CASE REPORT

Thrombocytopenia as an Immune-Related Adverse Event in Malignant Pleural Mesothelioma: A Case Report

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ABSTRACT

A 69-year-old man presented with a pulmonary opacity at a regular medical check-up. He had been exposed to asbestos in a chemical fiber manufacturing setting. Result of positron emission tomography with computed tomography (CT) revealed fluorodeoxyglucose accumulations along the right pleura in areas with multiple nodules and irregular pleural thickening. On the basis of analysis of a CT-guided needle biopsy result, he had been diagnosed with having epithelioid malignant pleural mesothelioma. He received neoadjuvant chemotherapy, and subsequently, a pleurectomy and decortication. After 6 months, malignant pleural mesothelioma recurred with multiple tumors in the pleural cavity. Nivolumab was administered as salvage immunotherapy. A CT scan result revealed marked tumor reduction; however, his platelet count was low (8000/μL), and he was diagnosed with having nivolumab-induced immune thrombocytopenia. Oral prednisone and thrombopoietin receptor agonist were delivered, and the platelet count improved; therefore, a sustained cycle of nivolumab was resumed. This case revealed that nivolumab could be readministered for continued antitumor effects, with careful management of immune-related adverse events.

Keywords: Mesothelioma; Nivolumab; Thrombocytopenia; Thrombopoietin receptor agonist; Case report

Introduction

Malignant pleural mesothelioma (MPM) is a rare malignant disease that occurs in the pleura, peritoneum, and less often, in other sites. Asbestos exposure is considered the main cause of MPM.

Nivolumab is an antibody that acts as an immune checkpoint inhibitor (ICI) by targeting the programmed death-1. Nivolumab was approved for patients with recurrent MPM in Japan in 2018, based on results from a phase 2 trial.[1] ICIs cause various immune-related adverse events (irAEs). Here, we describe a patient with MPM who developed severe thrombocytopenia during treatment with nivolumab.

Case Presentation

A 69-year-old man presented with a pulmonary opacity on a chest radiograph at a regular medical check-up. He had been exposed to asbestos for 3 years, while working in a chemical fiber manufacturing setting, and he had a history of smoking (20 cigarettes/d) for 18 years from the age of 20 years. In addition, he had been

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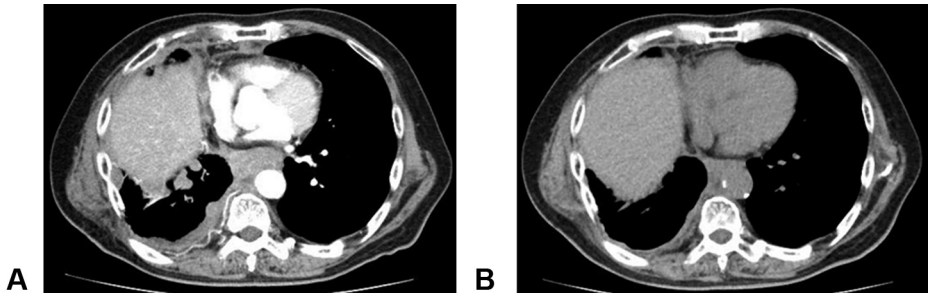

Figure 1. CT images of the chest reveal nivolumab treatment of recurrent MPM. (*A*) At 6 months postsurgery, multiple tumors are present in the pleural cavity, which suggest MPM recurrence. (*B*) CT images after four administrations of nivolumab reveal marked improvement in recurrent MPM tumors. CT, computed tomography; MPM, malignant peritoneal mesothelioma.

diagnosed with having type 2 diabetes mellitus at the age of 59 years.

Result of a positron emission tomography–computed tomography (CT) analysis revealed fluorodeoxyglucose accumulations along the right pleura, in areas with multiple nodules and irregular pleural thickening. On the basis of a CT-guided needle biopsy analysis, he had been diagnosed with having epithelioid MPM. Clinical staging revealed a TNM stage of T3N0M0 (Union for International Cancer Control TNM Classification of Malignant Tumors, seventh edition). The patient received three cycles of neoadjuvant chemotherapy (cisplatin and pemetrexed), and subsequently, underwent a pleurectomy with decortication. At 6 months postsurgery, MPM recurrence was detected, when multiple tumors were found in the pleural cavity (Fig. 1*A*). Nivolumab (240 mg/d) was administered as salvage immunotherapy, every 2 weeks. After four cycles, a CT scan result revealed marked tumor reduction (Fig. 1*B*).

