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CASE REPORT

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Drug-induced immune-mediated thrombocytopenia secondary to durvalumab use

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Abstract

Immunotherapy is an expanding area of cancer treatment with significant promise. Despite their efficacy, checkpoint inhibitors are associated with a number of immune-related adverse events; here, we described thrombocytopenia secondary todurvalumab.

KEYWORDS

ITP, medical oncology, pharmacokinetics, platelets—acquired platelet disorders, thrombocytopenia

1 | INTRODUCTION

Durvalumab is a human monoclonal antibody targeting the programmed death ligand 1 (PD-L1) pathway approved for the treatment of non-small cell lung cancer (NSCLC) and other malignancies. Among other immune-related adverse events (irAEs), thrombocytopenia has rarely been reported with durvalumab use, though is a potentially life-threatening complication of treatment.

Durvalumab is a human IgG1 monoclonal antibody approved for the treatment of multiple malignancies, including urothelial carcinoma and non-small cell lung cancer (NSCLC).[1,2] As a checkpoint inhibitor (CPI), durvalumab targets and blocks programmed death ligand 1 (PD-L1) on tumor cells, resulting in increased T-cell activation and destruction of cancer cells.[3,4] While CPIs are an expanding area of cancer treatment with significant promise, multiple side effects of treatment, or immune-related adverse events (irAE), have been reported.[5-7] Cytopenias have also been reported with CPI use, and for durvalumab specifically, have been noted to occur in less than 1% of individuals treated.[8]

Drug-Induced thrombocytopenia (DITP) is an immune-mediated process wherein drugs covalently linked to proteins or other macromolecules induce a humoral immune response, with the antibodies produced binding to and destroying platelets in the presence of the drug.[8] The typical time course for development of such antibodies with resultant thrombocytopenia is 1 to 2 weeks following initiation of a new drug, however, if a patient has previously been exposed, the effects can occur more acutely.[9] Cessation of the offending agent is critical to management of this condition.

In this clinical report, we detail the presentation, evaluation, and diagnosis of a case of drug-induced thrombocytopenia secondary to durvalumab use. To our knowledge, this is only the second reported case of this irAE with durvalumab, and represents the first case of steroid-responsive immune-mediated thrombocytopenia with this specific CPI.

2 | CASE PRESENTATION

A 45 year-old woman, current smoker without significant medical problems presented to oncology clinic for a follow-up

Written informed consent was obtained from the patient prior to manuscript composition

visit for management of her unresectable, stage IIIB NSCLC. She had been diagnosed with poorly differentiated adenocarcinoma four months prior and was treated with definitive cisplatin and pemetrexed with concurrent radiation therapy (66Gy in 33 fractions). Her platelets were normal throughout concurrent chemotherapy and radiation (CTX + RT). Two weeks after completing CTX + RT, she began durvalumab consolidation therapy every two weeks. She tolerated the first two cycles of durvalumab without evidence of irAEs, though noted increased bruising on her arms following the third cycle. She denied any overt bleeding episodes, epistaxis, hematuria, fever, rash, diarrhea, or dyspnea.

On physical examination, her temperature was 36.9 degrees Celsius, blood pressure was 127/84 mm Hg, heart rate was 108 beats per minute, and respiratory rate was 18 breaths per minute. She had multiple ecchymoses visible on the arms and abdomen, though no petechial rash or purpura of the lower extremities was seen. She did not have palpable hepatosplenomegaly or lymphadenopathy.

A complete blood count revealed a white blood cell count of 6.73 × 10^9/L, hemoglobin of 13.7 grams/dL, and platelet count of 24 × 10^9/L. She did not have a history of thrombocytopenia, and her platelets had previously been within normal limits prior to and during treatment (Figure 1).

A peripheral blood smear was reviewed and did not have evidence of platelet clumping, fragmented platelets, or schisctocytes, though large platelets were present. A bone marrow biopsy was not performed in this patient given the high suspicion for DITP secondary to durvalumab.

