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Case Report

Granulomatous Cardiomyopathy Presenting As a Paraneoplastic Syndrome in Metastatic Melanoma

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Malignancy and treatment thereof is associated with granulomatous reactions that can mimic metastatic disease. We present a rare manifestation of metastatic melanoma with paraneoplastic cardiopulmonary granuloma deposition, first thought to represent malignant infiltration of the myocardium. Multi-modality imaging with positron emission tomography-computed tomography and cardiac magnetic resonance imaging, along with histologic examination, was critical in reaching a diagnosis. Interdisciplinary management was essential to achieving the best outcome for the patient, for managing both the primary malignancy and its cardiac complications.

Case Presentation

A 64-year-old man with recently diagnosed metastatic melanoma was referred to the cardiology clinic for evaluation of dyspnea on exertion. He was started on immune-checkpoint inhibitor therapy (ICI) 3 months prior to referral, but he had developed shortness of breath before therapy. Initial positron emission tomography-computed tomography (PET-CT) staging scans showed bilateral hypermetabolic activity in the lungs as well as the right (RV) and left ventricle (LV), which was interpreted as metastatic lesions among his other sites of malignancy (bone, muscle, lymph nodes). An electrocardiogram obtained during the clinic visit showed sinus rhythm with right bundle branch block, first-degree AV block, and low voltage (Fig. 1). Cardiac magnetic resonance imaging (CMR) was notable for preserved LV systolic function, severely reduced RV function, diffuse late gadolinium enhancement (LGE) in the RV, and patchy LGE in the LV. The LGE involved 50% of the LV.

The patient's symptoms, taken in conjunction with the CMR and PET findings, were concerning for RV failure as a result of an infiltrative cardiomyopathy. He was referred for right heart catheterization with endomyocardial biopsy, which yielded well-formed non-necrotizing granulomas as well as multinucleated giant cells embedded in a fibrous background, involving the myocardium and endocardium, respectively. The lesions abutted myocytes without evidence of necrosis (Fig. 2). The histochemical stains were negative for fungal elements and acid-fast bacilli. The presence of metastatic melanoma was excluded by negative immunohistochemical stains for Sox-10, HMB-45, and Melan-A (not shown). The patient was seen by the pulmonology department, which performed endobronchial biopsy of his lymph nodes, also showing non-necrotizing granulomas. Overall, the findings were most consistent with a sarcoid-like reaction, and given the patient's precipitous decline, we elected to treat his condition as such.

There was clinical equipoise regarding steroid therapy, as this would run directly counter to melanoma treatment. After multidisciplinary consultation, steroids were prescribed, as significant reduction occurred in bony, muscular, and lymphatic metastases. The patient had immediate improvement in symptoms and near-total resolution of hypermetabolic activity on PET-CT.

Two months after he started steroid therapy, the patient's PR interval lengthened to 240 ms. Due to the patient's risk for progressive conduction system disease, he was referred for

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Novel Teaching Points

- Interdisciplinary care is necessary for achieving optimal outcomes in patients with CS.
- Early electrophysiology consultation is recommended in patients with CS.
- Cancer is often a precursor to granulomatous reactions and should be considered in patients presenting with cardiac symptoms who have a history of malignancy.
- Immune-checkpoint inhibitors can induce granulomatous deposition but are not always the culprit.

device implantation. Typically, the recommendation for cardiac sarcoidosis (CS) requiring pacing is to have an implantable cardioverter defibrillator (ICD) due to the risk of ventricular arrhythmias.[1] Consultation with oncology was invaluable once more, as they provided assurance that ICI therapy was expected to prolong the patient's life for several years. The patient underwent successful implantation of a dual-chamber ICD.

Discussion

Sarcoidosis is a systemic inflammatory disease wherein non-caseating granulomas deposit in multiple organs, leading to fibrosis and organ dysfunction.[2] A diagnosis of sarcoidosis can be made with tissue biopsy and the exclusion of other causes of granuloma formation, which should respond to treatment of the underlying disease. Treatment of malignancy, particularly with immunotherapy, also places patients at increased risk of developing granulomatous reactions.[3] Thus, granuloma formation may be a harbinger of malignancy, occur as a paraneoplastic syndrome, or result as a consequence of treating cancer. The observed relationship among solid tumours, hematologic malignancy, and granuloma deposition dates as far back as 1917, with several case series demonstrating a higher frequency of sarcoidosis in Hodgkin's lymphoma, breast cancer, and rectal carcinoma.[4,5] Our patient presented with cardiopulmonary granulomatous deposition that behaved as a de novo case of sarcoidosis; for the purposes of treatment, the distinction between primary and secondary granulomatous disease was of less import, given that immunosuppression was required to achieve control, and we referred to his diagnosis as being analogous to cardiac sarcoid. We followed standard guidelines that inform care for device implantation and treatment of CS.

