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Immune Checkpoint Inhibitor Induced Thrombocytopenia in Hepatocellular Carcinoma: A Case Report

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Case Report

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Abbreviations: PD: Programed-cell death; PD-L1: Programmed cell death ligand 1; irAE: Immune related adverse events; IVIG: Immune globulin; CBC: Complete blood count

ABSTRACT

Background: Immune checkpoint inhibitors have become part of the standard of care for many forms of solid tumors. Most immune checkpoint inhibitors target the PD (Programmed Cell Death)-1/PD-L1 (programmed cell death ligand 1) pathway. These agents are generally well tolerated but may be associated with unique immune related Adverse Events (irAEs), such as immune-related thrombocytopenia. Immune-related thrombocytopenia secondary to immunotherapy is a rare but possible side effect that has not been extensively studied. Treatment regimens remain uncertain, although most reported case reports in literature have described treatment with steroids, as recommended by the American Society of Clinical Oncology.

Case presentation: In this case report, we describe a patient who received one dose of immunotherapy, developed severe thrombocytopenia, and clinically responded to a course of dexamethasone and Immune Globulin (Ivig) Therapy.

Conclusion: This case report emphasizes the need for a standard of care and effective approach for immunotherapy induced thrombocytopenia. Further studies are needed to further assess the role of dexamethasone and IVIG in patients with immunotherapy induced thrombocytopenia.

INTRODUCTION

Immune checkpoint inhibitors are being increasingly used for the treatment of solid tumors. They commonly target the PD-1/PD-L1 pathway to activate the cytotoxic T cell response in the suppressive microenvironment of the tumor, and have proven to result in durable tumor remission [1]. irAEs are peripheral effects of an overly activated immune system that may interfere with any organ or tissue. The most frequently occurring irAEs include colitis, pneumonitis, hepatitis, nephritis, and thyroiditis, and are experienced in almost 50% of patients treated with PD-1/PDL-1 inhibitors [2]. Some less occurring toxicities of PD-1/PDL-1 inhibitors include eye, cardiac, neurological, and hematologic toxicities. Although irAE are generally considered less severe than the common toxicities of conventional chemotherapy agents, fatal irAEs still occur at an incidence between 0.3% and 1.3% [3,4]. Immune-related thrombocytopenia is a rare, but possibly fatal irAE that has been reported in the literature in several cases following administration of immune checkpoint inhibitors used for non-small cell lung cancer, melanoma, and other malignancies [5-9]. Our case described a patient who developed severe thrombocytopenia following one dose of atezolizumab for metastatic hepatocarcinoma, and had improvement in platelet counts following treatment with dexamethasone and IVIG.

CASE PRESENTATION

Our patient is a 74-year old Caucasian male with a significant past medical history of prostate cancer status post radiation therapy in 2019 and recently with diagnosed metastatic hepatocellular carcinoma. The patient was initiated on immunotherapy with atezolizumab 1200 mg on March 8 2022. The patient presented to the emergency department on March 15 2022 secondary to coffee-ground emesis and epistaxis, with associated weakness and lightheadedness. Laboratory workup was significant for severe thrombocytopenia, with a platelet count of less than 3,000/µL, (baseline count of 351,000/µL), hemoglobin of 6.5 g/dL, white blood cell count.72 with a neutrophilic shift, and an International Normalized Ratio (INR) of 1.5. The patient received two units of platelets with post transfusion Complete Blood Count (CBC) showing no improvement in platelet count, which remained less than 3,000/µL. Hematology was consulted and recommended to start dexamethasone 40 mg and IVIG 70 g daily for four days. Serial CBCs showed improvement in platelet count with above mentioned treatment (Figure 1).

