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Case report

Varying presentations of immune checkpoint inhibitor-associated myocarditis: A case report of the clinical characteristics and outcomes of three patients

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1. Introduction

Immune checkpoint inhibitors (ICIs) have come to play an integral role in the therapy of gynecologic malignancies. Their benefits, however, come with the potential for immune-related adverse effects (IRAEs). One rare toxicity is ICI-associated myocarditis. While the incidence of severe myocarditis is relatively low, estimated to be somewhere between 0.04 and 1.14%, recent evidence has demonstrated that the incidence of any grade of ICI-associated myocarditis is estimated to occur in 10–12% of patients receiving ICIs (Palaskas et al., 2020). Both the timing of onset and clinical presentation of this complication can be highly variable. Thus, it is imperative that practitioners be vigilant when caring for at-risk patients as it is associated with an exceedingly high mortality rate of 25–50% (Palaskas et al., 2020; Mahmood et al., 2018).

Here we present three cases of ICI-associated myocarditis that were diagnosed at our institution over the course of two months.

2. Case 1

Case 1 was a 60-year-old white female with recurrent stage IVB mixed serous and clear cell endometrial adenocarcinoma who presented as a transfer for management of acute respiratory distress syndrome and cardiogenic shock.

Within three weeks of initiating treatment with lenvatinib (20 mg) and pembrolizumab, the patient began to develop generalized fatigue and malaise. Upon presentation to a local hospital, their workup was notable for an elevated troponin with a peak to 1,495 ng/L (normal < 34 ng/L) and an elevated BNP with a peak to 4,490 pg/mL (normal < 100 pg/mL). Their ECG was normal. An infectious workup was negative. CT angiography of the chest demonstrated multifocal ground-glass opacities in bilateral lung fields suggestive of pulmonary edema or infiltrates. There was no evidence of a pulmonary embolus. A transthoracic echocardiogram was performed noting global hypokinesis with an ejection fraction of 25%. The patient was diagnosed with acute respiratory distress syndrome (ARDS) and cardiogenic shock; initiated on inotropic support and broad-spectrum antibiotics; and transferred to our institution on hospital day 3.

Upon arrival, the Gynecologic Oncology and Cardiology services were consulted. Leading differentials included immunotherapy-related cardiotoxicity or viral myocarditis. The patient was initiated on IV methylprednisolone 100 mg daily (2 mg/kg) on hospital day 4. Despite aggressive inotropic support, diuretic therapy, and resuscitative efforts, their clinical status quickly deteriorated, culminating in cardiac arrest on hospital day 5. Cardiopulmonary resuscitation was performed with return of spontaneous circulation, however they remained hemodynamically unstable and minimally responsive. After prognostic discussions with their family, the patient was transitioned to comfort care with ultimate demise on hospital day 7.

With regard to the patient's respiratory status in setting of ARDS, at the time of their initial transfer the patient was on BiPAP, but following arrival to our institution, they were weaned to and primarily maintained on supplemental oxygen via high-flow nasal cannula, with needs ranging from 4 to 8 L while largely maintaining an oxygen saturation > 90%. The patient was only every intubated at the time of their cardiac arrest.

3. Case 2

Case 2 was a 75-year-old white female with recurrent high-grade serous primary peritoneal carcinoma who presented to our emergency department for evaluation of subjective fevers, chills, and generalized malaise two days after their third cycle of lenvatinib (14 mg)/pembrolizumab.

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At the time of intake, their ECG, serum BNP, and serum troponins were within normal limits. An infectious workup was negative. Their initial chest radiograph showed patchy airspace disease in the upper and middle lobes, prompting their admission for empiric antibiotic therapy for presumed community-acquired pneumonia.

Their hospital course was subsequently complicated by acute hypoxic respiratory failure secondary to new pulmonary edema on hospital day 3. Their serum BNP at this time demonstrated a mild elevation to 187 pg/mL (normal < 100 pg/mL). ECG and troponins remained normal. CT angiography of the chest was negative for a pulmonary embolus. A transthoracic echocardiogram revealed a depressed ejection fraction of 40–45% and global hypokinesis.

Cardiology was consulted and while an immunotherapy-related etiology for their cardiac dysfunction was entertained, the team initially cited a low suspicion for myocarditis given a normal ECG and absence of troponin elevations. A follow-up cardiac MRI was performed on hospital day 6. This study revealed late gadolinium enhancement (LGE) in the form of non-ischemic myocardial fibrosis of the septal and lateral walls, diffusely elevated T2-mapping suggestive of myocardial edema/inflammation, and a significantly elevated myocardial extracellular volume fraction consistent with diffuse interstitial expansion. The calculated ejection fraction was 59%. Given these diagnostic MRI findings, their acute heart failure was thereafter managed as ICI-myocarditis.

