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Case Report

Combination therapy with corticosteroid and mycophenolate mofetil in a case of refractory cardiac sarcoidosis

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ABSTRACT

Management of cardiac sarcoidosis (CS) can be challenging. The first-line therapy for this condition is corticosteroids, but other immunosuppressive agents are sometimes co-administered to reduce the dosage of corticosteroid and to thereby avoid steroid-induced adverse effects or to increase its therapeutic efficacy. Mycophenolate mofetil (MMF) is a prodrug of mycophenolic acid, an inhibitor of inosine monophosphate dehydrogenase that acts more selectively on T and B lymphocytes when compared with azathioprine. A 40-year-old man was diagnosed with CS after presenting with ventricular fibrillation. His left ventricular ejection fraction was severely reduced (30%), and cardiac positron emission tomography (PET) showed abnormal uptake of ^{18}F-fluorodeoxyglucose. A cardioverter-defibrillator was implanted and prednisolone (30 mg/day) was administered. He was re-admitted with recurrent sustained ventricular tachycardia and a positive PET finding despite a 5-month course of prednisolone, and MMF (1000 mg/day) was administered. Six months later, he had not required re-hospitalization for heart failure or arrhythmia. We conclude that combination therapy with MMF and corticosteroids is useful for refractory CS.

<Learning objective: Management of cardiac sarcoidosis (CS) can be challenging. Although some immunosuppressive agents are co-administered to reduce the dosage of corticosteroids or to intensify the effect of corticosteroids, the optimal combination regimen has not yet been established. This case report shows that combination therapy with corticosteroid and mycophenolate mofetil was useful for CS that was refractory to corticosteroid monotherapy.>

Introduction

Sarcoidosis is a granulomatous disease that can affect multiple organs, including the lung, liver, nerve, skin, and heart [1]. Cardiac involvement can also occur and manifest as arrhythmias with ventricular tachyarrhythmia and sudden death or heart failure [2]. Cardiac magnetic resonance (CMR) and positron emission tomography (PET) can be used to diagnose cardiac sarcoidosis (CS) at an early time point [3]. Moreover, PET may be used to assess the activity of CS [4].

While early diagnosis and early treatment of CS may improve outcomes, treatment can be challenging. The main goal of treatment for sarcoidosis is to control and suppress the inflammation and activity of the disease. Corticosteroids comprise the first line of therapy [1]. However, the use of corticosteroids is frequently accompanied by serious adverse effects, such as gastric ulcers, osteoporosis, diabetes, and infectious diseases. Other immunosuppressive agents (e.g. methotrexate, azathioprine, leflunomide) are sometimes added to reduce the dosage of corticosteroids or to intensify therapy, but some patients do not respond to or tolerate these agents [5]. Mycophenolate mofetil (MMF) is a prodrug of mycophenolic acid, an inhibitor of inosine monophosphate

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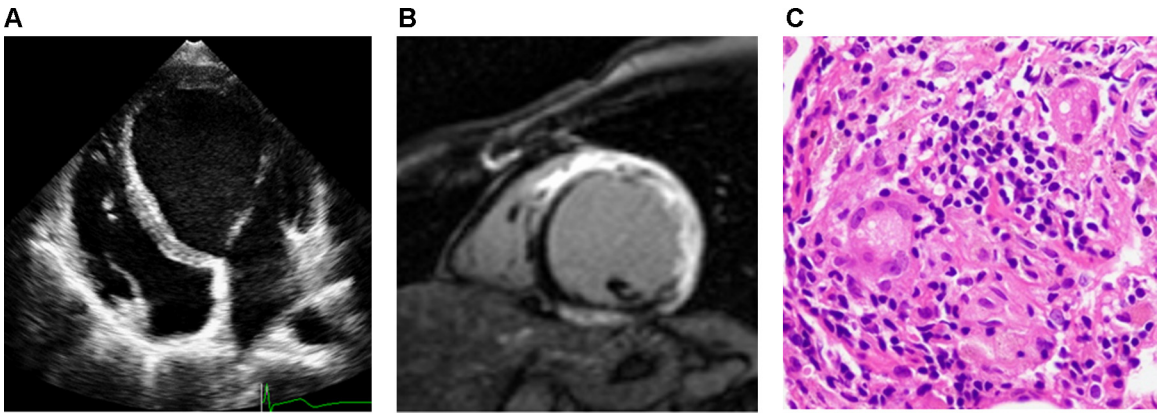

