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A Clinician's Approach to Checkpoint Inhibitor Therapy Following Inflammatory Events from Nivolumab

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Abstract

With the growing number of monoclonal antibody therapies for oncologic conditions, timely identification and management of their complications are increasingly important for practitioners. This is a case of a 74-year-old female with primary metastatic melanoma who presented with progressive shortness of breath shortly after initiation of nivolumab. The patient's endomyocardial biopsy was significant for myocyte damage with inflammatory infiltrate and positive PD-1 staining, indicating myocarditis. The hospital course was complicated by cardiac arrest leading to temporary pacemaker placement, atrial fibrillation with rapid ventricular rate, and concomitant thyroiditis. The patient was started on high-dose (1 mg/kg) steroids and mycophenolate for treatment of myocarditis.

Keywords

Immune Checkpoint Inhibitor, Myocarditis, Thyroiditis, Treatment of ICI Myocarditis

1. Introduction

Cytotoxic chemotherapies are the traditional mainstay of many oncologic conditions. Their complications are well known throughout medical education and literature [1]. However, immunotherapies have complications that are less understood due to their novelty. With their growing use as first-line therapy, our recognition of immune-related adverse effects continues to expand [2]. Nivolumab is a Programmed Cell Death Protein 1 (PD-1) monoclonal antibody used in the treatment of melanoma, non-small cell lung cancer, renal cell carcinoma, and Hodgkin lymphoma, among others [3]. One such complication of checkpoint inhibitors is

checkpoint inhibitor-associated myocarditis (ICI-myocarditis). In this presentation, we describe a case of nivolumab-associated myocarditis with associated thyroiditis.

2.Case Presentation

A 74-year-old female presented with a 10-day history of progressive dyspnea. Her past medical history was most notable for recently diagnosed malignant melanoma, actinic keratosis, psoriasis, type 2 diabetes mellitus, hyperlipidemia, and essential hypertension. Surgical history included cholecystectomy, cesarean section, appendectomy, and hysterectomy. She had a family history of dermatoses and diabetes mellitus in her mother. Coronary heart disease was noted in her brother and father, but no other significant family history of skin cancer. She was a non-smoker, had no history of second-hand smoke exposure, and reported no significant alcohol or illicit drug use.

Her melanoma was located on the left lateral calf. A preliminary biopsy confirmed malignant melanoma, and the patient subsequently underwent wide local excision of the lesion, revealing invasive melanoma measuring 30 mm in largest diameter with a Breslow Depth of 3.9 mm. Sentinel lymph node biopsy demonstrated two positive nodes out of three examined, leading to a final staging of pT3aN2a with no distant metastases.

The patient was started on nivolumab in the outpatient setting by her primary oncologist. Twenty-eight days following her first cycle, she presented for her second dose but exhibited significant respiratory symptoms and fatigue. Before the second cycle could be administered, she was transported to the emergency department via emergency medical services from clinic.

On admission, she was in moderate respiratory distress. A systolic murmur (2/6) was noted at the left lower sternal border, and pulmonary examination revealed decreased breath sounds bilaterally without lower extremity edema. She required 2 liters of oxygen via nasal cannula but remained afebrile and hemodynamically stable.

2.1. Investigations

An electrocardiogram (ECG) demonstrated sinus rhythm with a new right bundle branch block and interventricular conduction delay without significant ST changes (**Figure 1**). Initial labs were notable for an elevated troponin of 0.94 ng/mL (normal: <0.05 ng/mL), AST/ALT of 149/146 U/L, BNP of 54 pg/mL, and venous blood gas with pH 7.42, pCO2 48 mmHg, and bicarbonate of 31 mmol/L. A respiratory viral panel, including COVID-19 PCR, was negative.

A chest X-ray (CXR) showed no evidence of interstitial edema. Computed tomography angiography (CTA) of the chest was negative for pulmonary embolism, with the heart size at the upper limit of normal and mild coronary artery and aortic valve calcification. Transthoracic echocardiography revealed mild concentric left ventricular hypertrophy, an ejection fraction of 75% - 80% with hyperdynamic

function, mild aortic stenosis, and an elevated central venous pressure of 5 - 10 mmHg.

