Current Problems in Cancer 43 (2019) 504–510

Contents lists available at ScienceDirect

Current Problems in Cancer

journal homepage: www.elsevier.com/locate/cpcancer

Pericardial effusion due to pembrolizumab-induced immunotoxicity: A case report and literature review

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A B S T R A C T

The advent of immune checkpoint inhibitors has revolutionized cancer treatment. These novel agents have provided promising treatment options in patients with different types of cancers. One of these agents is pembrolizumab, which works by blocking the binding of T-lymphocytes to programmed cell death ligand 1 receptors on tumor cells, thus enabling immune activation of T-lymphocytes against tumor cells. Pembrolizumab is commonly used in metastatic nonsmall cell lung cancer and melanoma. However, despite the remarkable efficacy this agent has achieved, multiple immune-related adverse events have been reported including hepatitis, colitis, thyroid dysfunction, and pneumonitis. Only 2 other cases of pericardial effusion as a side effect of pembrolizumab have been cited in the literature; however, its incidence may be on the rise. Despite the rarity of this side effect, its complications are potentially life threatening and no clear platform currently exists to help guide healthcare professionals in the management of these adverse events. Herein we present the case of a 66-year-old female who developed pericardial effusion as a side effect of pembrolizumab and review the data currently available to assist in the management of this life-threatening condition.

A R T I C L E I N F O

Keywords: Pembrolizumab; Immunotherapy; Pericardial effusion; Nonsmall cell lung cancer; Immunotoxicity

Introduction

Pembrolizumab is a humanized IgG4 antibody used in cancer immune therapy.[1] It has been tested in 12 categories of malignancy,[2] some of which include melanoma,[3] nonsmall cell lung

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https://doi.org/10.1016/j.currproblcancer.2019.01.001
0147-0272/

cancer (NSCLC),[4] gastric cancer,[5] Hodgkin's lymphoma,[6] head and neck cancer,[7] and urothelial carcinoma.[8] It is highly specific against the programmed death-1 (PD-1) receptors on T-lymphocytes.[9] PD-1 receptors are a family of receptors expressed on T-lymphocytes that bind to programmed death ligand 1 and 2 (PD-L1 and PD-L2) on other cells to ensure self-tolerance and protect the body against autoimmunity.[10] Pembrolizumab binds to the PD-1 receptors on T-lymphocytes and prevents their interaction with PD-L1 and PD-L2 on the tumor cells, thus restoring immune activation of T-lymphocytes against tumor cells.[1] However, T-cell immune function is not specific against tumor cells; they could be activated to attack body organs thus leading to multiple immune side effects.[11,12]

PD-1 and PD-L1/PD-L2 are overexpressed in the cancer microenvironment to suppress the immune activation of T-lymphocytes against tumor cells. Clinical studies have shown that overexpression of these receptors and ligands on T-lymphocytes and tumor cells is associated with a poor prognosis.[13,14]

Immunotherapy has fewer side effects as compared to chemotherapy. The side effects of pembrolizumab arise from nonspecific activation of T-lymphocytes leading to autoimmune toxicity. Although most side effects are mild and could be treated conservatively, more serious immune-related side effects may occur and include pneumonitis, colitis, hepatitis, and nephritis.[15,16] The cardiovascular system is among the least systems commonly affected by immunotoxicity.[15] However, it is noteworthy to mention that the number of cases of pericardial effusion being caused by another PD-1 inhibitor known as nivolumab is on the rise.[17,18] To our knowledge, only 2 other cases of pericardial effusion have been linked to pembrolizumab.[19,20] Given the rarity of this occurrence, no clear guidelines exist in treating pericardial effusions caused by immunotoxicity. However, general guidelines are available to guide physicians in the treatment of cardiovascular toxicities resulting from immune check inhibitors.[21]

Herein we report the third case of pembrolizumab-induced pericardial effusion. Despite the rarity of this side effect, physicians should be mindful of it as rapid deterioration due to cardiovascular collapse may ensue. In addition, malignancies commonly result in pericardial effusion either due to direct invasion or pseudoprogression, and thus, differentiating side effects of immunotherapy vs disease progression may be a true challenge.

