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Pembrolizumab-induced Takutsubo's, Pneumonitis, and Hypophysitis

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Abstract

Immune Checkpoint Inhibitor (ICI) therapy is an evolving landscape. Beyond its initial application in advanced melanoma, it knows occupies a key role in various malignancies, including Non-Small Cell Lung Cancer (NSCLC). While ICIs, such as pembrolizumab, effectively target programmed cell death receptors (programmed death ligand 1) the escalating use of these agents has led to an increased incidence of reported side effects, notably coronary artery spasms, myocarditis, and Takotsubo cardiomyopathy. The presented case involves a 72-year-old woman undergoing single-agent pembrolizumab for metastatic NSCLC, who developed Takotsubo cardiomyopathy, immune-mediated pneumonitis, and hypophysitis. Despite aggressive medical management, including high-dose glucocorticoids, the patient passed away from sudden cardiac death two months post-discharge. Immune-mediated injury can potentially span various organ systems. Given this, clinicians should be aware of known medication-related adverse effects in patients on ICIs. As ICI use becomes increasingly prevalent, prompt recognition and intervention in immune-related adverse events is necessary. The reported prevalence of ICI-induced cardiac side effects is potentially higher than acknowledged. More work is needed in this space for a more comprehensive understanding of these adverse effects and guidelines for management.

Introduction

The initial use of Immune Checkpoint Inhibitors (ICI) was limited to the treatment of advanced melanoma, however, advancements in the field of research have expanded its utility in the treatment of malignancies like Non-Small Cell Lung Cancer (NSNLC), renal cell carcinoma, and Hodgkin's lymphoma [1,2]. These agents target T-lymphocyte programmed cell death receptors and their respective ligand, the Programmed Death Ligand-1 (PDL-1). However, with increased use of ICI, more of their side effects are being reported as well. Coronary artery spasms, myocarditis, and Takotsubo cardiomyopathy are the reported side effects of pembrolizumab [3-5]. We report a case of Takotsubo cardiomyopathy, immune-mediated Pneumonitis, and Hypophysitis in a patient with NSCLC treated with pembrolizumab.

Case Presentation

A 72-year-old woman, undergoing single-agent pembrolizumab for metastatic non-small cell lung cancer, presented with a 3-day history of worsening shortness of breath and weakness. On admission, she was hypotensive and tachycardic at 160 beats/min. An EKG revealed an SVT. Treatment with phenylephrine and amiodarone stabilized her vitals. Further evaluation revealed troponin elevation, echocardiographic findings consistent with Takotsubo cardiomyopathy (Figure 1,2), and hypophysitis (low ACTH, aldosterone, TSH, FSH, LH). A CXR showed bibasilar infiltrates (Figure 3). CT chest showed new infiltrates (Figure 4), but the infectious workup was negative. Methyl prednisone was administered for suspected immune-related myocarditis, and later she was maintained on low-dose prednisone due to adrenal insufficiency. Pembrolizumab was discontinued. Despite medical management, she passed away at home from sudden cardiac death two months after discharge.

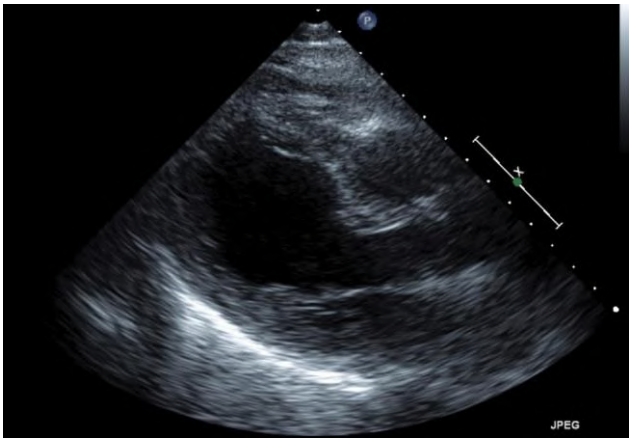

Figure1: Para-sternal long axis view showing dilated and ballooned left ventricle.

