Case Report

Delayed thrombocytopenia as a rare but serious adverse event secondary to immune checkpoint inhibitor: a case report

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Abstract: Immune checkpoint inhibitors (ICIs) are a recent breakthrough in antitumor drugs, although their overall safety has not been fully defined. Compared to conventional chemotherapy, ICIs exhibit different patterns of immunotoxicity, and immune-related adverse events (irAEs) have an immunological basis that is more toxic than usual and have a broad spectrum of manifestations involving different organ systems. Early recognition of symptoms and timely intervention are very important in managing immune-related adverse events (irAEs). In this study, we report a case of delayed immune thrombocytopenia in a patient treated with nivolumab for small cell lung cancer (SCLC). We found that thrombocytopenia was associated with the presence of platelet antibodies, autoantibodies, and thyroglobulin antibodies, accompanied by a decrease in the number of helper T cells and regulatory T cells. Platelets returned to normal after the removal of antibodies by plasma exchanges and methylprednisolone. We hypothesized that thrombocytopenia in patients was an antibody-driven and T-cell-mediated process. Although these observations indirectly suggest that cytokine changes contribute to immune dysregulation during irAE, prospective validation is needed to explain the confounding etiologies that may contribute to cytokine dysregulation. Therefore, studying the relationship between T cell subpopulations, cytokines and irAE in a larger population may be crucial for identifying biomarkers for ICI.

Keywords: Thrombocytopenia; immune-related adverse events (irAEs); T cell activation; immune checkpoint inhibitor (ICI); case report

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Introduction

Immune checkpoint inhibitors (ICIs), including antibodies against cytotoxic T lymphocyte-associated protein 4 (CTLA4) and programmed cell death 1 or its ligands (PD1/PDL1), are a widely effective class of immunotherapies that block inhibitory immune checkpoint pathways to reactivate immune response against cancer (1). They provide a physiological way of unleashing the adaptive immune response (2).

Nivolumab can inhibit the expression of PD-1 on the surface of activated T cells, increase the number of effector T cells, and enhance the antitumor effect. CheckMate-032 studied the efficacy of nivolumab in small cell lung cancer (SCLC) patients with disease progression after platinum chemotherapy. Based on the results of this study, nivolumab monotherapy was approved by the US Food and Drug Administration (FDA) on August 16, 2018, as an alternative therapy for patients with metastatic SCLC with progression after platinum-based chemotherapy and at least one other line of therapy (3). However, their overall security has not

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been fully reflected (4). The novel mechanisms of action of ICIs have resulted in a unique set of side effects, so called immune-related adverse events (irAEs) (5). The incidence, unique tissue specificity, time, and severity of irAEs are variable, and are believed to depend on the type of ICI antibody and the underlying malignancy (6).

In this study, we report a case of delayed hematocrit in a SCLC patient treated with nivolumab. We found that the presence of thrombocytopenia was related to platelet antibodies, autoantibodies, and thyroglobulin antibodies. Platelets returned to normal after antibody removal. The basic findings of previously reported cases of hemocytopenia discuss the possible mechanisms responsible for this toxicity and briefly explain the management strategies that seem to be most suitable.

We present the following article in accordance with the CARE reporting checklist (available at http://dx.doi.org/10.21037/apm-21-794).

Case presentation

A 78-year-old female patient with an Eastern Cooperative Oncology Group (ECOG) score of 1 presented to hospital for 3 days due to cough and sputum. A chest computed tomography (CT) scan revealed a 4 cm × 3 cm × 3.0 cm left upper lung mass and multiple mediastinal enlarged lymph nodes. The patient then underwent a CT-guided lung biopsy, and pathological findings showed SCLC, and she was finally diagnosed with SCLC (T2N3 M0). She was given four cycles of etoposide + cisplatin (EP) chemotherapy. After chemotherapy, she suffered repeated leukopenia and pneumonia, and thus, chemotherapy ceased. Approximately 3 months after the discontinuation of chemotherapy, CT examination showed that the disease had progressed, so EP chemotherapy was given again, however it was no longer effective. Therefore, the patient was given two cycles of the ICI, nivolumab 120 mg (3 mg/kg, 40 kg) each time, in October 2018.