Case presentation

A 66-year-old female with a significant medical history of metastatic squamous cell carcinoma of the left lung, tobacco smoking, atrial fibrillation, vocal cord paralysis, emphysema, and hypertension initially presented to an outside hospital with worsening shortness of breath and increasing oxygen requirement. Around several months prior, she had been diagnosed with metastatic squamous cell carcinoma of the left upper lobe with an 80% PD-L1 expression and extension to the left superior pulmonary vein, mediastinum, and left hilar lymph nodes. Several weeks prior to this hospitalization, the patient was also admitted to the hospital for left-upper postobstructive necrotizing pneumonia and was discharged home on 2 L of oxygen and amoxicillin-clavulanate antibiotic therapy. Around 10 days prior to this current presentation, she had received her first dose of pembrolizumab and was not deemed a suitable candidate for chemotherapy or radiation therapy. Upon presenting to the outside hospital, vital signs showed a blood pressure of 107/67 mmHg, heart rate of 100 beats/min, respiratory rate of 24 breaths/min, and an oxygen saturation of 90%-93% on 3 L of oxygen. Physical exam was significant for an irregularly irregular heart rate with diminished breath sounds in the left lower lung and bilateral lower limb edema. No jugular venous distention was noted. Computed tomography (CT) scan of the chest showed a new, moderate-to-severe pericardial effusion in addition to improvement in the postobstructive pneumonia diagnosed in her prior hospitalization. An echocardiogram was obtained and showed a mildly reduced ejection fraction of 40%-45% with no signs of tamponade physiology. However, due to concerns of future cardiac compromise given the

moderate-to-severe pericardial effusion, she was transferred to our hospital for further management. Upon presenting to our hospital, she remained clinically and hemodynamically stable. Heart sounds were irregular, diminished, and distant yet no evidence of pulsus paradoxus was noted on clinical exam. She then underwent CT-guided pericardiocentesis with pericardial drain placement. Fluid analysis was consistent with an exudative effusion with lymphocytic predominance. Infectious etiology for the pericardial effusion was ruled out by negative cultures for bacteria, fungus, and acid-fast bacilli. Work-up for rheumatologic and neoplastic etiologies was also negative. This raised the concern for immune-mediated pericardial effusion caused by pembrolizumab. However, due to the challenge of differentiating between pericardial effusion caused by direct invasion from malignancy or pseudoprogression due to pembrolizumab immunotoxicity, fluid samples were sent for cytology twice again and were also negative. Pericardial drainage was approximately 300 cc/d. Prednisone 60 mg daily was initiated 2 days after pericardiocentesis due to copious drainage. There was a dramatic decrease in pericardial drainage after starting corticosteroids, which on the following day decreased from 300 cc/d to 40 cc/d. After 3 days corticosteroid therapy, drainage decreased to 25 cc in 24 hours. Repeat CT scan showed trace pericardial effusion (Fig) and a repeat echocardiogram showed an improvement in ejection fraction to 60%-65%. The significant decrease in pericardial drainage permitted the removal of the drain almost 5 days after initiating steroids. This raised concerns that the pericardial effusion was most likely due to an exaggerated autoimmune reaction caused by pembrolizumab. The second dose of pembrolizumab was held and the patient was discharged on a steroid taper course. Outpatient records show that immunotherapy was not started again.

Discussion

The most common side effects reported with pembrolizumab appear to be autoimmune.[15,22-25] General immune-related side effects are common and include fatigue, diarrhea, and rash, with fatigue being the most commonly reported.[15] Organ specific immune-related side effects are less common and include pneumonitis, colitis, hepatitis, hyper/hypothyroidism, arthritis, pancreatitis, diabetes, and nephritis.[15] All organs could be affected as a result of the nonspecific activation of T-cells; however, the most common organs affected are skin, colon, endocrine organs, liver, and lungs.[15] Prompt recognition of immune-related side effects is highly important for timely management and patient safety. There is very limited data with regards to the risk factors and markers that predict the occurrence of immune-related side effects in patients receiving immune check inhibitors like pembrolizumab. One small study suggests that eosinophilia may be a predictor of immune toxicity.[26] Other potential predictive factors include family history of autoimmune disease, concurrent medications known to cause immune toxicity, and history of HIV or hepatitis infection.

The cardiovascular system is among the least systems commonly affected by immunotoxicity.[15] Very few cases of immune-mediated pericardial effusion have been reported with antiprogrammed cell-death-1 immunotherapy. Kushnir and Wolf reported a NSCLC patient who developed a massive pericardial effusion with tamponade physiology secondary to nivolumab, who was treated by pericardiocentesis and subsequent steroid treatment with discontinuation of nivolumab therapy.[17] Kolla and Patel reported 2 cases of lung cancer with recurrent pericardial effusion and cardiac tamponade caused by nivolumab, mimicking cancer progression.[18] Although pembrolizumab shares many immune-related side effects with other immune check inhibitors, immune-mediated pericardial effusion has been reported only 2 other times in the literature. Oristrell et al reported the first case of pericardial effusion linked to pembrolizumab, which was treated with pericardiocentesis and corticosteroids. Their diagnosis was supported by improvement noted with corticosteroid therapy and the presence of other immune toxicities including hypophysitis, hypothyroidism, and adrenal insuffi-

