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CASE REPORT

Pembrolizumab-Induced Broken Heart Syndrome, Pneumonitis, and Hypophysitis Occurring Concurrently; A Deadly Triad

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Abstract

Immune checkpoint inhibitors are novel medications used to treat a wide range of solid organ tumors and work by stimulating the cellular immune response. With their increasing use, more and more multiorgan side effects are reported in the literature. Prompt recognition of these findings is vital for the safe clinical use of these agents. Most side effects are immune-mediated injury, and the treatment involves stopping the ICI drug and systemic steroids. We report a case of a 72-year-old female treated with pembrolizumab monotherapy for non-small cell lung cancer. She presented for dyspnea and generalized weakness after the second session of pembrolizumab. She was found to have a triad of Takotsubo cardiomyopathy, hypophysitis, and pneumonitis. The patient was discharged home on steroids and heart failure treatment with the discontinuation of further sessions of pembrolizumab.

Keywords: Pembrolizumab, Pneumonitis, Hypophysitis, Immune checkpoint inhibitors, Takotsubo cardiomyopathy

1. Introduction

Immune checkpoint inhibitors (ICI) are revolutionary novel anti-cancer agents. These were initially used in the treatment of advanced melanoma; however, their use has expanded to treat numerous other malignancies like non-small cell lung cancer NSCLC, breast cancer, renal cell carcinoma, Hodgkin's lymphoma, and others. Currently, available agents target T-lymphocyte programmed cell death receptors and their respective ligand programmed death ligand-1 (PDL-1). Anti-PD-1 antibodies (including pembrolizumab) reverse T-cell suppression and induce antitumor responses. As the use of ICI in different malignancies is increasing, more side effects are becoming apparent with this increased use. There are reported cases of coronary artery spasms, myocarditis, and takotsubo cardiomyopathy with pembrolizumab.[1-3] We describe a case of a pembrolizumab-induced triad of side effects, including takotsubo cardiomyopathy, immune-mediated pneumonitis, and hypophysitis in a patient with NSCLC.

2. Case report

A 72-year-old female with metastatic NSCLC on pembrolizumab monotherapy received her second session (400 mg dose) three weeks before the presentation. She arrived with three days of progressive shortness of breath and generalized weakness but no reported chest pain. The patient reported no fever or chills. Upon admission, her vitals included BP of 82/62 mmHg and HR of 160/min; EKG showed new-onset atrial fibrillation with a rapid ventricular response but no acute ischemic changes. Physical

Abbreviations: ICI, Immune checkpoint inhibitors; NSCLC, non-small cell lung cancer; PDL-1, Programmed death ligand-1

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examination revealed a pale lady in distress due to shortness of breath. She had engorged neck veins and bilateral crackles through mid-lung fields. No loud murmur was appreciated on cardiac auscultation. She had 1+ pitting edema to her bilateral ankles.

Past medical history included well-managed and stable DVT on apixaban, hypertension on amlodipine 5 mg, hyperlipidemia on atorvastatin 40 mg, and invasive ductal carcinoma of breast s/p surgery in remission other than non-small cell lung cancer with metastasis to the brain and spine. There were no recent changes or addition to her medications for these chronic medical conditions. Septic shock, cardiogenic shock, primary or secondary adrenal insufficiency, acute ST elevation MI, pneumonitis, pneumonia, pulmonary embolism, and immune-mediated multiorgan injury were the initial considerations.

Her labs were significant for peak troponin-I of 1.96 ng/ml (0.013 ng/ml), BNP 144 pg/ml (0–100 pg/ml), serum lactate 2.7 mmol/L (0.5–2.2 mmol/L), WBC 8.6 k/ul (4–11 k/ul), Hb 10.7 g/dl (11.5–15.8 g/dl), serum creatinine 0.9 mg/dL (0.7–1.3 mg/dL). Further laboratory studies revealed hypophysitis with ACTH <5 pg/ml (7.2–63 pg/ml), aldosterone <4 ng/dl (<21 ng/dl), TSH 0.26 uIU/ml (0.34–4.94 Uiu/ml), FSH 8.4 mIU/ml (low for age), LH 1.6 mIU/ml (low for age). CXR showed bilateral infiltrates concerning infection or interstitial edema. She was resuscitated with intravenous fluids, phenylephrine, and amiodarone infusion, which improved her vital signs to normal range. She was started on empiric antibiotics that were discontinued shortly after as her shock was thought to be cardiogenic more than septic. The echocardiogram demonstrated an ejection fraction of 25–30% and apical ballooning, indicating takotsubo cardiomyopathy (Figs. 1 & 2). CT scan of the chest showed new infiltrates concerning interstitial edema vs. infection but was negative for pulmonary embolism (Fig. 3). The infectious workup, including blood and urine cultures, urine serology for legionella/pneumococcal antigen, and nasal MRSA PCR, resulted in a negative.

