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CASE REPORT

A Double-Edged Sword - Multiorgan Dysfunction as a Rare Complication of Dual Checkpoint Immunotherapy

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Introduction

There are many immune checkpoints in the body which serve different functions. Some Immune checkpoints are molecules involved in the maintenance of immunologic homeostasis, and therefore help to maintain peripheral tolerance to self-molecules. Other immune checkpoints such as CTLA-4 and PD-1, are important for augmenting or inhibiting the immune response [1]. Yervoy (Ipilimumab) and Opdivo (Nivolumab) are monoclonal antibodies developed to target CTLA-4 and PD-1 respectively to augment the immune system and to enhance clearance of tumor cells. Programmed cell death- 1 (PD-1) is an inhibitory receptor expressed on activated T and B cells, which normally function to dampen the immune response. PD-1 is engaged by ligands PD-L1 and PD-L2, which are expressed by tumor cells and infiltrating immune cells causing inactivation of T cells against tumor cells. Nivolumab is a monoclonal antibody which causes inhibition of the interaction between PD-1 and PD-L1. This effect enhances anti-tumor responses, delays tumor growth, and facilitates tumor rejection [2]. Ipilimumab is an anti-CTLA-4 monoclonal antibody that prevents CD80 and CD86 on APCs from binding to CTLA-4 on T cells. This blockage of CTLA-4 signaling allows T-cell activation, proliferation, and amplification of T-cell-mediated immunity, which allows the patient's immune system to mount a better response [3]. The use of this drug may serve to increase a baseline T-cell-specific immune response that turns the immune system against the tumor. This disruption in the functioning of immune checkpoint molecules can lead to imbalances in immunologic tolerance that results in an unchecked immune response. This may clinically manifest with autoimmune-like/inflammatory side-effects, which cause collateral damage to normal organ systems and tissues. Such adverse events, termed 'immune-related adverse events' (irAEs), are also thought to be principally T-cell mediated, however other immune cells may play a role in the development of irAEs, including B cells that secrete antibodies which mediate toxicity, as well as granulocytes that secrete inflammatory mediators and cytokines [1]. Of note, the incidence of cardiac toxicity owing to ICIs is rare (occur-ring in < 1% of patients) but can be fulminant and potentially fatal. Neurologic complications are also rare and when all neurological irAEs are pooled, an incidence of 3.8% for CTLA-4 inhibitors, 6% for PD-1 inhibitors and 12% for combination therapy has been reported in one review of 59 clinical trials, and encephalitis has been reported in 0.3% of patients taking ICIs. Lastly, an overall incidence of 2.2% was reported for acute kidney injury (0.6% for grades 3 and 4 renal events) in one systematic review of randomized controlled trials including 3,695 patients treated with ICIs [4]. Here we present a unique case that highlights the impact Opdivo and Yervoy induced irAEs had on our patient and explore this unique case of these monoclonal antibodies causing simultaneous damage to the central nervous system via immune checkpoint inhibitor induced encephalitis, cardiovascular system via acute decompensated left ventricular heart failure

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with reduced ejection fraction, and renal systems via acute kidney injury all of which are extremely rare.

Case Report

This case is of a 74-year-old black female with a past medical history of COPD, GERD, esophagitis, non-ischemic cardiomyopathy secondary to chemotherapy and stage IV non-small cell lung cancer diagnosed 4 years ago. Over the course of the diagnosis the patient has undergone treatment with various chemotherapeutic agents and multiple cycles of radiation. She has had a very complicated course of metastasis spreading from her lungs to the colon and subsequently the formation of a meningioma. Last year she was also found to have an isolated recurrence in a lymph node in the mesentery adjacent to the sigmoid colon, which was removed and found to be an isolated metastasis in the lymph node without any evidence of overt metastasis to other areas of the abdomen.