One month after treatment with nivolumab, she developed palpitations, and further investigation of thyroid function revealed hyperthyroidism and grade 2 immune thyroiditis, significantly increased thyroid antibodies, as well as negative autoantibodies and antineutrophil cytoplasmic antibody (ANCA). Later, due to the patient's concerns regarding the safety of the drug, nivolumab treatment was terminated, and hypothyroidism appeared after 2 months. Levothyroxine tablets 25 μg 1 time a day were given as oral replacement therapy. The thyroid hormones T3 and T4 subsequently returned to normal, however thyroid peroxidase and thyroglobulin antibodies remained high.

Thrombocytopenia occurred more than 6 months after taking nivolumab, with a minimum of 0×10^9/L. Methylprednisolone needle (40 mg twice a day), platelet transfusion, and thrombopoietin and eltrombopag olamine (Promacta) were ineffective. Leukopenia and neutropenia appeared the next half month. The minimum leukocytes, neutrophils, and platelets were 0.8×10^9/L, 0.34×10^9/L, and 0, respectively. Further laboratory tests revealed the following: Coomb 's test negative, antinuclear antibody, antimitochondrial antibody M2 subtype, anti-Ro52 antibody were positive, platelet alloantibodies were detected by agglutination reaction, and platelet-specific antibodies were detected by enzyme-linked immunosorbent assay (ELISA), which indicated that human leukocyte antigen (HLA) class I antibodies were positive. Flow cytometry analysis of T cell subsets showed that the number of helper T cells (CD4+ T cells) decreased, the number of regulatory T cells decreased, and there was no significant abnormality in cytotoxic T lymphocyte (CTL) numbers. Bone marrow morphology showed that the bone marrow hyperplasia was active, the grain-to-red ratio was inverted, and the plate production function was decreased. Bone marrow pathology showed lower bone marrow hematopoietic tissue hyperplasia, clustered immature juvenile cell proliferation, and increased proportions. Bone marrow immunotyping, fluorescence in situ hybridization (FISH) detection, single nucleotide polymorphism (SNP), and chromosomes were not special, and second-generation sequencing revealed 2.3% of TP3 mutations. So she was diagnosed as "Thrombocytopenia, Thyroiditis and SCLC". Severe hemorrhage, pulmonary infection, fungal infection, heart failure, and an ECOG score of 4 were observed after platelet reduction for one month. The improvement was not significant after treatment with granulocyte colony-stimulating factor and glycerin. After anti-infection, three plasma exchanges, methylprednisolone 40 mg ×7 d, and gradual reduction treatment, the blood gradually recovered after 2 months, the autoantibody test was negative, and the thyroid peroxidase antibody and thyroglobulin antibody decreased significantly. After that, the patient recovered well, and the infectious lesions in the lungs gradually improved and the tumorous lesions in the lungs became stable. The hemogram was within the normal range within 4 months after ceasing the hormone, and the ECOG score was 1. After follow-up for 2 years, the patient did not have disease recurrence or progression. All procedures

performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

Discussion

The PD-1 ICI has become a promising choice for the treatment of a variety of cancers (7). PD-1 is expressed by activated T cells and down-regulates the function of T cell effectors after binding to ligands PD-L1 and PD-L2 on antigen-presenting cells (8). The pharmacodynamics and pharmacokinetics of ICI immunotherapy are very different from chemotherapy or targeted therapy for cancer treatment. Similarly, the toxicity characteristics associated with anti-CTLA-4 and anti-PD-1/PD-L1 immunotherapy are significantly different from those of traditional anticancer therapies. In the clinical trials of each drug, the incidence range of irAE related to single-agent ICI treatment varies, and the span is wide. Reports show that the incidence of any level of irAEs and severe irAEs associated with single-agent ICI treatment is between 15–90% and 0.5–13%, respectively (9).

