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The Challenging Diagnosis of Myocarditis Induced by Immune Checkpoint Inhibitors: A Case Report and Review of the Literature

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Abstract

Immune Checkpoint Inhibitors induced Myocarditis is a serious adverse event. The clinical manifestation can be quite variable and the classic features of myocarditis are not always found. Although challenging, the diagnosis remains necessary in this potentially life-threatening complication. We present the case of a patient treated with nivolumab who developed a late immune checkpoint inhibitor induced myocarditis, without positive diagnostic findings in cardiac magnetic resonance imaging. Early initiation of corticosteroid therapy resulted in good outcome.

Keywords: Immunotherapy • Immune checkpoint inhibitors • Myocarditis • Nivolumab • Cardiotoxicity

Introduction

The advent of Immune Checkpoint Inhibitors (ICIs) in the treatment of metastatic melanoma has changed the prognosis of these cancers. Despite their reassuring profile compared to chemotherapy, some serious side effects have been reported. Cardiovascular complications are described in 1% of cases; myocarditis is among the most serious ones [1].

Case Report

We report the case of a 60-year-old man with recurring metastatic melanoma treated with Nivolumab. After a course of eight administrations, treatment had to be discontinued due to the manifestation of grade IV myalgia with proximal limb weakness. Blood test analysis performed at that moment showed an increase in troponin T level at 37.6 ng/l (normal, <14 ng/L) with normal creatine kinase level 33 U/L (normal, 39 U/L to 308 U/L). Two weeks later, the patient was admitted for dyspnea, asthenia and palpitations. Physical examination showed basal crackles in the right lung with hypoventilation at the left base. Chest radiography revealed diffused opacity in the right lung and a slight elevation of the left diaphragmatic dome. Sinus tachycardia and non-specific repolarization disorders were present on the Electrocardiogram (ECG). Troponin T level was 32.1 ng/L (normal, <14 ng/L), NT-proBNP level was 3233 ng/L (normal, <900 ng/L) and C-reactive protein level was 61.1 mg/L (normal, <5 mg/L). Transthoracic echocardiography revealed a severe left ventricular diffuse hypokinesia with a left ventricular ejection fraction of 15%. The coronary angiography was normal and the ventriculography confirmed diffuse hypokinesia.

Given the strong suspicion of ICIs induced myocarditis, treatment with intravenous methylprednisolone 1 g/d was immediately started. Cardiac magnetic resonance imaging, performed two days later, confirmed the severely impaired left ventricular ejection fraction but did not show any structural myocardial disorder. Endomyocardial biopsy was then performed which showed myocyte necrosis with lymphocyte infiltrate confirming the diagnosis of myocarditis (Figure 1). Oral corticosteroid therapy was pursued with prednisolone 1 mg/kg/day combined with a heart failure treatment based on angiotensin-converting enzyme inhibitors, diuretics and beta-blockers. A few days after initiating this treatment, the patient began to improve with an increase in functional capacity, decreased dyspnea, decreased inflammatory syndrome and troponin levels. Echocardiographic control one month later showed a near-normalization of the left ventricle ejection fraction to 50%.

Discussion

ICIs offer a new therapy option for many solid cancers. To fight tumor cells, ICIs reactivate immunity by acting on T cells through PD-1 receptors (Nivolumab) or through CTLA-4 receptors (other ICIs). Unfortunately, the benefit of ICIs can be offset by severe immune related adverse events. Cardiovascular complications are described in <1% of cases [2]. Myocarditis is a serious complication and is present in 0.06% patient treated with Nivolumab [3]. The pathophysiology is still unclear but the hypothesis is that the adverse event is due to an antigen that is common to both myocardium and tumor cells leading to an inappropriate immune response [4]. Although myocarditis is a rare adverse event, it should be noted that about one in three cases presents a negative outcome with up to 50% mortality [1]. For this reason, clinicians should keep a vigilant eye on immune checkpoint inhibitors related myocarditis. Unfortunately, diagnosis is challenging. The last European Society for Medical Oncology (ESMO) consensus published in January 2020 recommends appropriate workup (ECG, troponin, BNP or NT-pro-BNP, C-reactive protein, viral titer, echocardiogram with left ventricular function analysis including global longitudinal strain, cardiac MRI) for patients who develop new cardiovascular symptoms or are incidentally noted to have any arrhythmia, conduction abnormality on ECG or Left Ventricular Systolic Dysfunction (LVSD) on echocardiogram, while undergoing or after completion of ICI therapy. If the diagnosis is highly suspected despite negative test results, Endo Myocardial Biopsy (EMB) should be considered. The EMB remains the gold standard for the diagnosis of myocarditis. However, it is an invasive procedure with a risk of cardiac perforation and a poor diagnostic power due to the localized nature of the biopsy sample. Given these reasons together with the contributory role of MRI in the diagnosis, the biopsy test is no longer performed as first-line procedure [5]. However, when carried out, it usually reveals predominant lymphocytic myocardium infiltrates in the case of ICIs induced myocarditis with multiples lesions of focal necrosis [6,7]. With either suspicion or confirmation of ICI associated myocarditis, high-dose corticosteroids (methyl-prednisolone 1000 mg/day followed by oral prednisone 1 mg/kg/day) should be promptly initiated. Corticosteroid therapy with progressive tapering should continue until resolution of symptoms, normalization of troponin levels, left ventricular systolic function and conduction abnormalities [5,8].

