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Immune Checkpoint Inhibitor Myocarditis with Normal Cardiac Magnetic Resonance Imaging: Importance of Cardiac Biopsy and Early Diagnosis

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Keywords: Immune checkpoint inhibitor; Endomyocardial biopsy; cardiac magnetic resonance; myocarditis; cancer

Abstract

Immune checkpoint inhibitors (ICI) have improved the management and the prognosis of patients with cancer but are associated with an increased risk of toxicities that can affect every organ. ICI-associated myocarditis has a low incidence (<1%) but a high fatality rate (30–50%). Here, we report a patient treated with ICI admitted for suspicion of myocarditis. Cardiac magnetic resonance imaging (cMRI) was normal. An endomyocardial-biopsy (EMB) was in favour of ICI-related myocarditis with cardiac lymphohistiocytic infiltrate. This case highlights the role of a systematic evaluation with ECG and troponin and the potential value of EMB in patients without a suggestive cMRI

Summary

A patient treated with immune-checkpoint inhibitors (ICI) was admitted for suspicion of myocarditis. Cardiac magnetic resonance imaging results were normal. Endomyocardial biopsy was suggestive of ICI-related myocarditis with cardiac lymphohistiocytic infiltrate. This case highlights the role of systematic evaluation with an electrocardiogram and troponin, and the potential value of endomyocardial biopsy in patients without findings suggestive of myocarditis on cMRI.

Case Report

A woman in her 60s received three doses of a combination of immune checkpoint inhibitors (ICI) (nivolumab/ipilimumab) for metastatic lung cancer. She developed diplopia 10 days after the third infusion but was otherwise asymptomatic from a cardiovascular standpoint. During a systematic evaluation, an electrocardiogram (ECG) and a troponin measurement were performed before the fourth infusion. The ECG showed incident T-wave inversion absent from the baseline tracing. Troponin I was elevated (322 ng/L) (versus normal at baseline, <14 ng/L). The patient was admitted for suspicion of ICI myocarditis. The results of an echocardiogram and cardiac magnetic resonance imaging (cMRI) performed 12 h after admission were normal (without late gadolinium myocardial enhancement and with normal myocardial T1 and T2 values in relaxometry) (Figure 1). Endomyocardial biopsy (EMB) and coronary angiogram (normal results) were performed 24 h after admission. EMB was suggestive of ICI myocarditis with cardiac lymphohistiocytic infiltrate (Figure 2). The patient was treated with corticosteroids and plasmapheresis and had an uneventful cardiovascular evolution at 6 months. ICI treatments were permanently discontinued.

This case highlights the central role of EMB in the diagnosis of ICI myocarditis, even in paucisymptomatic patients (moderate alteration in biomarkers [i.e. troponin] and ECG) without a suggestive myocarditis syndrome and with normal structural and functional cMRI results. These cMRI findings are in line with Zhang et al. (1), showing that cMRI features could be normal in ~30% of patients with biopsy-proven ICI myocarditis, reinforcing the role of EMB in the diagnostic work-up (2). This case suggests that clinical presentation at admission is important, particularly in patients with myositis or myasthenia-like syndrome. Diplopia was considered an immune-related adverse event (irAE), representing the clinical manifestation of an ICI-induced myasthenia gravis-like syndrome. As shown previously, myocarditis was frequently (~30%) associated with myositis and myasthenia gravis-like symptoms (often manifesting as diplopia, ptosis, and respiratory failure) (3,4).

In our institution, patients receiving ICI are systematically evaluated with ECG and troponin measurement at baseline and before each infusion during the first doses. Early detection of changes in these biomarkers is needed to indicate the need for more extensive evaluation. Delays in diagnosis of ICI-induced myocarditis and in initiating appropriate management are critical in terms of negative outcome (up to 50% fatality). Prompt diagnosis is also required to determine whether ICI should be continued or withdrawn

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Legends

Figure 1 CMR was performed on a 3T scanner (MAGNETOM Skyra, Siemens Healthineers, Erlangen, Germany). T1 and T2 mapping sequences were acquired in three short-axis views (basal, median, and apical) with ECG triggering and breath-holding. The T1 mapping sequence was a single-shot balanced steady-state free-precession (bSSFP) modified Look-Locker inversion-recovery (MOLLI) sequence. Post-contrast T1 mapping was acquired 20 min after injection. The T2 mapping sequence was a single-shot T2-prepared gradient-echo fast low angle shot (FLASH) made of three acquisitions with three different preparation times (0, 30, and 55 ms) separated by three recovery heartbeats. The T1 and T2 maps were generated inline using pixel-wise curve fitting after in-plane motion correction.

Figure 1A PSIR sequence, 10 min after gadolinium administration, four-chamber view and noncontrast computed tomography, axial oblique view. No significant late gadolinium enhancement (LGE) was observed. Note that the thin peripheral rim of enhancement (arrow) corresponds to epicardial fat on computed tomography. Scant pericardial effusion is observed.