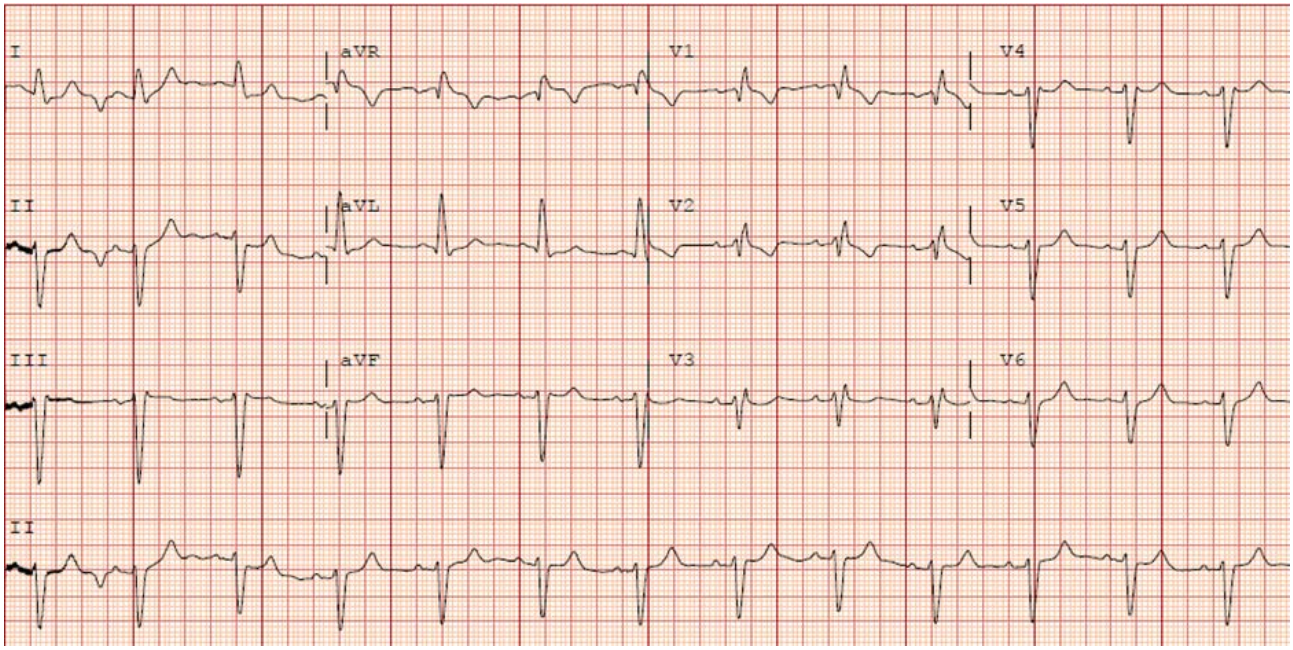

Figure 1. EKG demonstrating interventricular conduction delay with Right Bundle Branch Block.

Cardiology was consulted due to elevated troponin and concern for Immune Checkpoint Inhibitor (ICI) myocarditis. Cardiac catheterization was planned. However, the patient developed junctional rhythm before the procedure and subsequently progressed to complete heart block followed by cardiac arrest. Return of spontaneous circulation (ROSC) was achieved after one round of cardiopulmonary resuscitation (CPR). The patient underwent right and left heart catheterization, right ventricular endomyocardial biopsy, and temporary pacemaker placement.

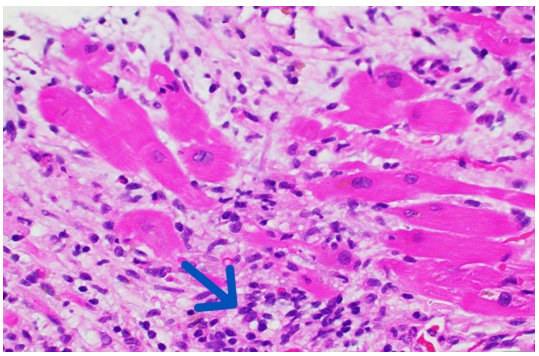

Figure 2. Native Cardiac Tissue Hematoxylin and Eosin Stain demonstrating lymphocytic infiltrate (indicated by arrow).