There are still many questions about the true nature of the relationship between irAEs characteristics, such as site, severity, onset time, and management, and ICI efficacy (10). A Systematic Review and Meta-analysis showed the median time to irAE onset was 15 days following treatment initiation (range, 3–543 days) (11). It is suggested that T cell receptor (TCR) diversity, CD8 + T cell clonal expansion and tumor mutation burden (TMB) may potentially predict irAE, although this is based on a single factor or under limited circumstances. Therefore, there is a lack of comprehensive methods to identify irAE biomarkers (12). The main aspects of irAE management include toxicity identification and classification, immunosuppression, and personalized modification of ICI management. The primary goal of immunotherapy-related toxicity management is the early recognition of symptoms and timely intervention. Important irAE usually requires immunotherapy. When certain severe irAEs occur, it is necessary to permanently stop the toxicity-related drugs. The first choice of treatment is a systemic steroid (13). Other treatments include Infliximab (anti-TNF-α), may be considered for patients that do not respond to systemic steroids (14). Due to the relatively high rate of severe but significant irAEs observed during re-challenge with anti-PD-1 agents (21%), patients presenting with irAEs need to consider immunotherapy with caution (15).

IrAEs are generally thought to be associated with damage to normal tissues as a result of immunotherapy, and immune tolerance is influenced by ICI, resulting in activated T cells targeting non-tumour antigens or self-peptides. IrAEs affect almost all organs. Early studies have begun to explore these molecular mechanisms. One group of studies suggests that perhaps IrAEs are triggered by antigens common to both tumors and inflamed organs (15). The most common irAEs are rash, pruritus, colitis, hypothyroidism, hyperthyroidism, and pneumonia. There are few reports of hematology-related adverse drug events (Hem-irAEs) related to immune checkpoint inhibitors (ICIs). In the practice guidelines recently issued by the European Society of Medical Oncology (ESMO), there is no consensus on the management of hematological toxicity of immunotherapy. Immune thrombocytopenia (ITP) is the second most common hematological toxicity. A meta-analysis of 9,324 patients showed that the incidence of anemia, neutropenia, and thrombocytopenia were 9.8%, 0.94%, and 2.8%, respectively. ITP does not have specific diagnostic indicators for cancer patients. It can mimic other types of thrombocytopenia caused by infection, tumor progression, or other chemical drugs used in combination with ICI. The literature recommends that A grade 1 TCP or PLT count below 50% of the baseline value needs to be closely monitored at least twice a week, and there is no need to suspend ICI. Grade 2 TCP requires suspension of ICI and use of corticosteroids for 2–4 weeks. For TCP grade 3 or 4, in addition to discontinuing immunotherapy, prednisone or methylprednisolone 1–2 mg/kg with or without IVIG should be started as soon as possible.If it does not work, consider using rituximab, spleen Resection, thrombopoietin receptor agonists or second-line immunosuppressive drugs, such as cyclosporine, azathioprine, etc. (16).

Although the pathophysiology of ICI-related irAEs has not been fully elucidated, some autoantibodies may have cross-reactivity with antibodies during immunotherapy, which suggest that autoantibodies play an important role in irAEs (17). Knowledge about the role of the immune checkpoint pathway in autoimmune diseases also provides some clues. Many autoimmune diseases are associated with loss of T-cell tolerance and uncontrolled activation of immune effector cells. Changes in genes encoding immune checkpoint proteins are associated with autoimmune diseases (18-21). CTLA-4 and PD-1 polymorphisms are associated with human autoimmune diseases, including

celiac disease, diabetes, lupus, rheumatoid arthritis, and autoimmune thyroid disease (22,23). It is reported in the literature that the levels of thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb) in patients with Hashimoto's thyroiditis are linearly and positively correlated with interferon (IFN)-γ, and the presence of TPOAb and interleukin-4 (IL-4) is linearly and positively correlated, however TgAb levels are wirelessly related to IL-4. It can be seen that the Th1/Th2 (Th, helper T cell) cell imbalance in patients with Hashimoto's thyroiditis is biased toward the predominant immunity of Th1, and the production of autoantibodies is related to this (24).