At the outset of the case, the working diagnosis for the thoracic PET imaging was metastatic disease. Despite ICI therapy with excellent response in the muscle, bones, and lymph nodes, he developed dyspnea and was referred to the cardiology clinic, primarily to evaluate for an immune-related adverse event. Although the time course did not fit an immune-related adverse event, ICIs are theorized to cause sarcoid-like reactions via upregulation of Th1 and Th17 lymphocytes. These cells are thought to play a key role in granuloma formation.[4] Distinguishing granulomatous inflammation from metastatic disease with PET imaging was not possible, but clinical signs, such as ventricular arrhythmia

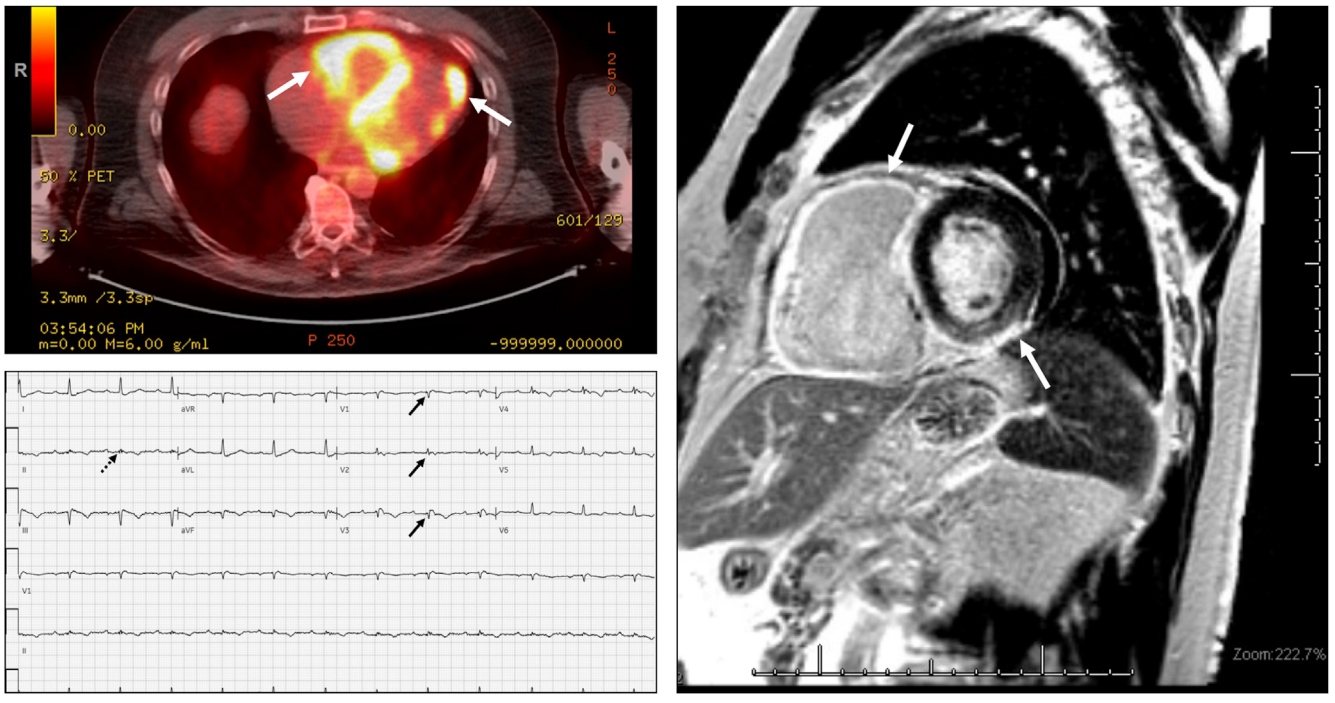

Figure 1. Noninvasive imaging of cardiac granuloma deposition. Initial staging positron emission tomography imaging (**left, top**) showing dense, extensive hypermetabolic activity in the right ventricle (**white arrow**) and left ventricle (**white arrow**). An electrocardiogram obtained in clinic (**left, bottom**) demonstrates PR prolongation, low voltage (**dashed arrow**), and right bundle branch block (**solid arrow**). Late gadolinium enhancement on cardiac magnetic resonance imaging (**right**) was diffuse throughout the right ventricle (**arrow**) and involved part of the left ventricle (**arrowhead**).

