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LETTER TO THE EDITORS

Recurrent cardiac sarcoidosis after heart transplantation

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Sirs:

A 42-year-old man with a history of arterial hypertension and aortic coarctation repair at the age of 25 received a dual-chamber pacemaker (PM) for a complete trifascicular block associated with a non-dilated mildly dysfunctional left ventricle (LV ejection fraction [EF], 45%). Angiography ruled out coronary artery disease. Progressive LV dysfunction leading to advanced heart failure (HF) (LVEF 27%) occurred in the next 3 years despite optimal medical therapy and upgrade to cardiac resynchronization therapy-defibrillator being performed when he was 44. The patient was diagnosed with a dilated cardiomyopathy resulting from long-standing arterial hypertension due to a lately repaired aortic coarctation; thus, no endomyocardial biopsy (EMB) or cardiac magnetic resonance imaging (CMRI) was performed in the early course of his disease. At the age of 45, the patient was referred to our transplant center for cardiogenic shock despite inotropic support, for advanced diagnostic workup and treatment. The patient was treated with an intra-aortic counterpulsation pump, listed for heart transplantation (HTx) and implanted with a left ventricular assist device (LVAD) as bridge to HTx. During HTx screening process, mediastinal/hilar lymphadenopathy was observed on chest X-ray and computed tomography (CT), suggestive of granulomatous disease (Fig. 1a, b). Bilateral hilar lymphadenopathy was confirmed on previous chest X-rays when requested to the transferring hospital (Supplemental Fig. 1). Tuberculosis was ruled out by a negative quantiFERON test and a negative bronchoalveolar lavage. Trans-bronchial biopsies of hilar lymphnodes were not diagnostic. Cardiac histological specimens of the apex collected during LVAD implantation showed no findings suggestive for an inflammatory cardiomyopathy. The patient progressively developed severe refractory right HF on LVAD, and he was finally transplanted a year later. Noncaseating granulomas with epithelioid histiocytes, sparse giant cells, lymphocytes and extended fibrosis were found on the explanted heart compatible with cardiac sarcoidosis (CS) (Fig. 1c). The patient was discharged with standard maintenance immunosuppressive regimen including cyclosporine, mycophenolate mofetil, and prednisone. Due to an epididymo-orchitis sustained by *Pseudomonas aeruginosa* complicated by systemic sepsis (positive blood cultures) at 45 days since HTx, steroid therapy was early withdrawn. Few weeks later, he was admitted for suspected rejection with severe graft dysfunction (LVEF 30%). Right ventricle (RV) EMB showed the presence of inflammatory lesions with multinucleated giant cells and diffuse lymphocytic infiltrates suggestive of myocarditis rather than rejection (Fig. 1d). 18-Fludeoxyglucose-positron emission tomography (FDG-PET)/CT revealed intense hilar/mediastinal lymphnodes uptake. CMRI showed diffuse biventricular and pericardial short tau inversion recovery (STIR) hyperintensity suggestive of edema (Fig. 1e) and diffuse biventricular late gadolinium enhancement suggestive of initial fibrosis. Recovery of cardiac function occurred after treatment with intravenous high-dose steroids (Supplemental Video 1), and a surveillance EMB performed after

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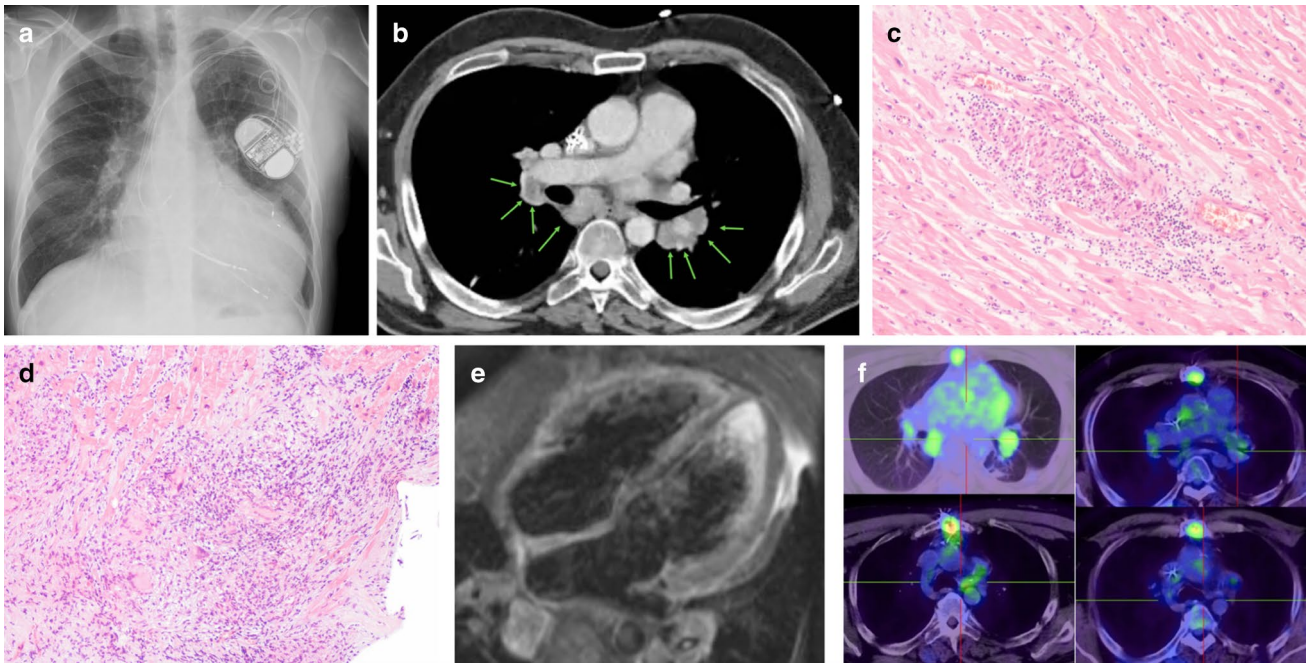

