Respiratory Medicine Case Reports 28 (2019) 100871

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Case report

Immune thrombocytopenia induced by nivolumab in a patient with non-small cell lung cancer

Hidenori Mori[a,b,*], Chizuru Sakai[b], Masamichi Iwai[b], Yuka Sasaki[b], Takenobu Gomyo[b], Sayaka Toyoshi[b], Daizo Kaito[b], Komei Yanase[b], Fumitaka Ito[b], Junki Endo[b], Norihiko Funaguchi[b], Yasushi Ohno[b], Shinya Minatoguchi[b]

[a] Department of Respiratory Medicine, Hashima Community Medical Center, Gifu, Japan
[b] Second Department of Internal Medicine Gifu University Graduate School of Medicine, Gifu, Japan

ARTICLE INFO

Keywords:
Immune checkpoint inhibitors
Nivolumab
Thrombocytopenia
Lung cancer
Immune-related adverse events
Platelet-associated IgG

ABSTRACT

Antibodies targeting the receptor programmed death 1 on T cells have been approved for the treatment of lung cancer. Immune checkpoint inhibitors (ICIs) induce various immune-related adverse events. Life-threatening hematotoxicity can be provoked by ICI therapy. Although ICI-related endocrinopathy and interstitial lung disease have been well documented, hematotoxicity requiring intensive treatment is relatively rare. We describe a case of nivolumab induced thrombocytopenia after transient mild fever. A 77-year-old man with non-small cell lung cancer was administered nivolumab (240 mg/body, every 2 weeks) as second line therapy. On the day 2 after the first nivolumab infusion, he had a fever and his C-reactive protein level was elevated. Thoracic computed tomography revealed no interstitial lung disease or pneumonia. The fever resolved on day 9 and was not seen thereafter. On day 15 after the first nivolumab infusion, severe thrombocytopenia suddenly emerged. A bone marrow examination revealed no dysplasia or invasion. Based on the presence of high platelet-associated IgG titer, normal bone marrow plasticity and a lack of effectiveness of platelet infusion, we diagnosed nivolumab-induced immune thrombocytopenia. Daily administration of 60 mg of prednisolone restored the patient's platelet count and platelet-associated IgG. We also found that there was significant shrinkage of the primary lesion and that stable disease was achieved. One must be aware of this relatively rare side effect and the unusual clinical findings that could be associated with immunoreaction.

1. Background

Immune checkpoint inhibitors (ICIs) are antibodies targeting the receptor programmed death 1 (PD-1) on T cells. They have been approved for treatment of various malignancies, including non-small cell lung cancer (NSCLC). Monoclonal antibodies that block PD-1 provide substantial benefit, prolonging both progression-free and overall survival [1]. However, immune-related adverse events (irAEs), including thyroid dysfunction, colitis, dermatitis, hypophysitis and pneumonitis are well documented [2], and less frequent events are now being reported. Organs affected by irAEs differ from those affected by cytotoxic chemotherapy. Moreover, the times at which irAEs appear are unexpected.

2. Case presentation

A 77-year-old man with chronic heart failure was referred to our hospital due to acute worsening of his condition. During his examination, the patient also mentioned a mass in his right lung. The patient's medical history included 120 pack-years of smoking, and he had been previously diagnosed with an old myocardial infarction, hyperlipidemia, hypertension, diabetes mellitus, chronic obstructive pulmonary disease and cement-related pneumoconiosis. The patient had no history of autoimmune or coagulation disorders. Computed tomography (CT) revealed a mass measuring 30 × 25 mm in right lower lobe and multiple swollen lymph nodes in the mediastinum. The biopsy specimen was diagnosed as NSCLC (not otherwise specified) and magnetic resonance imaging of the patient's head revealed multiple brain metastases. The patient was therefore staged as cT2aN3M1c. The tumor

Abbreviations: ICIs, Immune checkpoint inhibitors; PD-1, programmed death 1; NSCLC, non-small cell lung cancer; irAEs, immune-related adverse events; CT, computed tomography; CRP, C-reactive protein; PA-IgG, platelet-associated IgG; ITP, immune thrombocytopenia