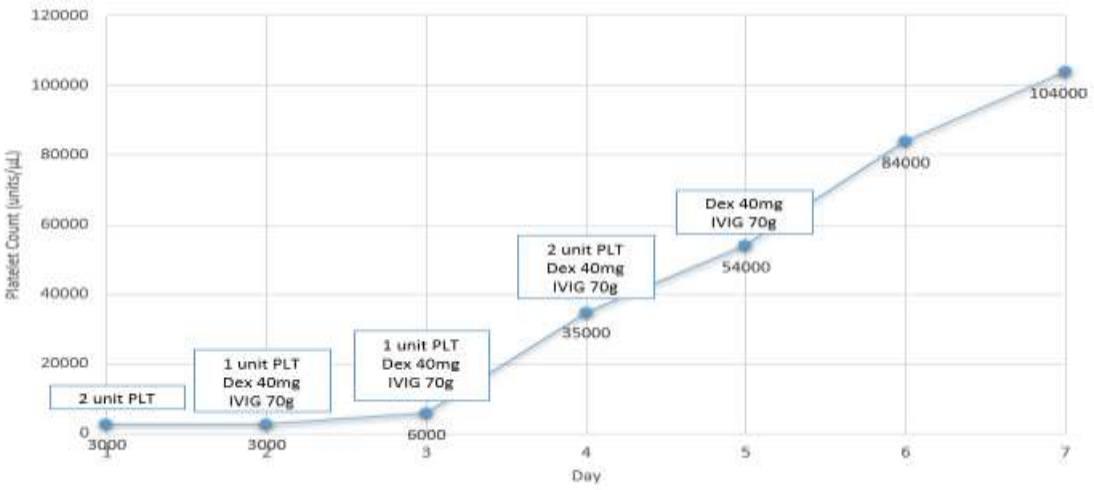

Figure 1. Serial CBCs showed improvement in platelet count with above mentioned treatment.

RESULTS AND DISCUSSION

Over recent years the paradigm in treatment for oncologic diseases has shifted toward more personalized medicine. These personalized regimens may not include chemotherapy; others will include both chemotherapy and non chemotherapeutic agents. Immune checkpoint inhibitors are one such additive to the treatment of cancer. Immune checkpoint inhibitors, also known as immunotherapy have captured the space in almost every oncologic pathology due to their ability to result in durable tumor remission.

Immunotherapy awakens the body's immune system to cause disruption and decrease progression of cancer cells. It performs this action through PD-1, PD-L1 and cytotoxic T-lymphocyte associated protein [10-16]. Along with new medical treatment come new associated side effects. Immunotherapy is different from conventional chemotherapy not only in mechanism of action but also in adverse reactions. In revving up the immune system it is associated with uncommon immune-mediated toxicities which can affect any organ or tissue. The more common of these side effects include hypothyroidism, fatigue, rash, pneumonitis and colitis. More severe toxicities include effects on the cardiac, muscular, endocrine, and hematologic systems. Disorders of the hematologic system are rare but include pancytopenia, aplastic anemia, bi-cytopenia, neutropenia and thrombocytopenia. At times, immunotherapy is administered in combination with chemotherapy; therefore it can be difficult to define the underlying cause of hematologic effects from immunotherapy. The rarity of these effects places it low on a physician's radar.

Presented in our case report is one such patient who ultimately decided on comfort measures. During the short course of his care, he developed significant thrombocytopenia after presenting with symptomatic severe anemia complicated by upper gastrointestinal tract bleeding all after one dose of immunotherapy. He was diagnosed with stage IV hepatocellular carcinoma involving multiple liver lesions and significant peritoneal disease after presenting with weight loss. Based on the standards provided by the National Comprehensive Cancer Network the patient was initiated on first line Atezolizmab. Just 7 days after receiving his one and only cycle of Atezolizumab, the patient presented to the emergency department with complaints of fatigue and hematemesis. Platelet count was initially less than 3,000 in the emergency room. 2 days prior to this episode of thrombocytopenia, his platelet count was noted to be 351,000. Any abnormal blood count such as new thrombocytopenia after immunotherapy should be clinically significant to a physician as it can lead to a quick and progressive decline.