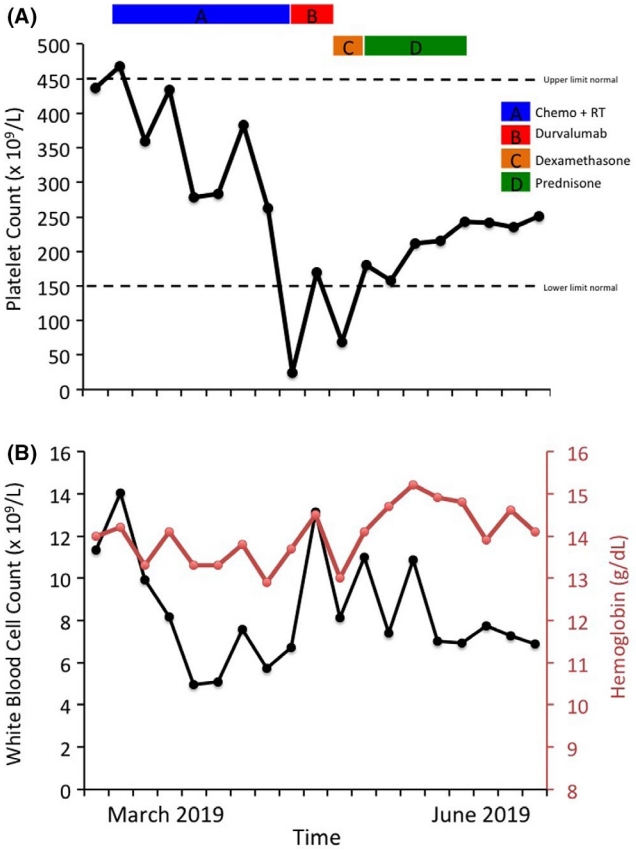

FIGURE 1 A, Patient's baseline platelet counts during treatment with chemotherapy and radiation (blue bar), followed by development of severe thrombocytopenia (platelet count of 24 × 10^9/L) with initiation of durvalumab (red bar), and then return of platelet counts to normal limits following initiation of corticosteroids. Initiation and duration of treatment with dexamethasone and prednisone are shown with orange and green bars, respectively. B, Patient's baseline white blood cell and hemoglobin counts during treatment with chemotherapy and radiation (blue bar), initiation of durvalumab (red bar), and following initiation of corticosteroids (orange and green bars). Despite development of severe thrombocytopenia with durvalumab use, our patient did not have evidence of pancytopenia

3 | DIFFERENTIAL DIAGNOSIS, INVESTIGATIONS, AND TREATMENT

The differential diagnosis for isolated thrombocytopenia is broad, and for this patient included immune-mediated thrombocytopenia, disseminated intravascular coagluation (DIC), hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), and pseudothrombocytopenia.

In regard to immune-mediated thrombocytopenia, given the previously normal platelet count and temporal relationship of the observed thrombocytopenia and recent initiation of durvalumab, this seemed most likely. Previously published case reports in the literature citing thrombocytopenia secondary to PD-1/PD-L1 blockade also supported this diagnosis.[10-12]

The diagnoses of DIC, HUS, TTP, and pseudothrombocytopenia were able to be excluded based on laboratory analysis and examination of the peripheral blood smear. The patient's hemoglobin was at her baseline (~13 g/dL) at the time of presentation, excluding hemolysis and thus HUS. Her creatinine was also at her baseline, further excluding HUS. DIC, TTP, and pseudothrombocytopenia were excluded based on the lack of schistocytes or platelet clumping in the peripheral blood smear and no evidence of overt coagulopathy.

4 | OUTCOME AND FOLLOW-UP

In the setting of grade IV thrombocytopenia suspected to be due to durvalumab, the patient received dexamethasone, 40 mg by mouth daily for four days. Her platelet count initially corrected to 170 × 10^9/L (without transfusion) one week after completion of steroids; however, when labs were rechecked the following week, her platelets had decreased to 69 × 10^9/L. She was then prescribed a prolonged prednisone taper over a four week period, with subsequent normalization of her platelets. Durvalumab was discontinued permanently,

and at the time of manuscript composition, the patient remains alive and well. She has not had any overt episodes of bleeding, and her platelet counts remain within normal limits. She has not received further immunotherapy, including durvalumab, and her stage IIIB NSCLC is stable based on repeat imaging without evidence of local or distant metastatic progression.