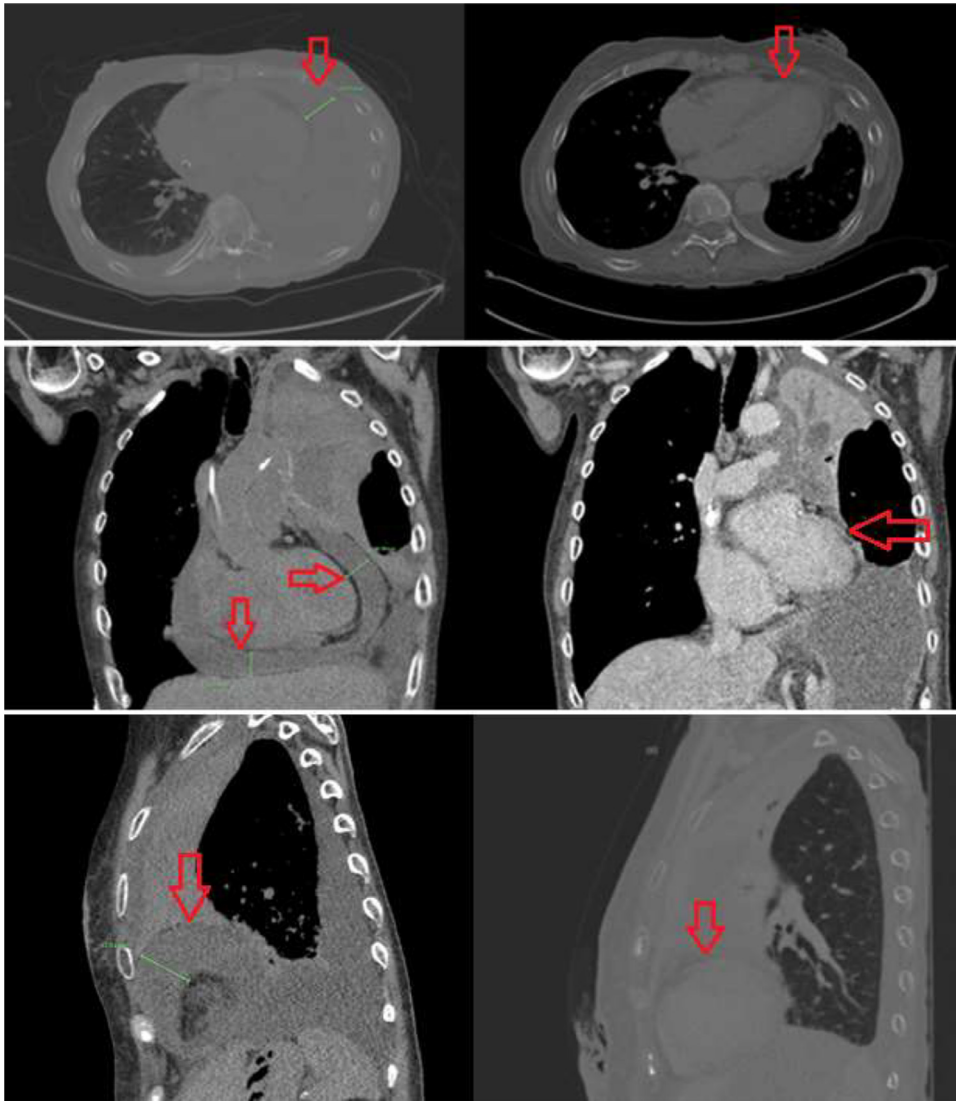

Fig. Axial (top), coronal (middle), and sagittal (bottom) helical CT scan images showing a large pericardial effusion (left) measuring up to 3.0 cm at the apex, which appears to have completely resolved (right) 9 days following drainage and steroid therapy.

ciency.[19] Li et al recently reported the second case of pericardial effusion related to pembrolizumab in a complex patient with HIV and NSCLC who died despite discontinuation of immunomodulator therapy and initiation of appropriate steroid therapy.[20] In this paper, we present, to our knowledge, the third case of pembrolizumab immune-mediated pericardial effusion.