The existing theory of immune thrombocytopenia is that autoantibodies produced by autoreactive B cells are primarily autoantibodies directed against autoplatelet membrane glycoprotein IIb/IIIa and/or Ib/IX antigens, especially immuno globulin gamma (IgG) antibodies, which play an important role in the pathogenesis of immune thrombocytopenia (ITP). In addition, a variety of cellular immune mechanism abnormalities, such as Th1 polarization, defects in the number of regulatory T cells or inhibitory functions, and CTL-mediated platelet destruction, all play important roles in the pathogenesis of ITP (25). In our case, it was found that the patient's thrombocytopenia was related to autoantibodies, and at the same time, the number of helper T cells and regulatory T cells was reduced. Therefore, multiple mechanisms participated in this process.

IrAE may be caused by some combination of autoimmune T cells, autoantibodies, and/or pro-inflammatory cytokines (e.g., interleukin-17) (26). One possible mechanism is that the activity of T cells is directed against antigens present in tumor cells and healthy tissues. Inflammation in other normal tissues may be caused by increased levels of inflammatory cytokines, which are a downstream effect of T cell activation. Another possible mechanism is that direct binding of immune checkpoint antibodies to targets expressed in normal tissues may lead to complement-mediated inflammation. Finally, immunotherapy may increase existing levels of autoantibodies (26,27).

Conclusions

Based on our serological and biomarker test results, we hypothesized that the patient's thrombocytopenia was an antibody-driven and T-cell-mediated process. Although these observations indirectly suggest that cytokine changes promote immune disorders during irAEs, prospective validation is needed to explain the confounding causes of cytokine disorders. That is, in addition to indicating ICI benefits, compared to the baseline, the number of specific T cell subpopulations exceeding a critical threshold or a significant change between subsequent cycles may be a sign of imminent imbalance of irAE (18). Therefore, understanding the relationship between T cell subpopulations, cytokines, and irAEs in larger populations may be critical to identifying biomarkers of early irAEs and selecting the best ICI candidate. "Thanks to ICIs" our old patient said, although she has suffered such serious adverse reactions, she has achieved better tumor-free survival and a good quality of life.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-21-794). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