5 | DISCUSSION

DITP is a potentially life-threatening condition that occurs when drug-dependent anti-platelet antibodies are produced against specific macromolecules of a drug and result in platelet destruction. The typical time to presentation of thrombocytopenia following initiation of the offending drug is 1 to 2 weeks, though this may be more acute if the patient has previously been exposed to the drug. The diagnosis is generally made clinically, though assays able to confirm the presence of anti-platelet antibodies are available. Despite their availability, as with immune thrombocytopenia (ITP), these assays are generally not recommended, as they are labor-intensive, take a significant amount of time to complete, and are nonspecific, as platelet-associated IgG levels are elevated in both immune and nonimmune thrombocytopenia.[13,14] Management of this condition includes indefinite cessation of the offending drug, platelet transfusions as necessary to control overt bleeding episodes, and corticosteroids for immunomodulation.

DITP secondary to CPI use has previously been reported with ipilimumab, pembrolizumab, and nivolumab.[10-12,15] The average time to presentation following initiation of therapy varied greatly, with thrombocytopenia being noted as early as one week following treatment, and up to 16 months later. Patient presentations also varied greatly, with overt hemorrhage, epistaxis, and other bleeding episodes reported in some individuals, whereas other patients were asymptomatic. The mainstay of treatment in these cases included stopping further infusions of the offending agent and initiation of corticosteroids, with methylprednisolone, 1 mg/kg generally being used. Other immunomodulatory drugs, including intravenous immunoglobulins, rituximab, and cyclosporine have also been used.[15]

Immune-mediated thrombocytopenia in the setting of durvalumab use has also been previously reported, however, despite initiation of steroids and platelet transfusions, this case was unfortunately fatal.[16] There were two mechanisms of thrombocytopenia reported in this case: the first was the production of anti-human platelet antigen auto-antibodies due to decreased tolerance with durvalumab use, and the second was development of platelet alloimmunization and production of anti-human leukocyte antigen antibodies in the setting of platelet transfusions received. The authors of this case report hypothesized that it was the latter mechanism, and not durvalumab use, that explained the refractory and deadly nature of the thrombocytopenia.

Our case highlights the need for continued surveillance for irAEs after initiation of treatment, as these can occur months after patients receive immunotherapy. Despite previous presentations of overt bleeding with checkpoint inhibitor-induced thrombocytopenia, our patient was asymptomatic aside from minor bruising of the bilateral upper extremities and abdomen. She developed thrombocytopenia approximately 6 weeks following initiation of durvalumab and during her third cycle of consolidation therapy. She was treated with dexamethasone, 40 mg by mouth daily for four days, a common ITP treatment regimen, and initially responded to this treatment. However, her platelets quickly declined with steroid discontinuation, and she was started on a four-week prednisone taper for management of an irAE per American Society of Clinical Oncology guidelines.[17] Her platelets then stabilized within normal limits without further intervention or transfusion, highlighting the importance of treating this as an irAE with a prolonged steroid taper and not as ITP.

As noted above, durvalumab can result in immune-mediated thrombocytopenia via production of anti-platelet antibodies generated in the presence of the drug. Another mechanism by which CPI may cause thrombocytopenia involves the PD-1:PD-L1 pathway itself, as it is known that PD-1 regulates peripheral T-cell tolerance in multiple ways.[18-20] The first way involves PD-L1-dependent development of regulatory T cells (Treg), in turn dampening autoimmune tissue damage through the Treg-mediated response; the second involves direct suppression of the activation and function of self-reactive T cells.

In conclusion, as CPI and immunotherapy use for the management of NSCLC and other malignancies continues to increase, clinicians should remain aware of potential irAE that occur as a result of therapy. Cytopenias, in particular thrombocytopenia, can commonly occur and be potentially fatal if under recognized and under treated.

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None

CONFLICT OF INTEREST
All authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS
SD: involved in manuscript writing and designed figure under the mentorship of RH. AL: helped in manuscript writing and assisted in pharmacologic management of the patient. RH: supervised case report formulation, acquired and interpreted clinical data, aided in the diagnosis of disease and the physician of record.