These findings prompted the patient's continuation on dual immunotherapy with Opdivo and ipilimumab. Our patient was admitted to the hospital 6 days after her last infusion due to shortness of breath, wheezing tachycardia, and generalized weakness which she states had started 6 days ago after the infusion and progressively worsened. Upon admission she was found to have hypokalemia, hypomagnesemia, elevated AST, elevated BNP and acute kidney injury. She was afebrile with tachycardia at 133 bpm, a blood pressure of 89/61, and a respiratory rate of 18. Chest CT and head CT and MRI were negative for any acute pathology. Lower extremity doppler and D-dimer were obtained and did not reveal evidence of DVT. Urine and blood cultures were found to have no growth, and testing for common viral infections was negative, thus reducing the likelihood of a pathogenic etiology. On the third day of admission, she began to have a change in mental status with increased confusion and was unable to recognize the faces of physicians, subsequently she was physically restrained for combative behavior. She was started on high dose IV methylprednisolone for susceptive autoimmune encephalopathy caused by the dual immunotherapy agents. Repeat echocardiogram showed an LVEF of 15% which was reduced from her baseline at admission of 41%. At this point the patient was started on hydralazine and isosorbide dinitrate. The patient began to decline as her kidney function continued to worsen and her cardiac function had also deteriorated. Her encephalopathy continued to worsen and due to her kidney function MRI with contrast was unable to be performed. On day 7 an EEG was performed and found mild diffuse background slowing with no seizures recorded. She was also found to have a dramatic change in her mental status and was more alert and oriented. On day 8 her kidney function began to improve as well. On day 10 she was started on IVIG and on day 11 her acute kidney injury had resolved, her electrolyte abnormalities were corrected, mentation was corrected to baseline, and her heart failure was compensated at which point she was discharged. Based on the findings, this patient likely had cardiac and neurologic decline caused by an autoimmune reaction secondary to dual immunotherapy which was resolved with high dose steroids.

Discussion

This case is unique in that this patient simultaneously acquired immune checkpoint inhibitor induced encephalitis, cardiovascular system via acute decompensated left ventricular heart failure with reduced ejection fraction, and renal systems via acute kidney injury all of which are extremely rare. When searching through BMJ Case Reports with keywords such as "immune checkpoint inhibitor acute kidney injury", "immune checkpoint inhibitor encephalitis", "immune checkpoint inhibitor heart failure", results are found for each individual disease, but a case highlighting all three of these diseases manifesting at once in relation to dual ipilimumab and nivolumab has yet to be reported.

Neurological

In general, CTLA-4 inhibitors (e.g., ipilimumab) are associated with a higher incidence of immune-related adverse events (IRaEs) than PD-1 inhibitors (e.g., nivolumab, pembrolizumab and lambrolizumab). When two ICIs (e.g., nivolumab + ipilimumab or pembrolizumab + ipilimumab) are given concurrently, the risk seems to be even higher. In a systematic review, 29/47 cases (62%) were caused by PD-1 inhibitor monotherapy, and 5/47 cases (11%) were caused by CTLA-4 inhibitor monotherapy. The concurrent or sequential use of ICIs caused encephalitis in 9/47 cases (19%) [5]. Of note, Immune checkpoint inhibitor induced encephalitis occurred at a median of 8 weeks (IQR, 3-16.5 weeks) after the first ICI administration, and for 17 patients (21%), their first symptoms occurred after the first ICI dose. Ten patients (12%) developed symptoms after 6 months of ICI treatment, and 2 patients (2%) developed symptoms after 12 months of ICI treatment [6]. The timing of our patient's altered mental status was noted to be 8 days since the most recent administration of her ipilimumab and nivolumab regiment.

The symptoms subsequently improved after 7 days of high dose methylprednisolone and IVIG treatment. The cause for development of autoimmune encephalitis after checkpoint inhibitor administration has yet to be agreed upon in the literature. When reviewing the potential cause of encephalitis in our case, the presentation and response to treatment points towards B cell changes, and cell surface autoantibody production as the cause for this acute presentation and rapid reversal of symptoms. Combination checkpoint blockade (CCB) was associated with distinct B-cell related changes in one study, including a decrease in overall circulating B-cell

populations and an increase in plasmablasts. These changes were significantly more prevalent amongst those who developed iRAEs and correlated with both time to onset and severity of toxicity. Patients with early B cell changes experienced higher rates of grade 3 or higher IRAEs 6 months after CCB. Thus, early changes in B cells following CCB may identify patients who are at increased risk of IRAEs, and preemptive strategies targeting B cells may reduce toxicities in these patients [7]. Autoantibody production has also been implicated as a potential cause for immune checkpoint inhibitor-associated autoimmune encephalitis.