In patients rapidly developing pericardial effusion after receiving pembrolizumab, an immune-mediated process should be highly suspected. In our patient, following the first cycle of pembrolizumab, rapid development of symptomatic pericardial effusion requiring pericardiocentesis ensued. The main challenge is in differentiating whether this may be due to malignancy vs

immunotoxicity. It is highly important to differentiate between both as management and prognosis are different. In addition, the development of immune-mediated pericardial effusion could suggest tumor response to the immune check inhibitor. One aspect that could aid in the differentiation between both is monitoring tumor response after starting the immune check inhibitor. Progression of malignancy after starting pembrolizumab, along with the appearance of a new pericardial effusion, could point toward a malignant pericardial effusion. However, a pericardial effusion that appears with regression of malignancy or stable findings on imaging may suggest a possible immune-mediated mechanism. Further work-up could also be beneficial as multiple negative cytology results makes malignant pericardial effusion less likely. Also, lymphocytic predominance in pericardial fluid supports an immune process. In our patient, imaging showed no progression of malignancy after starting pembrolizumab. Cytology results were negative for malignancy and an exudative fluid analysis with lymphocytic predominance was suggestive of an inflammatory process. Also, pericardial effusion that improves upon holding the immune check inhibitor and upon administration of corticosteroids or other immunosuppressants indicates autoimmunity. It is also important to note for other possible immune side effects that may further support the diagnosis of immunotoxicity. In our case, the patient did not have any other signs or symptoms suggestive of another underlying autoimmune disease process.

No data regarding the management of pericardial effusion caused by immune check inhibitors exist. However, the American Society of Clinical Oncology (ASCO) provides guidelines with moderate evidence regarding the management of cardiovascular toxicity caused by immune check inhibitors.[21,27] All grades of cardiotoxicity require intervention due to the risk of cardiac compromise, unlike other low-grade immune toxicities that could be managed conservatively with close monitoring. The ASCO guidelines recommend holding immune check inhibitors for all grades of cardiovascular toxicity.[21] High-dose corticosteroids, around 1-2 mg/kg, should be initiated rapidly in cases where risk of cardiac compromise is possible as was seen in our patient. Tapering of steroids for at least 1 month should only be initiated when immunotoxicity falls to a grade of 1 or less. If there is no obvious response, then transplant dose corticosteroids (methylprednisone 1 g/d) should be started, along with immunosuppressant therapy including either infliximab, mycophenolate, or antithymocyte globulin.[21] However, it is important to note that infliximab is contraindicated for use in patients with moderate-to-severe heart failure (New York Heart Association functional class III/IV).[28] Our patient improved with high-dose steroid treatment, 60 mg daily, and steroid taper was started 3 days later. However, if patients present with pericardial tamponade or are at risk of cardiac compromise then pericardiocentesis should be urgently performed, followed by administration of corticosteroids. The general approach to reintroducing immune check inhibitors has been described by the ASCO as the following: patients with grade 2 moderate immune toxicity could be rechallenged with the offending agent only when grade of immunotoxicity falls to grade 1 or less. Immune check inhibitors should never be reintroduced in patients who develop grades 3 and 4 immunotoxicity (severe to life-threatening toxicity).[21] However, the ASCO recommends permanent discontinuation of immune check inhibitors if resulted in cardiovascular toxicity higher than grade 1.[21] In our case, outpatient records show that the patient was never placed back on pembrolizumab. The reason this is so is likely due to the high grade of immunotoxicity reflected by the moderate-to-large pericardial effusion. Table illustrates the ASCO classification for the grades of immune-mediated cardiovascular toxicity resulting from immune check inhibitors.

Table
Grades of cardiovascular immune-related adverse events in patients treated with immune checkpoint inhibitors.[21]

Grade	Description
Grade 1	Abnormal cardiac biomarker testing, including abnormal ECG
Grade 2	Abnormal screening tests with mild symptoms
Grade 3	Moderately abnormal testing or symptoms with mild activity
Grade 4	Moderate-to-severe decompensation, IV medication or intervention required, life-threatening conditions

Conclusion

Very little data currently exist with regards to the management and reintroduction of immune check inhibitors following immunotoxicity.[26] Pericardial effusion related to pembrolizumab is a deadly complication and although very rare, may be on the rise. The increased incidence of side effects related to immunomodulator therapy is likely related to the evolution of cancer therapy over the past decade, which has seen an increased focus on the use of immunotherapy. As such, it is imperative that healthcare providers are aware of the multitude of potential side effects that may occur in the context of these novel treatment options. Despite the availability of general guidelines in dealing with cardiovascular immune-related adverse events, further research establishing more specific guidelines is necessary in dealing with this complex entity.

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