ETHICAL APPROVAL

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. This study did not require IRB approval and was not part of a registered clinical trial.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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REFERENCES

1. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med*. 2017;377(20):1919-1929. https://doi.org/10.1056/NEJMoa1709937
2. Powles T, O'Donnell PH, Massard C, et al. Efficacy and safety of durvalumab in locally advanced or metastatic urothelial carcinoma: updated results from a phase 1/2 open-label study. *JAMA Oncol*. 2017;3(9):e172411–https://doi.org/10.1001/jamaoncol.2017.2411
3. Sharma P, Allison JP. Immune checkpoint targeting in cancer therapy: toward combination strategies with curative potential. *Cell*. 2015;161(2):205-214. https://doi.org/10.1016/j.cell.2015.03.030
4. Moya-Horno I, Viteri S, Karachaliou N, Rosell R. Combination of immunotherapy with targeted therapies in advanced non-small cell lung cancer (NSCLC). *Ther Adv Med Oncol*. 2018;10:1758834017745012. https://doi.org/10.1177/1758834017745012
5. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med*. 2018;378(2):158-168. https://doi.org/10.1056/NEJMra1703481
6. Ayala FA, Dougherty SC, Swift W, Lapides DA. Overlapping NMDA-R and GFAP antibody autoimmune encephalitis after Nivolumab therapy. *Neurol Clin Prac*. 2020;10:1212. https://doi.org/10.1212/CPJ.0000000000001008
7. Brahmer JR, Lacchetti C, Thompson JA. management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: american society of clinical oncology clinical practice guideline summary. *J Oncol Pract*. 2018;14(4):247-249. https://doi.org/10.1200/JOP.18.00005
8. [8]Durvalumab [Package Insert]. Wilmington, DE: AstraZeneca Pharmaceuticals; 2017.
9. Aster RH, Curtis BR, McFarland JG, Bougie DW. Drug-induced immune thrombocytopenia: pathogenesis, diagnosis, and management. *J Thromb Haemost*. 2009;7(6):911-918. https://doi.org/10.1111/j.1538-7836.2009.03360.x
10. Aster RH, Bougie DW. Drug-induced immune thrombocytopenia. *N Engl J Med*. 2007;357(6):580-587. https://doi.org/10.1056/NEJMra066469
11. Karakas Y, Yuce D, Kilickap S. Immune thrombocytopenia induced by nivolumab in a metastatic non-small cell lung cancer patient. *Oncol Res Treat*. 2017;40(10):621-622. https://doi.org/10.1159/000477968
12. Ahmad S, Lewis M, Corrie P, Iddawela M. Ipilimumab-induced thrombocytopenia in a patient with metastatic melanoma. *J Oncol Pharm Pract*. 2012;18(2):287-292. https://doi.org/10.1177/1078155211411001
13. Le Roy A, Kempf E, Ackermann F, et al. Two cases of immune thrombocytopenia associated with pembrolizumab. *Eur J Cancer*. 2016;54:172-174. https://doi.org/10.1016/j.ejca.2015.10.073
14. Bougie DW, Wilker PR, Aster RH. Patients with quinine-induced immune thrombocytopenia have both "drug-dependent" and "drug-specific" antibodies. *Blood*. 2006;108(3):922-927. https://doi.org/10.1182/blood-2006-01-009803
15. Provan D, Arnold DM, Bussel JB, et al. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. *Blood Adv*. 2019;3(22):3780-3817. https://doi.org/10.1182/bloodadvances.2019000812
16. Sajjad MZ, George T, Weber JS, Sokol L. Thrombocytopenia associated with ipilimumab therapy of advanced melanoma at a single institution. *J Clin Oncol*. 2013;31(15_suppl):9072-9072. https://doi.org/10.1200/jco.2013.31.15_suppl.9072
17. Leroy L, Lafarge X, Blouin L, et al. A fatal allo- and immune-mediated thrombocytopenia with a PD-L1 inhibitor. *Ann Oncol*. 2018;29(2):514-515. https://doi.org/10.1093/annonc/mdx693
18. Brahmer JR, Lacchetti C, Schneider BJ, et al. management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: american society of clinical oncology clinical practice guideline. *J Clin Oncol*. 2018;36(17):1714-1768. https://doi.org/10.1200/JCO.2017.77.6385
19. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. *Immunol Rev*. 2010;236:219-242. https://doi.org/10.1111/j.1600-065X.2010.00923.x
20. Francisco LM, Salinas VH, Brown KE, et al. PD-L1 regulates the development, maintenance, and function of induced regulatory T cells. *J Exp Med*. 2009;206(13):3015-3029. https://doi.org/10.1084/jem.20090847
21. Keir ME, Liang SC, Guleria I, et al. Tissue expression of PD-L1 mediates peripheral T cell tolerance. *J Exp Med*. 2006;203(4):883-895. https://doi.org/10.1084/jem.20051776

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