One autoantibody of note, anti-NMDAR, has led to an encephalitis which has been associated with dual checkpoint inhibitor therapy, and is believed to be caused by direct effects of pathogenic antibodies rather than T-cell-mediated responses. Patients also had marked clinical improvement after immunosuppressive treatment. These features suggest that immune checkpoint inhibition favored the development of immune responses against neuronal antigens [8]. One other study further emphasized autoantibodies as the potential etiology. In a study of 31 patients tested for CSF autoantibodies, 44% had none and 10% had surface-antigen autoantibodies (NMDA receptor and CASPR2). Forty-six percent had intracellular, that is, onconeural, antibodies, which were a negative predictor for outcome after first-line immunosuppressive treatment. This correlates well with previous data showing that paraneoplastic CNS syndromes with onconeural antibodies show limited response to immunosuppression, while autoimmune encephalitis with cell surface antibodies typically respond better to immunosuppressive therapy. Furthermore, onconeural antibodies can be seen in 16% of patients with small-cell lung cancer but without paraneoplastic CNS syndrome [9]. Although autoantibody panels were never ordered on our patient, the possibility that her condition was caused by anti-NMDA receptor or other cell surface antibodies is a possible explanation for her encephalitis. The rapid resolution of her encephalitis after immunosuppression further implicates anti-NMDA antibodies because cell surface antibodies respond better to immunosuppression compared to onconeural antibodies.

Cardiac

In the case of our patient, administration of combination therapy of ipilimumab and novilimumab resulted in acute decompensated heart failure with reduced ejection fraction of 15%. When looking at the adverse effects of dual immunotherapy administration regarding the occurrence of events in patients treated with nivolumab, ipilimumab or both, cardiac toxicity induced by ICIs treatment has been estimated to occur in less than 1%. Combination therapy with both drugs was associated with more severe and frequent myocarditis than nivolumab alone (0.27% versus 0.06%) [10]. A 2017 meta-analysis of 22 anti-PD-1 and anti-PD-L1 trials in patients with NSCLC reported a slightly higher incidence of serious cardiovascular events than data from the Bristol- Myers Squibb pharmacovigilance database, although the absolute incidence of each cardiac event was still comparatively low (cardiorespiratory arrest 1%; cardiac failure 2%; myocardial infarction 1%; and stroke 2%). ICI-associated cardiotoxic effects can extend beyond myocarditis. Heinzerling and colleagues reported details of eight cases of ICI-mediated cardiotoxicity, which included myocarditis, heart failure with left ventricular dysfunction but without myocarditis on biopsy, myocarditis or fibrosis identified on post-mortem, and cardiac arrest secondary to Takotsubo syndrome. The presence or absence of troponin might reflect the difference between inflammatory-mediated cardiotoxic effects (both BNP and troponin elevated) and functional non-inflammatory cardiotoxic effects (BNP elevated and troponin normal) [11]. Our case presented with acute decompensated left heart failure with reduced ejection fraction of 15%. During hospital evaluation, echocardiogram indicated a severely dilated left ventricle with LV systolic dysfunction, and lab values showed negative troponin and an elevated BNP. These findings are consistent with functional non-inflammatory cardiotoxicity. The etiology of the non-inflammatory cardiotoxicity is unclear but can likely be explained by the influence CTLA 4 and PDL1 have on the cardiac tissue. PD-1 and CTLA-4 function in different ways and at different steps in a T cell response to antigen. Studies in mice have established that genetic deficiencies of checkpoint molecules, including PD-1, PD-L1, CTLA-4, and lymphocyte activation gene-3, result in enhanced risk of autoimmune T cell-mediated myocarditis and increased pathogenicity of heart antigen-specific effector T cells. The PD-1/PD-L1 pathway appears to be particularly important in cardiac protection from T cells. PD-L1 is markedly up-regulated on myocardial cells by interferon-gamma secreted by T cells and PD-1 or PD-L1 deficiency synergizes with other defects in immune regulation in promoting myocarditis [12]. CTLA-4-knockout mice also develop autoimmune myocarditis with infiltration of CD4-positive and CD8-positive T lymphocytes in the myocardium, reinforcing the importance of immune checkpoint signaling in controlling T-cell immune responses in the heart. Pre-existing cardiovascular disease might also be affected by ICIs. If T-cell-mediated responses contribute to acquired heart disease progression, as shown preclinically, ICIs could cause acceleration or decompensation of pre-existing heart failure in susceptible individuals [11].