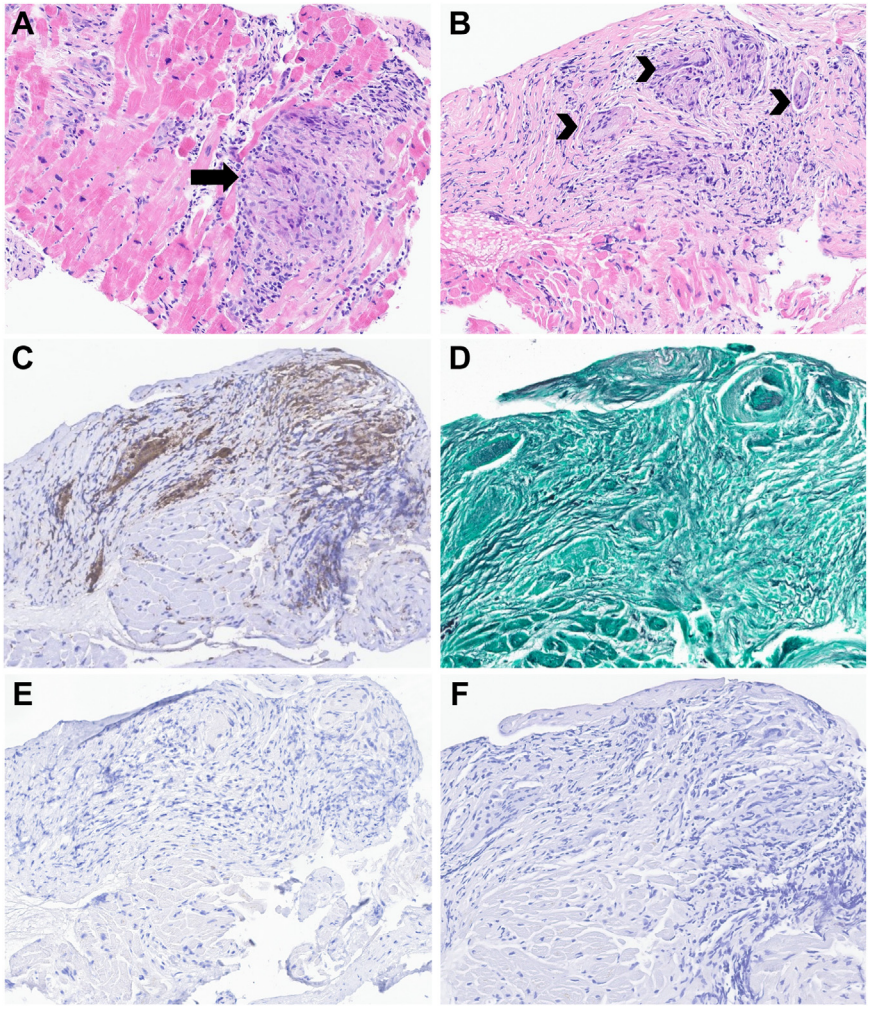

Figure 2. Cardiac biopsies showing involvement by granulomatous inflammation (×20). (**A**) Epithelioid granuloma (**arrow**) abutting the myocytes, with no evidence of necrosis. (**B**) Multinucleated giant cells (**arrowheads**) in fibrous background, extending to the endocardium. (**C**) CD68 stain highlights the histiocytic origin on the infiltrating cells (**in brown**). (**D**) Histochemical stain Grocott methenamine silver (GMS) is negative for fungal elements. (**E, F**) Negative staining for Sox-10 and HMB-45, respectively, confirms the absence of inconspicuous melanoma.

or progressive atrioventricular block, would have been powerful signals to obtain direct myocardial sampling earlier.

Endomyocardial biopsy was pursued for a definitive answer (Fig. 2). CS can be diagnosed via tissue sampling from the myocardium, or a combination of extracardiac histology and compelling evidence of infiltrative cardiomyopathy.[2] Although myocardial biopsy is the gold standard for diagnosis of CS, in practice, the sensitivity from blind sampling is low. Electroanatomic mapping for low-amplitude signals can increase the success of biopsy; however, we performed myocardial sampling due to the global RV involvement on CMR.[2]

Interdisciplinary communication was essential to deliver optimal care for this complex patient.[6] Immunosuppression was not indicated from an oncologic perspective and raised the risk for relapsing melanoma. Following multidisciplinary discussion, steroids were initiated, as no detectable tumour markers were present in the serum, and the RV dysfunction placed the patient at high risk for arrhythmias and hemodynamic compromise.

Interdisciplinary consultation was needed once again when the patient developed conduction system disease.[6] The risk for ventricular arrhythmia in CS patients is well established, and ICD implantation is recommended whenever permanent pacing is indicated.[1] However, ICD implantation is not recommended in patients who have a life expectancy of less than 1 year. The oncology team provided reassurance that in spite of metastatic cancer, ICI therapy would most likely prolong the patient's life by several years.

Conclusion

To our knowledge, this case is the first reported of granulomatous cardiomyopathy developing in conjunction with metastatic melanoma. We believe our patient had de novo sarcoidosis, based on the fact that it did not respond to treatment of malignancy or cessation of ICI therapy; it did not behave as a secondary process but rather as a distinct clinical entity requiring targeted therapy for resolution. This behaviour suggests a putative link between development of

melanoma and concurrent sarcoidosis, but many cancers are associated with sarcoid reactions.[5] A high degree of suspicion for infiltrative disease should be maintained when evaluating oncologic patients with cardiac symptoms, and multidisciplinary communication is essential to providing high-quality care. Early involvement of electrophysiology consultation is recommended in patients with CS.

Ethics Statement

All of the findings in this publication have adhered to institutional ethical guidelines and standards.

Patient Consent

This is a retrospective case report using de-identified data; therefore the IRB did not require consent from the patient.

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Disclosures

The authors have no conflicts of interest to disclose.

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