She was managed with methyl prednisone 60 mg twice daily for seven days, followed by a taper to a final maintenance dose of 5 mg prednisone due to adrenal insufficiency. Cardiac catheterization was not done as she had one with clean coronaries about two weeks ago. Further, she was a poor candidate for any invasive procedures. Pembrolizumab was stopped moving forward. The patient was discharged home in stable condition without any oxygen requirement after the 13 days of hospital stay. Her limited echocardiogram before discharge showed an EF of 40–45%, which was a significant improvement. Discharge medications included losartan, spironolactone, Lasix, metoprolol, digoxin, amiodarone, enoxaparin, and prednisone. Her

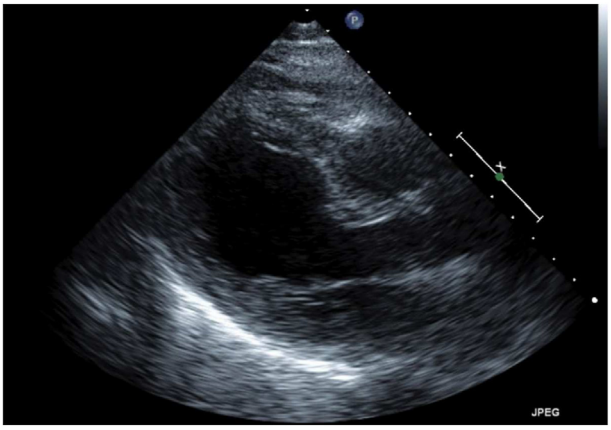

Fig. 1. Echocardiogram para-sternal long axis view showing dilated and ballooned LV.

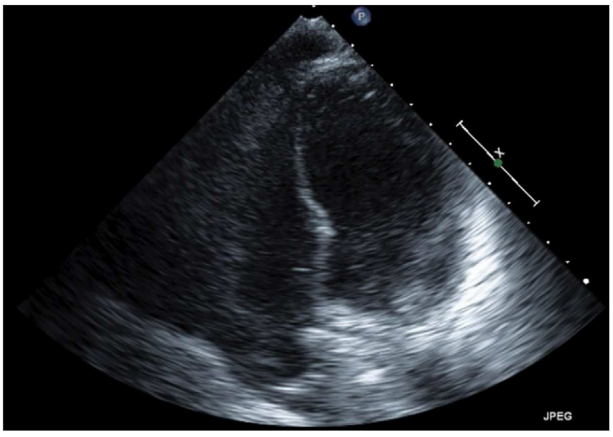

Fig. 2. Echocardiogram 4-chamber view illustrating dilated LV.

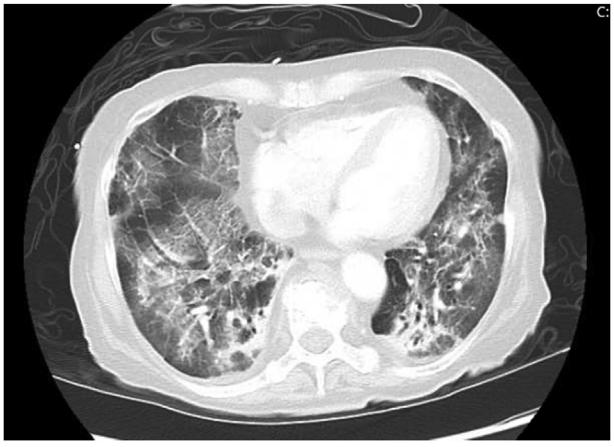

Fig. 3. CT Chest shows bilateral lower lobe infiltrates.

symptoms were well in remission, with stable lab work on the initial post-hospital follow-up with PCP. Unfortunately, two months post-discharge, she passed away at her home due to sudden cardiac death.

3. Discussion

The stimulation of the immune system by ICI can cause immune-mediated injury to several organ systems, including the cardiovascular system, where it can manifest as myocarditis, arrhythmias, pericardial disease, MI, noninflammatory cardiomyocyte dysfunction, and takotsubo cardiomyopathy.[3,4] ICI are increasingly used for different malignancies and are frequently linked to various immune-mediated entities. These entities can affect multiple organ systems simultaneously or at separate times. Therefore, It is imperative to consider these in the differentials when such diagnoses are made, and therapy with ICI should be immediately held. The adverse effects involving the endocrine system are hypo- or hyperthyroidism, hypophysitis, adrenal insufficiency, and type 1 diabetes mellitus.[5] In the respiratory system, it has been reported to cause pneumonitis and sarcoidosis.[5] Immune-mediated Takotsubo cardiomyopathy pneumonitis and hypophysitis are treated with systemic steroids with a slow taper and close monitoring of side effects from corticosteroids.[4-6] Other options include pulse steroids, mycophenolate mofetil, and plasmapheresis on a case-by-case basis.[4,6,7] The prevalence of cardiac involvement is reportedly up to 1% for patients on ICI therapy; however, in the light of recent reports, it can be higher than reported.[7] Myocarditis and takotsubo cardiomyopathy appear to occur early with a median onset of 17−34 days, consistent across all cancers and are associated with poor outcomes.[8] The mortality rate is relatively high with these complications. In one retrospective study of patients receiving ICIs, death occurred in 50% of patients with cardiac involvement.[5] The median onset of hypophysitis and pneumonitis was noted to be 76 and 90 days from the initiation of ICIs, respectively.[5] Our case report underscores the importance of provider awareness for closely monitoring patients treated with ICI for various multisystem complications. We anticipate that reporting these rare complications will help providers recognize these entities early on in their patients being treated with ICI and take appropriate steps to limit the morbidity and mortality in this patient population.

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Conflict of interest

The authors have nothing to disclose.

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