Likely in the case of our patient, her previously reduced ejection fraction of 45% and her chemotherapy induced cardiomyopathy signify there was preexisting damage to her heart, and dual treatment with these ICIs exacerbated her condition and led to her further

reduction in ejection fraction, and her non-inflammatory cardiotoxicity.

Renal

The third IRAE our patient experienced was acute kidney injury superimposed on chronic kidney disease stage III. Just as the heart failure with reduced ejection fractions as well as encephalopathy are rare complications of ICIs, acute kidney injury was also exceedingly rare. A study evaluated more than 1000 patients receiving a variety of different checkpoint inhibitors for a wide range of malignancy types and found that AKI and sustained AKI events were common (17% and 8%, respectively) within 12 months of initiating therapy. This is the first report to define the incidence of checkpoint inhibitor-related AKI using a consistent approach and definition; we found that it affects 3% of patients and occurs a median of 15 weeks after starting therapy. This is slightly higher than the reported treatment-related incidence of 2% from clinical trials data and consistent with the previously described timing of AKI [13]. Another study analyzed the incidence of acute kidney injury with administration of immune checkpoint inhibitors, and found that in ipilimumab and nivolumab combination therapy, the incidence was higher, with 4.9% (any grade) and 1.7% (grade 3 or 4) creatinine elevation reported. A similar trend was seen with sequential administration of ipilimumab and nivolumab, with 5.1% (any grade) and 2.2% (grade 3 or 4) of AKI events. Based on these results, the combination or sequential anti-CTLA4/anti-PD-1 therapy should be considered a higher risk for AKI, as well as for other irAEs reported in the literatures [14].

The exact mechanism of how checkpoint inhibitors cause acute kidney injury remains unclear. Murine models have shown that PD-1 signaling is essential to peripheral tolerance of self-antigens by limiting the activation and expansion of self-reactive T cells and stimulating tolerogenic dendritic cells. Specific to the kidney, PD-1 signaling limits CD8-positive T-cell-mediated inflammatory injury and PD-1 knockout mice spontaneously develop glomerulonephritis [15]. Furthermore, the hypothesis highlighting the development, the proliferation and the aberrant activation of a clone of self-reactive T-cells can be supported by the presence of a robust infiltration of effector T-cell in organs not related to the tumor, which presented an impressive high level of similarities in T Cell Receptor sequence. Intriguingly, Johnson DB, et al. reported the cases of patients with melanoma treated with ipilimumab and nivolumab in whom fatal myocarditis developed. Within the tumors of these patients, Authors observed high levels of self-muscle-specific antigens (desmin and troponin) indicating that T cells could be targeting an antigen shared by the melanoma, skeletal muscle, and the heart [16]. This varied finding of T cells targeting multiple different tissues can explain why our patient experienced encephalitis, acute kidney injury, and heart failure with reduced ejection fraction simultaneously upon administration of the dual therapies.

Conclusion

Combined treatment with Immune Complex Inhibitors manifested a variety of autoimmune symptoms attributed to both T and B cell dysfunctions. In our patient, this manifested as autoimmune encephalitis, acute kidney injury, and acute decompensated heart failure. This is a unique case of multiorgan failure which heralds a potentially fatal consequence of dual ICI therapy. This case report serves as a warning of the potential harm dual ICI therapy can have on the patient being treated, and it emphasizes that consistent monitoring of the patient receiving the treatment is necessary because fatal consequences can occur. We implore physicians to be aware of these possible complications, and we hope that it remains clear that rapid immunosuppressive treatment can reverse these effects, and hopefully preserve organ function in patients.

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