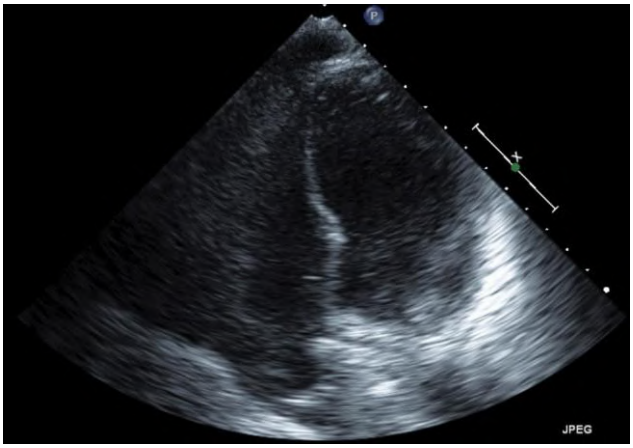

Figure 2: 4-Chamber view illustrating dilated left ventricle.

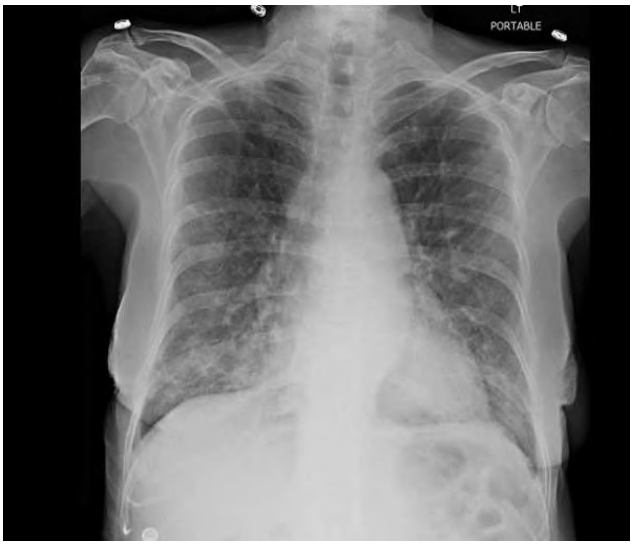

Figure 3: Chest X-ray shows bilateral infiltrates, predominantly in the lower lobes.

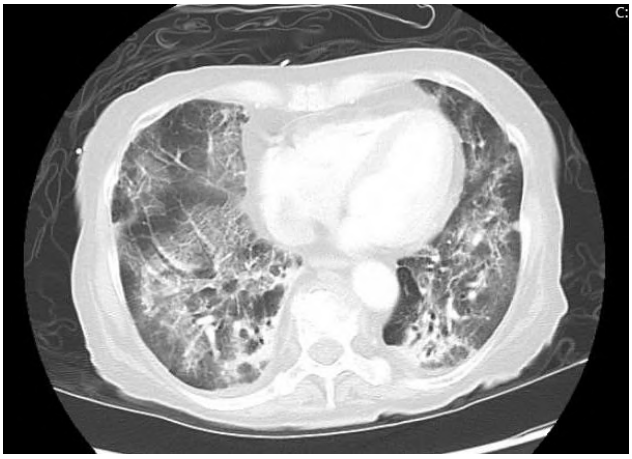

Figure 4: CT Chest shows bilateral lower lobe infiltrates.

Discussion

The stimulation of the immune system by ICI can cause immune-mediated injury to several organ systems including the cardiovascular system [5]. ICI is increasingly used for different malignancies and is frequently linked with different immune-mediated entities. Given increasing reports in the literature, any patient in ICI admitted for usual findings should be considered to have medication-related adverse effects. Treatment of immune-mediated Takotsubo cardiomyopathy and pneumonitis requires the administration of high-dose glucocorticoids (1 mg/kg bid) [1,2] If this fails further therapies including pulse steroids, mycophenolate mofetil, and plasmapheresis should be considered [1,2,6]. ICI therapy-induced cardiac side effects are as high as 1%, however, new reports suggest an even greater prevalence, considering this may be an underreported phenomenon [6]. The median time for the onset of myocarditis and Takotsubo cardiomyopathy across all the centers is 17-34 days and is associated with poor prognosis [7].

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