References

1. Lee HW, Cho KJ, Park JY. Current Status and Future Direction of Immunotherapy in Hepatocellular Carcinoma: What Do the Data Suggest? Immune Network 2020;20:e11.
2. Qin A, Coffey DG, Warren EH, et al. Mechanisms of immune evasion and current status of checkpoint inhibitors in non-small cell lung cancer. Cancer Med 2016;5:2567-78.
3. Ready N, Farago AF, de Braud F, et al. Third-Line Nivolumab Monotherapy in Recurrent SCLC: CheckMate 032. J Thorac Oncol 2019;14:237-44.
4. Raschi E, Mazzarella A, Antonazzo IC, et al. Toxicities with Immune Checkpoint Inhibitors: Emerging Priorities From Disproportionality Analysis of the FDA Adverse Event Reporting System. Target Oncol 2019;14:205-21.
5. Michot JM, Bigenwald C, Champiat S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. Eur J Cancer 2016;54:139-48.
6. Khoja L, Day D, Wei-Wu Chen T, et al. Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review. Ann Oncol 2017;28:2377-85.
7. Hida T. Nivolumab for the treatment of Japanese patients with advanced metastatic non-small cell lung cancer: a review of clinical trial evidence for efficacy and safety. Ther Adv Respir Dis 2018;12:1753466618801167.
8. de Andrea CE, Perez-Gracia JL, Castanon E, et al. Endoscopical and pathological dissociation in severe colitis induced by immune-checkpoint inhibitors. Oncoimmunology 2020;9:1760676.
9. Wang DY, Salem JE, Cohen JV, et al. Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-analysis. JAMA Oncol 2018;4:1721-8.
10. Thompson JA, Schneider BJ, Brahmer J, et al. Management of Immunotherapy-Related Toxicities, Version 1.2019. J Natl Compr Canc Netw 2019;17:255-89.
11. Samaan MA, Pavlidis P, Papa S, et al. Gastrointestinal toxicity of immune checkpoint inhibitors: from mechanisms to management. Nat Rev Gastroenterol Hepatol 2018;15:222-34.
12. Jing Y, Liu J, Ye Y, et al. Multi-omics prediction of immune-related adverse events during checkpoint immunotherapy. Nat Commun 2020;11:4946.
13. 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;14:247-9.
14. Wang C, Thudium KB, Han M, et al. In vitro characterization of the anti-PD-1 antibody nivolumab, BMS-936558, and in vivo toxicology in non-human primates. Cancer Immunol Res 2014;2:846-56.
15. Thompson JA, Schneider BJ, Brahmer J, et al. Management of Immunotherapy-Related Toxicities, Version 1.2019. J Natl Compr Canc Netw 2019;17:255-89.
16. Zhuang J, Du J, Guo X, et al. Clinical diagnosis and treatment recommendations for immune checkpoint inhibitor-related hematological adverse events. Thorac Cancer 2020;11:799-804.
17. Benfaremo D, Manfredi L, Luchetti MM, et al. Musculoskeletal and Rheumatic Diseases Induced by Immune Checkpoint Inhibitors: A Review of the Literature. Curr Drug Saf 2018;13:150-64.
18. Sato R, Imamura K, Sakata S, et al. Disorder of Coagulation-Fibrinolysis System: An Emerging Toxicity of Anti-PD-1/PD-L1 Monoclonal Antibodies. J Clin Med 2019;8:762.
19. Upadhrasta S, Elias H, Patel K, et al. Managing cardiotoxicity associated with immune checkpoint inhibitors. Chronic Dis Transl Med 2019;5:6-14.
20. Zhou YW, Zhu YJ, Wang MN, et al. Immune Checkpoint Inhibitor-Associated Cardiotoxicity: Current Understanding on Its Mechanism, Diagnosis and Management. Front Pharmacol 2019;10:1350.
21. Anderson R, Theron AJ, Rapoport BL. Immunopathogenesis of Immune Checkpoint Inhibitor-Related Adverse Events: Roles of the Intestinal Microbiome and Th17 Cells. Front Immunol 2019;10:2254.
22. Rowshanravan B, Halliday N, Sansom DM. CTLA-4: a moving target in immunotherapy. Blood 2018;131:58-67.
23. Santaguida MG, Nardo S, Del Duca SC, et al. Increased interleukin-4-positive lymphocytes in patients with Hashimoto's thyroiditis and concurrent non-endocrine autoimmune disorders. Clin Exp Immunol 2011;165:148-54.
24. Audia S, Mahevas M, Samson M, et al. Pathogenesis of immune thrombocytopenia. Autoimmun Rev 2017;16:620-32.
25. Young A, Quandt Z, Bluestone JA. The Balancing Act between Cancer Immunity and Autoimmunity in Response

to Immunotherapy. Cancer Immunol Res 2018;6:1445-52.
26. Illouz F, Briet C, Cloix L, et al. Endocrine toxicity of immune checkpoint inhibitors: essential crosstalk between endocrinologists and oncologists. Cancer Med 2017;6:1923-9.
27. Naqash AR, Appah E, Yang LV, et al. Isolated neutropenia as a rare but serious adverse event secondary to immune checkpoint inhibition. J Immunother Cancer 2019;7:169.

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