Hematologic immune mediated findings are rare. Based on clinical suspicion for thrombocytopenia related to recent immunotherapy in this patient, he was initiated on pulse dose steroids and IVIG. Suspicion was elevated as chemotherapy was not part of his treatment regimen. Chemotherapy most commonly causes cytopenias and this could have resulted in a delayed diagnosis.

Trials of immunotherapy did report findings of solitary thrombocytopenia even with immunotherapy alone regimens, although it is reported to be more common when combined with chemotherapy. On review of the literature immune-related thrombocytopenia is more likely an occurrence in non-small cell lung carcinoma followed by melanoma as well as renal cell carcinoma, lymphoma, and pancreatic cancer. The frequency of immunotherapy induced thrombocytopenia is unknown, but Kramer et al estimates the incidence as 0.04%–3.6% with an estimated mortality rate of 14%, making them one of the most serious adverse events. In fact, there are multiple reports with complicated hospitalizations and fatal outcomes.

It is unknown the mechanism of action for immunotherapy induced thrombocytopenia. A proposed mechanism of action for checkpoint blockade induced thrombocytopenia includes upregulated circulating immune response antibodies resulting in destruction of circulating platelets. Cases with Nivolumab, the first FDA approved

immunotherapy, have demonstrated increased production of IgG auto-antibodies specific to platelets to induce their demise.

The risk of an immune related reaction was found to be highest in the initial four weeks from immunotherapy treatment. Effects from immunotherapy can continue to be reported even after the medication has been discontinued. For thrombocytopenia the earliest reports occur after the first or second cycle.

In a case study published in International Journal of Pharmacology and Therapeutics in 2019 presented a patient who developed life-threatening pneumonitis, thrombocytopenia and cardiac dysfunction with atezolizumab. After treatment with corticosteroids, pneumonitis had completely resolved and passed away 28 days after a single dose of atezolizumab.

Diagnosis of immune blockade induced thrombocytopenia is challenging. A complete workup should ensue for other alternative inducing diagnosis. After excluding chemotherapy as a cause, it is important to rule out nutritional deficiencies, such as B12, viral etiology including hepatitis, anatomical in regards to splenomegaly, and other drug inducing medications as well as disseminated intravascular coagulation and thrombotic thrombocytopenic purpura. Bone marrow biopsy can be considered based on history and presentation.

In immunotherapy induced thrombocytopenia a bone marrow biopsy is found as normal. Our patient presented here did not undergo a bone marrow biopsy due to high suspicion for his thrombocytopenia being immunotherapy induced.

Currently there is no standard for treatment of immunotherapy induced thrombocytopenia that is highly effective. The treatment course includes medication similar to that of idiopathic thrombocytopenia. Management includes steroids, IVIG, splenectomy or agents such as rituximab or azathioprine. Thrombopoietin receptor agonists as well as platelet transfusions are used as well [17-20].

CONCLUSION

In summary, throughout our patient's course with the expeditious initiation of therapy including platelet transfusions, pulse dose steroids and intravenous immunoglobulin, the patient's platelet count did respond up to 104,000 on the day of his discharge to home on hospice.

Hematologic immune related side effects have shown high mortality rates and are difficult to diagnose and treat. Immunotherapy induced thrombocytopenia generally develops within the first 12 weeks of immune checkpoint inhibitor initiation. In this case the absence of other etiologies such as platelet consumption, platelet sequestration, drug-induced thrombocytopenia, hematological malignancy or infection suggests that this was immunotherapy induced thrombocytopenia caused by atezolizumab. Unfortunately a few weeks after his admission he passed away from his cancer diagnosis.

Hopefully in the near future, a standard of care and effective approach will be available for immunotherapy induced thrombocytopenia. In the meantime this paper was written to address the seriousness, highlight this fatal side effect as well as the need for quick action with treatment.

DECLARATIONS

Ethics approval and consent to participate

Our institution does not require ethical approval for reporting individual cases or case series.

Consent for publication

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors contributed to the writing, editing, and approval of this case report.

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