* Corresponding author. Department of Respiratory Medicine, Hashima Community Medical Center, Shinsei-cho 3-246, Hashima-city, Gifu 501-6206, Japan
E-mail address: hidenori03jp@yahoo.co.jp (H. Mori).

https://doi.org/10.1016/j.rmcr.2019.100871
Received 24 March 2019; Received in revised form 30 May 2019; Accepted 2 June 2019
Available online 04 June 2019

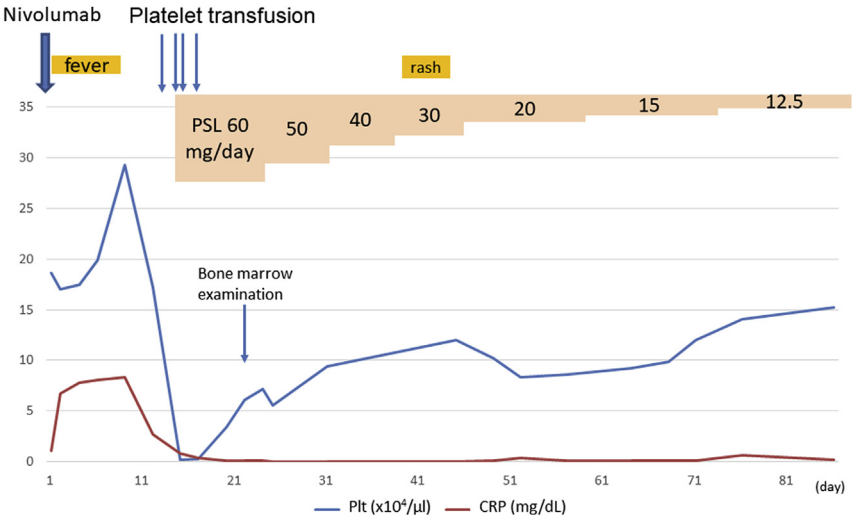

Fig. 1. Clinical course. . A 77-year-old man experienced severe thrombocytopenia (0.2×10^4/mcl) on day 15 after 240 mg of first nivolumab administration. Daily administration of 60 mg of prednisolone started from on day 17 restored the patient's platelet count. Despite of prednisolone tapering, the platelet count could keep > 10×10^4/mcl on and after day 71. Subsequent nivolumab treatment was discontinued and provided best supportive care. Shown are the changes in platelet number and CRP concentration throughout the treatment period.

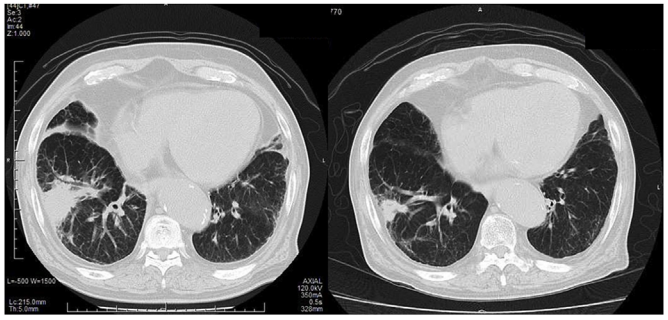

Fig. 2. On day 29 after a single cycle of nivolumab administration, thoracic CT revealed significant shrinkage of the primary lesion, and stable disease was achieved. Thoracic CT before treatment (Left) and after one cycle of nivolumab (Right).

showed no EGFR mutation, ALK translocation or ROS1 rearrangement, but more than 90% of tumor cells expressed PD-L1.