They were initiated on IV methylprednisolone 1,000 mg daily for three days starting on hospital day 6. They were successfully weaned off supplemental oxygen and were discharged on a steroid taper in stable condition on hospital day 12. They had follow-up with Cardiology as an outpatient two weeks post-discharge and continued to demonstrate clinical stability. Lenvatinib and pembrolizumab were discontinued and they were transitioned to a regimen of paclitaxel and bevacizumab.

4. Case 3

Case 3 was an 81-year-old white female with recurrent stage IV high-grade serous ovarian carcinoma who presented for evaluation of a new transaminitis 27 days after initiation of their first cycle of durvalumab/cediranib (20 mg).

Following an outpatient lab draw remarkable for a new transaminitis, they presented to our institution for management of suspected grade 3 immunotherapy-related hepatotoxicity characterized by a peak ALT of 207 U/L (normal < 48 U/L) and a peak AST of 392 U/L (normal < 39 U/L). Bilirubin was within normal limits. Upon arrival, they incidentally reported persistent fatigue and worsening dyspnea since the onset of their new therapy regimen, prompting a cardiac evaluation. Their ECG was normal. Their serum troponin was markedly elevated to 6,021 ng/L (normal < 34 ng/L). Serum BNP was within normal limits. CT angiography of the chest was negative for a pulmonary embolus. Cardiology was consulted and while there was immediate concern for immunotherapy-related cardiotoxicity, NSTEMI could not be excluded. Thus, the patient was concurrently managed for both conditions. They were promptly administered therapeutic aspirin, started on a heparin infusion, and initiated on IV methylprednisolone 1000 mg daily on hospital day 1 while additional cardiac workup was in progress.

Their serum troponin peaked at 7,573 ng/L on hospital day 2. An echocardiogram was performed that same day which showed a normal ejection fraction of 70% and no acute cardiac abnormalities. A cardiac MRI was performed on hospital day 4, demonstrating significant myocardial edema/inflammation in the septal area on T2-mapping as well as basilar LGE of both the myocardium and pericardium consistent with myopericarditis, which solidified the diagnosis of ICI-associated myopericarditis.

They continued IV methylprednisolone for a total of three days and was subsequently transitioned to an oral prednisone taper. Their transaminitis also improved. They were discharged in stable condition on hospital day 9 with the plan for outpatient follow-up with Cardiology. However, they were re-admitted less than a month later for altered mental status in the setting of urosepsis. Upon return to baseline mentation, a goals of care discussion was had and the patient decided to transition to comfort care with hospice. They passed away three days later.

5. Discussion

ICI-associated myocarditis portends a grim prognosis if not recognized and treated promptly, with an estimated mortality rate of 25–50% (Palaskas et al., 2020; Mahmood et al., 2018). The most common presentation of cardiac toxicity as a result of immunotherapy is myocarditis, but it can also manifest as pericarditis, cardiomyopathy, arrhythmias, conduction disorders, and myocardial infarction (Shalata et al., 2021). Our cases describe three different presentations of myocarditis.

Myocarditis often presents with complaints of dyspnea, palpitations, fatigue, and/or weakness. Laboratory abnormalities that raise suspicion for myocarditis include an elevated troponin and/or BNP and are present in 94% and 66% of cases, respectively (Mahmood et al., 2018). Other findings include ECG abnormalities, most commonly sinus tachycardia associated with non-specific ST wave changes. However, the sensitivity of ECG for acute myocarditis is generally poor and cannot exclude the diagnosis (Buttà et al., 2020). Reduced systolic functioning may be detected on echocardiogram, but a preserved ejection fraction does not preclude the diagnosis nor does it necessarily confer a more favorable prognosis (Mahmood et al., 2018; Jiménez-Alejandre et al., 2022). More than half of patients with ICI-associated myocarditis have a normal ejection fraction and 38% of those who suffer major adverse cardiac events (MACEs) have a normal ejection fraction (Mahmood et al., 2018). Thus, while an echocardiogram is helpful, it should not be relied upon as the sole, definitive diagnostic modality (Palaskas et al., 2020; Mahmood et al., 2018; Armenian et al., 2017).

