Pericardial Effusion with Tamponade Physiology as an Immune-related Adverse Event Secondary to Nivolumab

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Abstract

The relatively recent development and adoption of immunotherapeutic cancer treatments called immune checkpoint inhibitors has led to a tremendous advancement in cancer therapy. These medications work by increasing recognition of tumor cells by the immune system by blocking immune checkpoints to facilitate attack by T cells. Adverse events associated with these therapies are generally mild and can be managed by clinicians with minimal disruption in drug administration. More severe immune-related adverse events are rare but can lead to significant morbidity and mortality. The characterization of immune-related adverse events allows further understanding in how to manage these novel therapies. To the best of our knowledge, there are 5 previous cases documenting pericardial effusions associated with checkpoint inhibitor therapy. We present a case of pericardial effusion with tamponade physiology in a patient receiving nivolumab for stage IV lung adenocarcinoma.

Introduction

Cancer therapy has evolved over the years with an increased emphasis on immunotherapeutic strategies that prevent evasion of tumors from immune surveillance. One such target includes the immune system checkpoint receptor, programmed cell death-1 (PD-1), an inhibitory receptor seen on activated T and B cells that, when bound by tumor cell ligands, leads to proliferative tumor growth. By blocking the interaction between PD-1 and its tumor cell ligands, anti-PD-1 antibodies can facilitate tumor cell destruction [1]. Nivolumab (BMS-936558, ONO-458, or MDX1106, trade name Opdivo) is an anti-PD-1 antibody developed for the treatment of melanoma, renal cell carcinoma, and other cancers. In October 2015, based on the results of Phase II trials demonstrating the safety and efficacy of anti-PD-1 antibodies, the US Food and Drug Administration (FDA) expanded its approval of nivolumab to include the treatment of advanced, refractory metastatic non-small cell lung cancer (NSCLC) [2]. Adverse events associated with nivolumab treatment of NSCLC tend to be low-grade in nature, with the most common being fatigue, decreased appetite, diarrhea, nausea, cough, dyspnea, constipation, vomiting, rash, pyrexia, and headache [3]. Of the more severe immune-related adverse events (irAEs) associated with nivolumab treatment of NSCLC, pneumonitis was the most commonly noted, although its occurrence was still rare [4,5]. A meta-analysis of rare but severe irAEs noted during various phase trials of PD-1 inhibitors showed a single incident of pericardial effusion [6]. To the best of our knowledge, there are 5 previous cases documenting pericardial effusions associated with nivolumab treatment [7-10]. Here we present a case of pericardial effusion that led to pericardial tamponade in a patient treated with nivolumab for stage IV lung adenocarcinoma.

Case Report

A 46-year-old male with stage IV adenocarcinoma with cerebral metastatic disease was initially treated with carboplatin, pemetrexed, and bevacizumab. He later received maintenance therapy with bevacizumab and pemetrexed for 6 cycles. Restaging imaging showed disease progression and the patient was initiated on nivolumab as a second-line treatment. After the 12th cycle of nivolumab, the patient presented to the hospital with a 4-day history of general malaise, nausea, vomiting, and shortness of breath. A computed tomography scan of his abdomen and pelvis showed evidence of massive pericardial effusion. Electrocardiogram showed electrical alternans. A transthoracic echocardiogram confirmed massive pericardial effusion with tamponade physiology as demonstrated by right atrial and right ventricle collapse (Figure 1 & 2). An urgent pericardiocentesis was performed under fluoroscopic and echocardiography guidance and 1.4 liters of serosanguineous fluid was drained. The fluid was bloody with 915,000 red blood cells and 12,804 white blood cells containing 39% neutrophils, 34% macrophages and 26% lymphocytes. No malignant cells were seen on cytology. The chest tube remained...
in place with continued fluid drainage. A repeat transthoracic echogram 3 days later showed persistent moderate posterior effusion up to 1.9 centimeters but no echocardiographic findings to suggest hemodynamically significant pericardial effusion. The patient was taken to the operating room the following morning for subxiphoid pericardial window creation and pericardial biopsy. 100 milliliters of sanguineous pericardial effusion was drained and cytology review showed blood, mesothelial cells, and macrophages but no malignant cells. Pathology evaluation of the pericardial tissue showed signs of acute and chronic pericarditis. Follow-up transthoracic echocardiogram showed small posterior pericardial effusion measuring up to 1.1 centimeters. The patient was discharged from the hospital and eventually transitioned to palliative gemcitabine.

Discussion

Programmed death-1 inhibitors and other immune checkpoint inhibitors represent an important advancement in targeted cancer therapy but are not without their risks. While most immune-related adverse effects are mild and can be managed conservatively or with corticosteroids, some, including cardiotoxicity, are severe and can lead to disruption of drug therapy or significant morbidity [6]. Indeed, studies in mice demonstrated that disruption of the gene encoding for PD-1 caused dilated cardiomyopathy [11]. Fortunately, severe immune-related adverse events are rare. Studies performed by Bristol-Myers Squibb of 20,594 patients showed that those receiving combination therapy with two checkpoint inhibitors, the CTLA-4 inhibitor and PD-1 inhibitor nivolumab had more frequent and severe myocarditis than those receiving nivolumab alone (0.27% vs 0.06%) [12]. Additionally, our literature review demonstrated the scarcity of documented cases of pericardial effusions secondary to checkpoint inhibitors. Despite the rarity of adverse cardiac events, the acuity with which they tend to present warrants further characterization.

We present a patient with NSCLC with pericardial effusion with tamponade physiology after 12 cycles of nivolumab. After investigation, we were able to exclude common etiologies of pericardial effusions including trauma, infection, uremia, or myocardial infarction. Analysis of the pericardial fluid appeared inflammatory with elevated leukocytes and pericardial biopsy showed active acute and chronic pericarditis, which suggested inflammation. Additionally, given the chronology of the nivolumab therapy with the development of pericardial effusion, we suspect a rare immune-related adverse event as the cause.

While there are no clear guidelines regarding the management of adverse cardiovascular events secondary to immune checkpoint inhibitors such as nivolumab, it is generally advised to maintain a high level of suspicion for cardiac events in patients receiving such therapy. The typical approach to severe adverse events is to suspend immunotherapy and consider administering high dose glucocorticoids however there is no formal study demonstrating efficacy of that strategy [13].

Lastly, it is important to note that the overall safety and efficacy of nivolumab for the treatment of various cancers has been demonstrated in numerous trials [14]. Therefore, the documentation and characterization of rare immune-related adverse events and their management serves an important role in providing a more comprehensive understanding of the use these novel drugs.

References