The patient showed progress after 6 cycles of nab-paclitaxel and carboplatin, and was given single-agent nivolumab (240 mg/body, every 2 weeks) as second line therapy (Fig. 1). The pre-treatment platelet count was 18.6×10^4/mcl, and C-reactive protein (CRP) was 1.08 mg/dl. On the day 2 after the first nivolumab infusion, the patient had a fever > 38 °C and CRP was elevation to 6.7 mg/dl. As empiric therapy, we administered moxifloxacin, cefozopran and azithromycin, but there was no decrease in CRP. Other than fever, no symptoms were seen, and serum procalcitonin was 0.06 ng/ml. Thoracic CT on day 6 revealed no interstitial lung disease or pneumonia. The mild fever and elevated CRP (6.7–8.3 mg/dl) persisted from day 2 to day 8. Considering the possibility of a nivolumab-related immunoreaction, we administered acetaminophen as needed. On day 9, the patient was admitted to our hospital again due to a worsening of his CHF. Intravenous nitroglycerin plus noninvasive positive airway pressure ventilation rapidly relieved his dyspnea. We also administered biapenem intravenously. No fever was seen during this hospitalization.

On day 15 after initiating nivolumab infusion, the patient's platelet count suddenly decreased to 0.2×10^4/mcl, and he developed a petechial rash, hemosputum and bloody stool. CRP was 0.78 mg/dl, vital signs were stable, and no disseminated intravascular coagulation was detected. A platelet transfusion was administered on the same day, but to no effect. A test for anti-platelet antibody was negative, though the platelet-associated IgG (PA-IgG) level was elevated to 1130 ng/10^7 cells. A serological assessment was negative for anti-nuclear antibodies and hepatitis B/C, and a helicobacter pylori stool antigen test was also negative. Bone marrow examination revealed normal plasticity with no obvious morphological abnormalities, phagocytosis or malignant invasion. The nuclear cell count was 15×10^4 cells/ml, and the myeloid:erythroid ratio was 1.6. The number of megakaryocytes was 64 cells/ml, and G-banding analysis of the bone marrow was normal (46XY). Although megakaryocyte numbers were maintained, the cells were relatively small and immature, and platelets infrequently adhered to them. We diagnosed nivolumab-related immune thrombocytopenia (ITP) and administered intravenous prednisolone at 1 mg/kg/day (60 mg/day) for one week. Three additional platelet transfusions along with the steroid therapy restored the platelet count. Prednisolone was then switched to oral administration and tapered. During the tapering period, at a prednisolone dose of 30 mg/day, an itchy rash transiently appeared on one of the patient's legs and his abdomen. His PA-IgG titer rapidly declined to 64 ng/10^7 cells by day 36 and to 32 ng/10^7 cells by day 64. No further decline the patient's ejection fraction was seen.

On day 29 after initiating nivolumab administration, thoracic CT revealed significant shrinkage of the primary lesion, and stable disease was achieved (Fig. 2). The anticancer effect of a single cycle of nivolumab was very good.

3. Discussion and conclusion

For patients with NSCLC, PD-1/PD-L1 inhibitors are generally safer and better tolerated than cytotoxic chemotherapy, though a 0.7% incidence of thrombocytopenia has been reported [3]. In a retrospective chart review of 2360 patients with melanoma treated with an ICI, < 1% experienced thrombocytopenia and, of those, most showed spontaneous resolution and did not require treatment [4]. In some cases, however, the thrombocytopenia reportedly persisted for an extended period and was not resolved by standard treatment protocols; intravenous administration of immunoglobulin and a thrombopoietin-receptor agonist was required [5–7]. The prolonged duration may have been in part because the concentration of PD-1 blocking antibody in serum or plasma does not reflect its functional efficacy on T cells. Nivolumab binding is detected more than 20 weeks after the last infusion, regardless of the total number of nivolumab infusions or subsequent treatments. For example, sequential chemotherapeutic regimens do not affect the prolonged binding of nivolumab after its discontinuation [8].