Catheterization findings included elevated right and left-sided filling pressures,

mild pulmonary hypertension, and mildly reduced cardiac output. Coronary angiography showed no significant coronary artery disease. Endomyocardial biopsy revealed histiocyte-rich inflammatory infiltrate with myocyte damage, eosinophils (**Figure 2**) and lymphocytes (**Figure 3**).

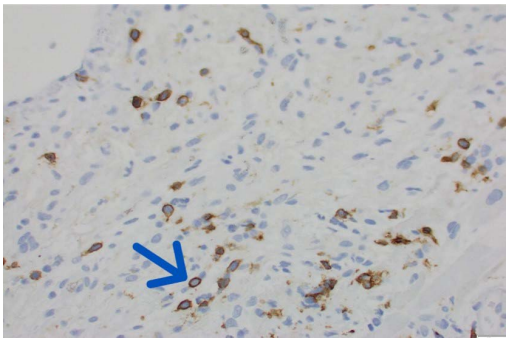

Figure 3. Native Cardiac Tissue CD8+ stain, demonstrating CD8 cell reactivity (indicated by arrow). This is consistent with suspected checkpoint-inhibitor myocarditis.

PD-1 staining was positive in affected areas, consistent with ICI-myocarditis [4] (**Figure 4**).

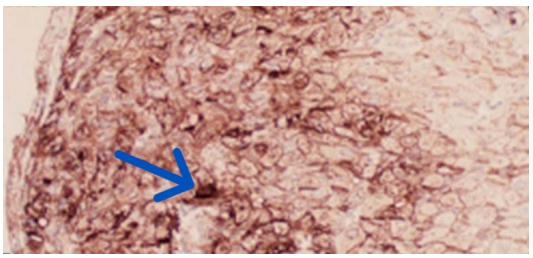

Figure 4. Native Cardiac Tissue PDL-1 Immunostain is positive in myocytes in areas of damage (indicated by arrow). This phenomenon has been reported in checkpoint-inhibitor myocarditis.

2.2. Outcome and Follow Up

The patient was treated with 1 mg/kg intravenous methylprednisolone for three doses, followed by an oral prednisone taper and mycophenolate mofetil 500 mg twice daily for four weeks [4]-[6]. Diuresis was initiated after follow-up CXR showed increased vascular congestion. Troponin measurements trended downward with immunosuppressive therapy, and the temporary pacemaker was removed after resolution of heart block.

On hospital day 9, the patient developed atrial fibrillation with rapid ventricular response. She was started on a heparin and amiodarone drip, later converting to sinus rhythm and transitioning to oral amiodarone. Thyroid function tests showed TSH < 0.01 U/mL (normal: 0.35 - 5.00), free T4 of 3.5 ng/dL (normal: 0.6 - 1.6), and total T3 of 125 ng/dL (normal: 87 - 180). Endocrinology was consulted for suspected nivolumab-induced thyroiditis, given the profound elevation of free T4.

Thyroid ultrasound showed mild thyroid enlargement with heterogeneous echotexture. Methimazole was considered for treatment of autoimmune thyroid disease. However, anti-TPO and TSH receptor antibodies were negative. These findings were consistent with nivolumab-induced thyroiditis rather than autoimmune thyroid disease. Subsequently, therapy for checkpoint inhibitor thyroiditis was initiated [3]. The patient was started on high dose corticosteroids with methylprednisolone 1 mg/kg and mycophenolate [5] [6].

The patient progressed through her hospital course and was discharged on a prednisone taper, mycophenolate, pneumocystis prophylaxis due to the prolonged taper of prednisone, and apixaban because of atrial fibrillation.

