on cardiac magnetic resonance imaging (MRI) and were consistent with areas of active inflammation. His clinical presentation and radiologic findings were highly suspicious for CS and he underwent electrogram-guided EMB for both prognostic and therapeutic purposes. Electroanatomic mapping of the RV was performed in the EP lab. Fragmented signals were identified in the basal anterior septum and in the posterior septal proximal portion of the RV outflow tract and biopsies were taken from these sites without complication.

Histopathology of the RV biopsy specimens revealed focally clustered giant cells with a vague granuloma-like appearance, as well as lymphocytes and eosinophils, suggesting the diagnosis of cardiac sarcoidosis with features of a late-phase idiopathic GCM. He was treated as

having acute GCM with an aggressive immunosuppression regimen including oral cyclosporine, mycophenolate mofetil, and a slow prednisone taper.

Patient 4:

A 50 year-old female was transferred to our institution for management of recurrent VT. She had been diagnosed with sarcoidosis four years prior, with biopsy-proven involvement of the kidney and parotid gland. One year ago she developed heart failure symptoms and was found to have an LV ejection fraction of 22%. At that time, she was initiated on oral prednisone and mycophenolate mofetil in addition to standard heart failure treatment. Ejection fraction improved to 57% and her symptoms resolved. EP study demonstrated easily inducible monomorphic VT so ICD was placed and she was commenced on amiodarone. Due to multiple shocks on amiodarone, she had been trialed on sotalol and mexiletine which failed to suppress her VT.

On arrival to our institution's coronary care unit, she was hemodynamically stable and loaded with intravenous amiodarone. Myocardial PET scan demonstrated a small area of perfusion-metabolism mismatch in the mid/basal lateral wall consistent with inflammatory cardiomyopathy. Ejection fraction had dropped to 46%. Due to poor RV sensing, her RV lead was revised (with insertion of a coronary sinus lead and superior vena cava coil) and she was continued on mycophenolate mofetil and prednisone. Due to recurrent VT despite amiodarone, she was sent for an EP study for possible VT ablation and biopsy. During the EP study, both ventricles were mapped. Multiple sustained VTs (over ten morphologies) were induced and the most clinically significant morphologies were ablated. There was electrical evidence of active

CS, particularly along the left free wall midportion. Although the most markedly abnormal fragmented signals were present in the LV, the lowest amplitude signals in the RV were identified and targeted for RV biopsy. Pathology from the RV biopsy specimens demonstrated one small focus of replacement fibrosis with mild lymphocytic infiltrate consistent with CS. She was diagnosed as having active refractory CS. Mycophenolate mofetil was discontinued and she was transitioned to a regimen of infliximab plus prednisone.

Patient 5:

A 51-year-old female presented with progressive heart failure symptoms over two years. ECG one year prior demonstrated interventricular conduction delay with a first degree AV block (PR interval 290 msec) and normal voltage. Coronary angiogram had shown no occlusive coronary artery disease and LV ejection fraction was mildly depressed to 40% on TTE at the time. She subsequently underwent colon resection for stage 1 colon cancer and her LV ejection fraction decreased to 25% although she did not receive radiation or chemotherapy. She was treated medically with carvedilol, lisinopril, and spironolactone and was found to have frequent asymptomatic multifocal premature ventricular contractions and nonsustained VT seen with Holter-monitoring. Due to concern for an inflammatory process, cardiac MRI was performed which demonstrated extensive delayed gadolinium enhancement in an epicardial and mid-myocardial pattern extending into the RV septum, consistent with a nonischemic process such as severe myocarditis or CS. Myocardial metabolism-perfusion PET scan corresponded with the MRI, demonstrating mild LV enlargement with a large apical, inferior, and septal defect with reduced perfusion accompanied by increased fluorodeoxyglucose uptake, suggestive of active

inflammation. Due to the high clinical suspicion for CS, she underwent electrogram-guided EMB. During the procedure, a full RV voltage map was created. Using an intracardiac ultrasound catheter and His catheter to guide the biopsy, a Bioptome was placed at the exact areas of abnormal potentials and abnormal voltage in the RV. Five biopsies were obtained via a combination of femoral and internal jugular approach, and the pathology demonstrated prominent noncaseating granulomas, consistent with CS. She was commenced on mycophenolate mofetil for immunosuppression and sotalol for her frequent ventricular extrasystoles. She underwent ICD implantation for primary prevention of sudden death prior to hospital discharge.