Fig. 1 A case of cardiac sarcoidosis undergoing heart transplantation with recurrent disease in the transplanted graft. **a** Chest X-ray anterior–posterior view at the time of referral to our center. Notice the enlargement of the cardiac silhouette and bilateral hilar enlargement. Cardiac resynchronization therapy-defibrillator leads correctly positioned. **b** Contrast-enhanced chest computed tomography performed during heart transplant screening process showing mediastinal and bilateral hilar lymphadenopathy with spotted calcifications (right hilum lymphnodes 26×24 mm, mediastinal paraaortic 28×13 mm, left hilum 19×16 mm), suggestive of granulomatous disorder. **c** Hematoxylin and eosin of the explanted heart showing noncaseating granuloma with epithelioid histiocytes, giant cells and lymphocytes embedded in collagenous stroma. **d** Right ventricle endomyocardial biopsy specimen showing presence of multinucleated giant cells, diffuse fibrosis and lymphocytic inflammatory infiltrates (hematoxylin and eosin), suggestive of acute myocarditis rather than rejection. **e** Short time inversion recovery sequences showing diffuse biventricular and pericardial increased signal intensity at cardiac magnetic resonance imaging. **f** On the left, positron emission tomography/computed tomography performed after steroid withdrawal during graft dysfunction highlighting intense hilar and mediastinal lymphnodes fludeoxyglucose uptake, suggestive of increased sarcoidosis activity. On the right, repeated positron emission tomography/computed tomography on corticosteroid therapy showing resolution of fludeoxyglucose uptake in hilar and mediastinal lymphnodes (10-month follow-up)

2 weeks confirmed the resolution of the inflammation; nevertheless, diffuse areas of fibrosis were observed. Given the CS diagnosis in the native heart, the evidence of active disease in the mediastinal/hilar nodes during graft dysfunction and the presence of inflammation with giant cells at EMB, a plausible diagnosis of CS recurrence in the transplanted heart was finally considered. Thus, prednisone 25 mg od was maintained. Follow-up at 10 months showed mildly reduced LVEF (45%), absence of STIR hyperintensity at CMRI, no inflammation at EMB and a significant reduction of mediastinal/hilar lymphnodes FDG uptake (Fig. 1f and Supplemental Video 2). At 20 months from HTx, following an attempt to taper off steroids, deterioration of LVEF and new hilar/mediastinal lymphnodes FDG uptake at PET/CT were observed. Prednisone 30 mg od was reinstituted, methotrexate 15 mg od added and clinical stability achieved.

CS can be extremely challenging to diagnose and can be an unexpected finding in the explanted heart at the time of HTx [1–3], as highlighted in the present case. CS should be considered in all cases of unexplained dilated cardiomyopathy or new conduction abnormalities, particularly in young and middle-aged adults [1, 4–6]. Early diagnosis of CS is crucial, as tailored immunosuppressive treatment could alter the clinical course of this disease, even if compelling evidence is lacking [4]. A plausible cause of progression to dilated cardiomyopathy was initially considered in the current case (long-standing arterial hypertension as a consequence of a lately repaired aortic coarctation), potentially explaining the lack of further investigations at the time of PM implantation, when an integrated use of EMB, CMR and FDG-PET could have anticipated CS diagnosis. Noncaseating granulomas represent the hallmark for CS diagnosis; however, the presence of multinucleated giant cells with lymphocytic infiltrates can represent common histological findings in CS [7, 8]. CS can relapse after HTx, even if very few cases are reported [3, 9–11], making the management of this case further challenging. Based on the present report, an integrated approach including CMRI and FDG-PET beyond serial EMB may be useful in transplanted CS patients to monitor the activity of sarcoidosis also after HTx [12, 13],

especially following discontinuation or down-titration of steroids. Given the recent evidence underscoring the importance of B-cells in the pathogenesis of sarcoidosis [14], prolonged steroid therapy and titration of sarcoidosis-specific immunosuppressant drugs (e.g., methotrexate, rituximab) in addition to standard mostly T cell-targeted immunosuppressive HTx therapy may be warranted in selected CS cases.

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Compliance with ethical standards

Conflict of interest All authors agreed to submit this case report and declared no conflict of interests.

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