3. Discussion

Immune checkpoint inhibitors (ICI) have revolutionized cancer treatment by enhancing the body's immune response against tumor cells. However, their ability to stimulate immune activity can also lead to immune-related adverse events. These can be life-threatening and cause significant morbidity [6]. Among these, ICI-induced myocarditis is a particularly serious complication, with reported mortality rates as high as 50% [7]. The exact mechanism of ICI-induced myocarditis remains under investigation, but it is thought to involve an exaggerated immune response, in which activated T-cells infiltrate myocardial tissue, leading to direct cardiomyocyte damage [7].

Early recognition and intervention are critical in managing ICI myocarditis. In this case, the patient presented with dyspnea and fatigue following her first dose of nivolumab. Given the potential for cardiac involvement, immediate assessment with ECG and troponin levels was necessary. The presence of a right bundle branch block and elevated troponin raised suspicion for myocarditis, prompting a comprehensive cardiac evaluation. The decision to perform an endomyocardial biopsy was guided by the need for definitive histopathological confirmation, which revealed inflammatory infiltrates and myocyte damage with positive PD-1 staining, confirming ICI-induced myocarditis.

Treatment Strategy

The cornerstone of treatment for ICI-induced myocarditis is high-dose corticosteroids. Steroids exert broad immunosuppressive effects, reducing T-cell activation and cytokine-mediated damage. In this case, methylprednisolone (1 mg/kg IV) was initiated promptly. Studies have suggested that early initiation of steroids can improve outcomes by preventing progression to fulminant myocarditis. However, in severe or refractory cases, additional immunosuppressive therapy is warranted [4] [5].

Mycophenolate mofetil was introduced in this patient's treatment regimen due to the severity of her presentation, including complete heart block and cardiac arrest [4] [5]. Mycophenolate is a purine synthesis inhibitor that selectively suppresses T and B lymphocyte proliferation. Although its use in ICI-induced myocarditis is not yet standardized, case reports and small studies suggest that it may

be beneficial when corticosteroids alone are insufficient as was the case with this patient.

This case was further complicated by the development of atrial fibrillation with rapid ventricular response, which required anticoagulation and rate control with amiodarone following the patient's cardiac arrest. The decision to use amiodarone was based on its efficacy in rhythm control without significantly affecting blood pressure, which is particularly important in patients with myocarditis and potential cardiac dysfunction.

Thyroiditis is another recognized immune-related adverse events associated with ICI therapy. The pathophysiology involves immune activation against thyroid tissue, leading to an initial hyperthyroid phase due to hormone release from damaged follicular cells, often followed by hypothyroidism. This patient's thyroid function tests revealed a suppressed TSH and elevated free T4, indicating thyrotoxicosis. The absence of TPO antibodies and the clinical context of ICI use, nivolumab-induced thyroiditis was the most likely diagnosis.

Initial management focused on symptomatic control, with beta-blockers to mitigate the effects of excess thyroid hormone. Methimazole was not initiated because ICI-induced thyroiditis typically does not result from increased hormone production. Treatment of thyroiditis with methylprednisolone and mycophenolate was favored due to glandular destruction resulting in the release of free T4. The patient's thyroid function was monitored closely, with the expectation that a hypothyroid phase might follow, necessitating future thyroid hormone replacement therapy.

4. Conclusions

In conclusion, this case underscores the need for vigilance in patients receiving immune checkpoint inhibitors, particularly regarding cardiovascular complications. Current recommendations suggest regular monitoring of troponin levels and ECGs in high-risk patients, especially within the first few weeks of treatment. This patient presented emergently from her oncologist's office where the severity of her condition was recognized. While myocarditis remains a rare complication, its high mortality rate necessitates a high index of suspicion. Additionally, routinely monitoring thyroid function tests during ICI therapy is prudent, given the frequency of thyroid-related adverse events [8].

As ICI therapies become more widespread, further research is needed to refine management strategies for immune-related toxicities. The role of second-line immune suppression, the optimal duration of steroid therapy, and potential predictive biomarkers for immune related adverse events remain active areas of investigation.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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