Cardiac MRI is considered to be the "gold-standard" imaging modality for ICI-associated myocarditis, but it is not without its limitations (Zhang et al., 2020). Zhang et al. demonstrated that key diagnostic findings on cardiac MRI may be variable in their detection rate depending on the timing of its performance (Zhang et al., 2020). Specifically, in their study they reported a detection rate of only 21.6% for LGE when the study was performed within the first four days of admission compared to a detection rate of 72.0% when performed on day four or later (Zhang et al., 2020). However, delaying the performance of a cardiac MRI for the sake of improved diagnostic utility is not in the best interest of the patient given the elevated risk of MACE in the absence of expeditious therapy (Zhang et al., 2020; Zhang et al., 2020). Moreover, even in their subset of 56 pathologically-confirmed ICI-associated myocarditis cases, definitive markers such as LGE and abnormal T2-mapping on cardiac MRI were absent in 45% of those cases (Zhang et al., 2020). Thus, in instances in which non-invasive diagnostic studies are inconclusive and yet clinical suspicion for the disease remains heightened, the performance of an endomyocardial biopsy is of paramount importance (Zhang et al., 2020).

All 3 of these cases were ultimately no exception to the statistics regarding elevated troponin and/or BNP quoted by Mahmoud et al., in that each of these patients had elevated levels of at least one of these biomarkers by the end of their hospital course (Mahmood et al., 2018). However, what is interesting about case 2 is that at the time of their initial presentation, the patient did not demonstrate characteristic laboratory findings that would have immediately raised red flags for this clinical entity. None of the ECGs in these cases demonstrated signs of acute abnormalities, highlighting the poor sensitivity of ECG for the diagnosis of myocarditis (Buttà et al., 2020).

Early diagnosis and treatment are critically important when it comes to improving outcomes in ICI-associated myocarditis. Zhang et al. noted an inverse relationship between the elapsed time from admission to initiation of corticosteroid therapy and the occurrence rate of MACEs, which included cardiogenic shock, cardiac arrest, and cardiovascular

death (Zhang et al., 2020). Specifically, they noted a MACE rate of 7.0% when treatment was initiated within 24 h of admission compared to a MACE rate of 34.3% when initiated 24–72 h after admission and a MACE rate of 85.1% when initiated > 72 h after admission (Zhang et al., 2020). Moreover, they described an inverse relationship between the initial dose of corticosteroids and the occurrence rate of MACE, with the high-dose methylprednisolone cohort (501–1000 mg daily) demonstrating a lower rate of MACE compared to both the low-dose cohort (<60 mg daily) and the intermediate-dose cohort (60–500 mg daily) (Zhang et al., 2020). While the specific corticosteroid employed and its dosing regimen are variable dependent upon the grade of cardiotoxicity identified, the prompt initiation of steroid therapy is key (Zhang et al., 2020; Thompson et al., 2022; Schneider et al., 2021).

While risk factors for cardiac IRAEs remain to be fully elucidated, two putative risk factors are a history of coronary artery disease and hypertension, both of which the patients in cases 2 and 3 possessed (Huang et al., 2022; Jiménez-Alejandre et al., 2022). Importantly, patients with even a single IREA have been shown to be at an increased risk for the development of additional systemic toxicities, as was highlighted in case 3 (Koelzer et al., 2016). Thus, if a patient complains of new cardiopulmonary symptoms in the setting of a known history of IRAE, the likelihood of ICI-associated myocarditis is increased (Palaskas et al., 2020).

Lastly, as was shown in case 3, the diagnosis of NSTEMI versus ICI-associated myocarditis can be difficult to discern, especially in patients with baseline risk factors for coronary artery disease (Bolognesi and Bolognesi, 2013). Given the known morbidity and mortality of untreated NSTEMI, it is reasonable to initiate empiric therapy inclusive of systemic anticoagulation in cases in which the diagnosis remains ambiguous (Terkelsen et al., 2005; Tandon et al., 2019). However, it is imperative that a definitive diagnosis be pursued in an expedient manner when clinical suspicion for ICI-associated myocarditis is elevated as appropriate treatment and patient outcomes hinge on the establishment of an accurate understanding of the disease process at hand (Bolognesi and Bolognesi, 2013; Tandon et al., 2019).

6. Conclusion

ICI-associated myocarditis is a severe complication of ICI therapy with an extremely high mortality rate if not recognized and treated promptly. Its presentations are varied and its symptomatic harbingers can be subtle or vague. Moreover, patients do not always mention that they are on immunotherapy when they initially present to their care providers. Thus, the taking of a thorough history should always be performed and a healthy degree of clinical suspicion should be maintained in at-risk patients.

CRediT authorship contribution statement

Brandon Fox: Writing –original draft, Writing – review & editing. **Floor Backes:** Conceptualization, Supervision, Data curation, Writing - original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Floor Backes reports advisory board fees from Eisai, Merck, AstraZeneca, GlaxoSmithKline, Myriad, ImmunoGen, Clovis, GOG Partners.

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