ITP is a diagnosis of exclusion and may be challenging due to the lack of a specific test and its broad differential diagnosis. This makes it difficult to distinguish nivolumab-induced ITP from the other secondary forms of ITP. The CARMEN multicenter prospective cohort showed that among 113 adults with newly diagnosed ITP, 20.3% experienced an infection within the six weeks before ITP onset, including 12 viral lower respiratory tract infections and 3 cases of gastroenteritis [9]. In the

present case, the thrombocytopenia developed shortly after initiating systemic therapy with nivolumab, and a bone marrow examination confirmed that the thrombocytopenia was peripheral. Moreover, the lack of effectiveness of platelet infusion and the effectiveness of steroids suggest a diagnosis of ITP. Nivolumab may induce or increase production of platelet-specific IgG autoantibodies. Interestingly, Sato K et al. reported that patients with irAEs experienced significantly greater antitumor effect than patients without an irAE [10]. The flare up of an immunoreaction may reflect a marked antitumor effect.

In our patient, the clinical course and laboratory results suggest the thrombocytopenia was caused by nivolumab-induced antiplatelet autoantibodies via autoimmune activation. However, other possible causes of thrombocytopenia, particularly a viral infection, were not excluded. Although steroid therapy was effective in this case, considering the mechanism of ICI-induced hematotoxicity, thrombocytopenia induced by a PD-1 antibody could persist for a longer time than that induced by a cytotoxic chemotherapy agent. The lack of efficacy of transfusions during and after ICI administration is indicative of an immune-related hematic adverse event that must be dealt with immediately.

Conflicts of interest

The authors declare that they have no competing interests.

Funding

This manuscript did not entail any funding sources outside of our institution.

Authors' contributions

All authors contributed equally to this case report. All authors read and approved the final manuscript.

Consent for publication

Consent for publication form has been obtained.

Acknowledgments

Not applicable.

References

[1] S. Gettinger, L. Horn, D. Jackman, et al., Five-year follow-up of nivolumab in previously treated advanced non-small-cell lung cancer: results from the CA209-003 study, J. Clin. Oncol. 36 (2018) 1675–1684.
[2] L. Hofmann, A. Forschner, C. Loquai, et al., Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy, Eur. J. Cancer 60 (2016) 190–209.
[3] W. Luo, Z. Wang, P. Tian, et al., Safety and tolerability of PD-1/PD-L1 inhibitors in the treatment of non-small cell lung cancer: a meta-analysis of randomized controlled trials, J. Cancer Res. Clin. Oncol. 144 (2018) 1851–1859.
[4] E. Shiuan, K.E. Beckermann, A. Ozgun, et al., Thrombocytopenia in patients with melanoma receiving immune checkpoint inhibitor therapy, J. Immunother. Cancer 5 (2017) 8.
[5] K. Tokumo, T. Masuda, T. Miyama, et al., Nivolumab-induced severe pancytopenia in a patient with lung adenocarcinoma, Lung Cancer 119 (2018) 21–24.
[6] R. Takimoto, A. Otsuka, Y. Kaku, et al., No recurrence of nivolumab-induced idiopathic thrombocytopenic purpura in a metastatic melanoma patient switched to ipilimumab, Eur. J. Dermatol. 28 (2018) 84–85.
[7] S. Kanameishi, A. Otsuka, Y. Nonomura, A. Fujisawa, Y. Endo, K. Kabashima, Idiopathic thrombocytopenic purpura induced by nivolumab in a metastatic melanoma patient with elevated PD-1 expression on B cells, Ann. Oncol. 27 (2016) 546–547.
[8] A. Osa, T. Uenami, S. Koyama, et al., Clinical implications of monitoring nivolumab immunokinetics in non-small cell lung cancer patients, JCI Insight 3 (2018) pii: 59125.
[9] G. Moulis, J. Germain, T. Comont, et al., Newly diagnosed immune thrombocytopenia adults: clinical epidemiology, exposure to treatments, and evolution. Results of the CARMEN multicenter prospective cohort, Am. J. Hematol. 92 (2017) 493–500.
[10] K. Sato, H. Akamatsu, E. Murakami, et al., Correlation between immune-related adverse events and efficacy in non-small cell lung cancer treated with nivolumab, Lung Cancer 115 (2018) 71–74.