Figure 1B Native T1 mapping, short-axis views from left ventricular (LV) base to apex. Myocardial native T1 values were within normal ranges. Global native T1 was measured at 1296 ± 34 ms. Regional native T1 was measured, respectively, at 1313 ± 46 ms and 1311 ± 32 ms for the lateral and septal LV wall. Using these measures and the patient's hematocrit obtained on the day of study, global and regional ECV was measured at 26%.

Figure 1C T2 mapping, short-axis views from LV base to apex. Myocardial T2 values were within normal ranges. Global T2 was measured at 42 ± 3 ms. Regional T2 was measured, respectively, at 41 ± 2 ms and 43 ± 1 ms for the lateral and septal LV wall.

Figure 2 Results of the endomyocardial biopsy. Hematoxylin and eosin stain showing cellular infiltration of the myocardium (2A). Immunofixation showing CD4+ and CD8+ lymphocytic infiltration of the myocardium (2B, 2C, respectively). Immunofixation showing CD68+ macrophage infiltration of the myocardium (2D). Immunofixation negative for PDL1 expression (2E).

Figure 1 : Cardiac magnetic resonance features

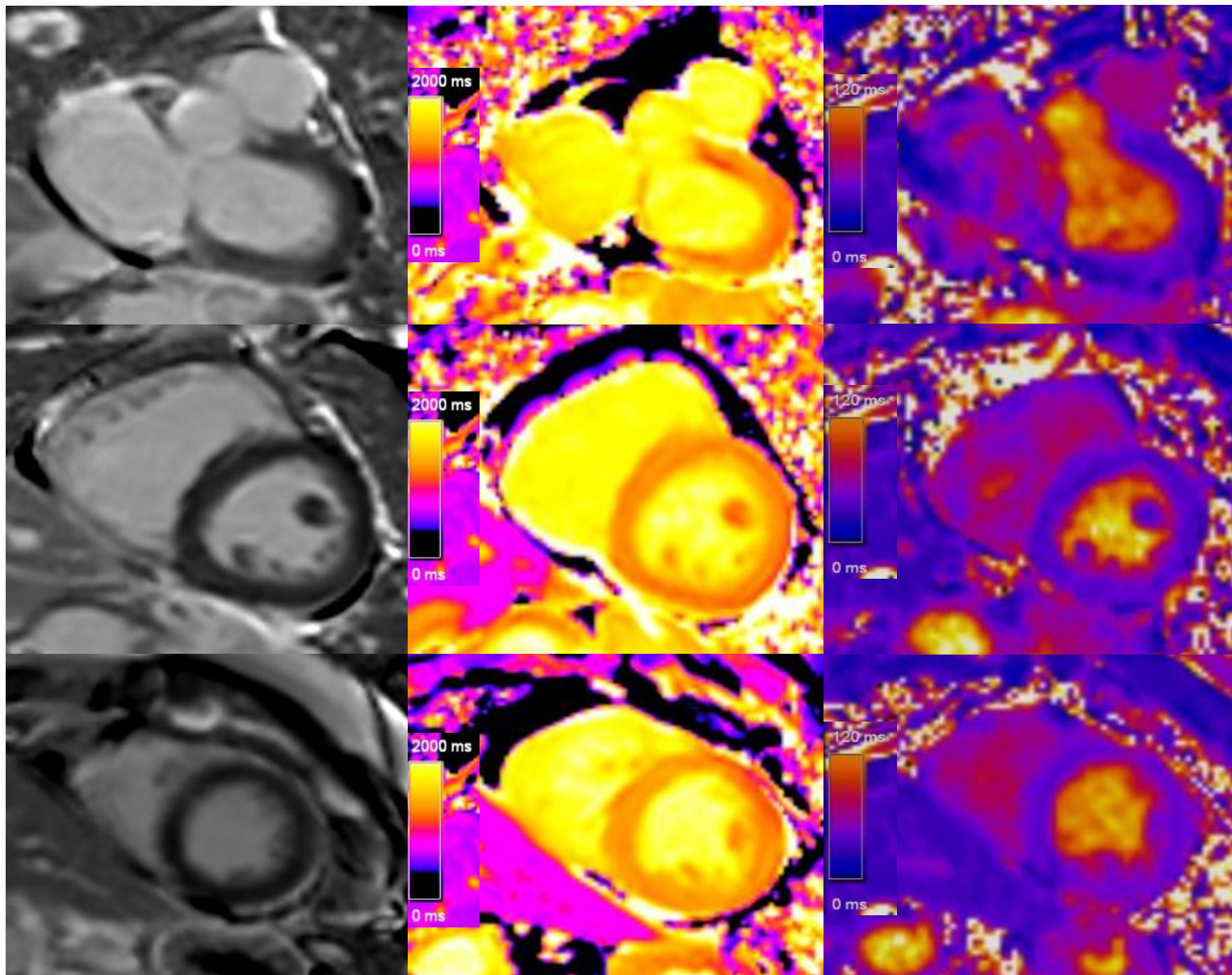


Figure 1A

Figure 1B

Figure 1C

Figure 2 : Results of the endomyocardial biopsy