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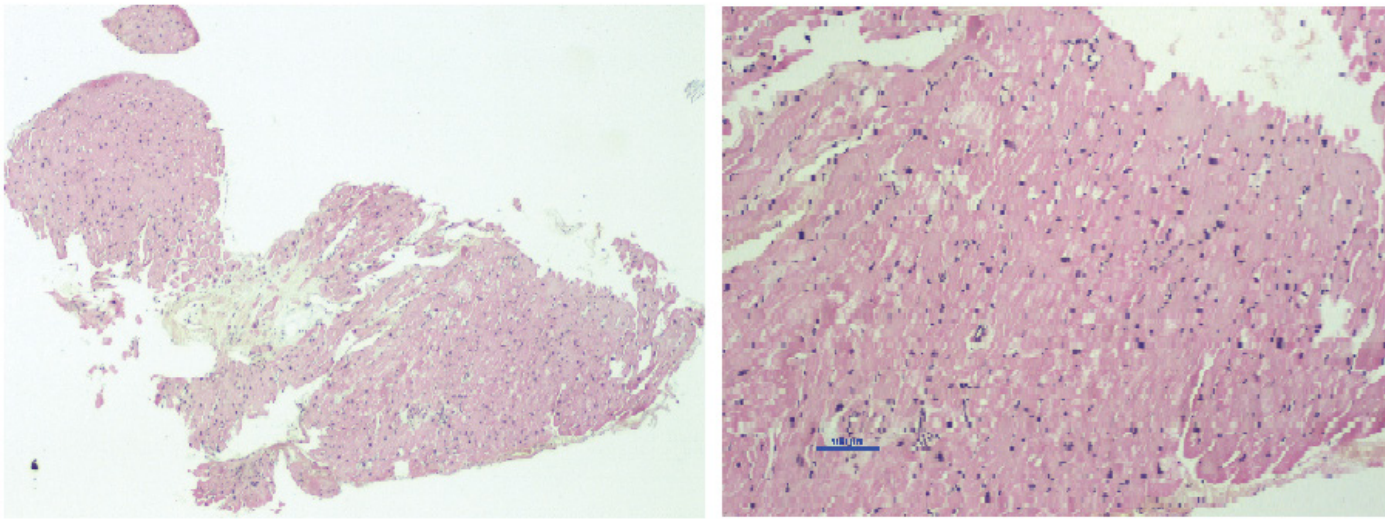

Figure 1. Histological examination of endomyocardial biopsy showing inflammatory myocarditis with a moderate lymphocyte infiltrate and myocyte necrosis. (A) Global view and (B) Close up view.

In some cases when corticosteroids are insufficient, other immunosuppressants such as infliximab, rituximab, and mycophenolate mofetil can be considered [9]. More recently, abatacept (CTLA-4 agonist), approved for use in patients with rheumatic diseases, was used in a glucocorticoid-refractory nivolumab induced myocarditis case. The same team also suggested a benefic role of plasmapheresis [10]. In our case, the late presentation of myocarditis after the start of ICI therapy is quite unusual and could have been misleading. We currently know that the majority of cases of myocarditis occur shortly after initiation of ICI therapy, but 7% can occur after the sixth dose and seems to be associated with a better prognosis [11]. Considering the high probability of ICI related myocarditis, we decided to start corticosteroid therapy before confirmation of the diagnosis to avoid further deterioration, while continuing further assessment. Two indicators supported our hypothesis, one is the presence of myalgia, an association between myocardial and muscle damage has been reported in 15 to 25% [12]. The other is the rapid positive response to treatment. Our patient has improved clinically, radiologically and biologically quickly under corticosteroid therapy. When the MRI results came back negative, we had to decide whether to continue treatment or not. However, knowing MRI sensitivity of 68 to 78% and the fact that the test was conducted two days after the start of corticosteroids, we postulated that the steroids could have contributed to the test negativity [13]. We have therefore decided to continue therapy. The yield of the EMB was able to confirm a posteriori our hypothesis. This case illustrates the importance of an early start of treatment, even in the absence of a confirmed diagnosis, and demonstrates the value of performing the myocardial biopsy especially when the MRI is negative despite the strong suspicion of ICIs induced myocarditis.

Conclusion

ICI induced myocarditis is a rare complication but its progression can be dramatic. When suspected, it must be actively sought with all diagnostic means including EMB. In the absence of other etiologies, treatment should start as early as possible even without diagnostic confirmation.

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