Fig. 1. Images leading to the diagnosis of cardiac sarcoidosis. (A) Transthoracic echocardiography shows a left ventricle (LV) ejection fraction of 30% and LV dilation. (B) Cardiovascular magnetic resonance shows the presence of a late enhancement of gadolinium contrast involving the interventricular septum and LV anterior-inferior-lateral-posterior walls. The pattern of enhancement involves the mid-myocardium and epicardium. (C) Trans-bronchial lung biopsy shows non-caseating epithelioid granuloma.

dehydrogenase [6], and is a key immunosuppressive agent used in solid organ transplant recipients [7]. A retrospective study demonstrated the efficacy and safety of MMF with corticosteroids in 10 patients with pulmonary sarcoidosis [8]. However, data regarding the use of MMF in cardiac sarcoidosis are limited. The present report describes a case of steroid-resistant CS that was successfully treated with combination therapy of MMF and corticosteroids.

Case report

A 40-year-old man was admitted due to ventricular fibrillation. He was resuscitated using an automated external defibrillator. On admission, he was alert and his electrocardiogram showed ventricular tachycardia. His coronary angiography revealed neither stenosis nor occlusion, and his echocardiogram showed a left ventricular (LV) ejection fraction (EF) of 30% and LV dilation (LV end-diastolic diameter, 61 mm) (Fig. 1A). Laboratory testing showed a serum angiotensin-converting enzyme (ACE) level of 12.5 U/L (normal range: 8.3–21.4 U/L). CMR showed a significantly enlarged left ventricle and severe diffuse hypokinesis. Late gadolinium enhancement (LGE) revealed extensive epicardial hyper-enhancement in the anterior, lateral, and inferior walls (Fig. 1B). An endomyocardial biopsy did not demonstrate granulomatous inflammation, but a trans-bronchial lung biopsy (Fig. 1C) showed sarcoidosis.

An implantable cardioverter-defibrillator (ICD) was placed, and medical therapy (including 20 mg of carvedilol) was initiated. Cardiac ^{18}F-fluorodeoxyglucose (FDG) PET was performed to evaluate for myocardial inflammation and showed significant FDG uptake in the wall that corresponded to the LGE area. The maximal standardized uptake value (SUV max) was 6.01 in the anterolateral wall (Fig. 2A and B). No active inflammation was observed in other organs (Fig. 2A).

One month later, the patient was re-admitted to the hospital with frequent but appropriate discharges of his ICD. His laboratory data on admission demonstrated high brain natriuretic peptide (1000 pg/ml), and prednisone (30 mg/day) and amiodarone therapy was initiated. Four months after starting prednisone, he was readmitted with recurrent ventricular tachycardia (VT). His serum ACE level remained low (6–7 U/L). Follow-up FDG-PET study revealed positive findings (SUV max = 4.46) despite an 8-month course of prednisolone (Fig. 3).

To intensify the therapy, we increased the amount of corticosteroid, but VT storm occurred again. MMF (1000 mg; CellCept®; Roche Laboratories, Basel, Switzerland) was added to corticosteroid in order to intensify the immunosuppressive effect. Using blood concentration monitoring, we adjusted the dosage of MMF to a target of 2.0 μg/ml, and the frequency of ICD discharges

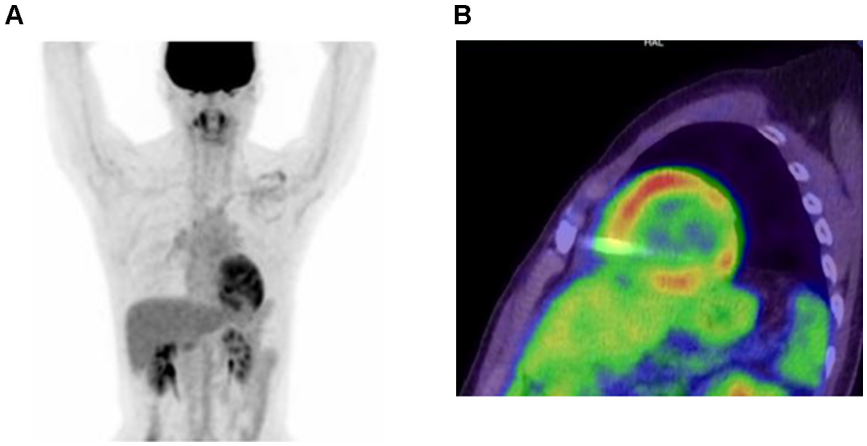

Fig. 2. ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) findings before immunosuppressive therapy. (A) PET scan shows significant abnormal FDG uptake in the heart and no abnormal extra-cardiac findings. (B) Significant abnormal FDG uptake is found in the wall and corresponds with the late gadolinium enhancement positive region. Standardized uptake value max is 6.01 in anterolateral wall.