Case report

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

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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

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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 × 10^-7 cells. A serological assessment was negative for anti-nuclear antibody-associated IgG (PA-IgG) level was elevated to 1130 ng/ml. No 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 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 bystandard 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 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.

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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.

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Consent for publication

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