After the ninth cycle, during a routine check-up, thrombocytopenia was detected (platelet count: 8000/μL) without anemia or leukopenia. Consequently, nivolumab administration was stopped. The thrombocytopenia was not associated with bleeding complications. A bone marrow biopsy result revealed no megakaryocytic abnormalities or chromosomal aberrations. The platelet-associated immunoglobulin G (PA-IgG) level was elevated (197 ng/10^7 cells). Antiplatelet antibodies were negative. Result of the serum test for hepatitis B c-antibody, hepatitis C antibody, *Helicobacter pylori* antibody, human T-cell lymphotropic virus type I antibody, and human immunodeficiency virus antibody was negative. On the basis of these examinations, the patient was diagnosed with having nivolumab-induced immune thrombocytopenia (ITP). Oral prednisone at 0.5 mg/kg/d was delivered to treat the ITP, and the platelet count improved on day 3 (50,000/μL). A thrombopoietin receptor (TPO-R) agonist was also delivered as the prednisone was tapered off. The platelet count improved to 200,000/μL on day 24 (Fig. 2). At 3 months after the onset of ITP, a 10th cycle of sustained nivolumab was resumed with the consent of the patient.

At the 14th cycle of nivolumab administration, there were no reappearance of ITP and no exacerbation of MPM.

Discussion

For the past several years, studies have revealed the efficacy of ICIs in various types of malignancies. Nevertheless, studies have also reported that ICIs cause a variety of irAEs.[2] Hematological irAEs are relatively rare; when all grades are considered, they occur at a rate of approximately 3.6% (the grade 3–4 rate is estimated at approximately 0.7%).[3] The occurrence of hematological irAEs was reported to increase with programmed death-1 and programmed death-ligand 1 antibody administration, compared with CTLA-4 antibody administration. In one review, among 63 patients treated with ICIs, nine patients died and 18 patients experienced ITP complications.[3] According to a previous observational study, there were 35 patients with hematologic irAEs including nine patients with ITP among 948 screened patients,[4] and median time to onset of ITP was 10.1 weeks. Only one case of nivolumab-induced ITP in MPM has been reported to date, in which ITP developed 16 weeks after the first administration of nivolumab.[5] ITP also

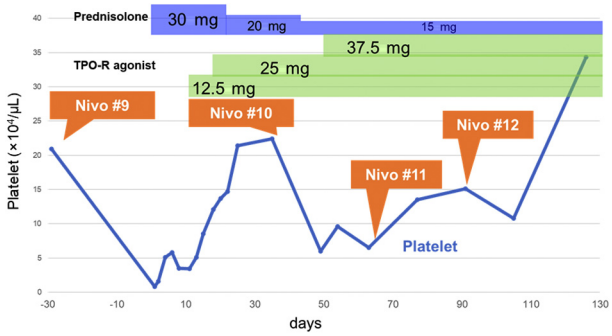

Figure 2. Clinical course of the case. #, number of the administration; Nivo, nivolumab; TPO-R, thrombopoietin receptor.

developed 16 weeks after the first administration of nivolumab in the current case.

In the current case, thrombocytopenia was likely caused by PA-IgG antibodies produced by activated lymphocytes. The elevated PA-IgG level and the negative finding for antiplatelet antibodies supported the notion that ITP had caused thrombocytopenia. It is generally known that steroids have an inhibitory effect on ICIs; consequently, they are often administered to treat ITP. Other treatment options include intravenous immunoglobulins, TPO-R, and other immunosuppressive therapies, such as azathioprine and rituximab.[5–7]

In the present case, we started treatment with steroids. In addition, we used TPO-R in a combinational therapy. We aimed avoiding to deliver steroids at high doses for a long term, because the patient had type 2 diabetes. We also aimed to readminister and continue nivolumab treatment because nivolumab had produced a remarkable antitumor effect. In fact, MPM exacerbation occurred during withdrawal of nivolumab in a previous reported case with nivolumab-induced thrombocytopenia.[5] We could resume nivolumab therapy after the ITP resolved without detectable MPM aggravation in the current case. The decision to resume ICI therapy after resolution of toxicity is challenging. A patient's tumor response status is an important factor in deciding whether to resume ICI. According to American Society of Clinical Oncology guideline, for some patients with a rapid resolution of certain moderate-to-severe irAEs after corticosteroid use, resumption of ICI may be less precarious.[7] We aimed to resume and continue nivolumab treatment because nivolumab had produced a remarkable antitumor effect.

A previous study revealed that nivolumab had clinical effectiveness as a second-line therapy for an unselected population of patients with mesothelioma.[8] More recently, nivolumab was approved as a first-line therapy for MPM in combination with ipilimumab.[9] Thus, in future, nivolumab will play a more prominent role in MPM treatment strategies. According to a recent report, nivolumab displayed more antitumor efficacy in patients with irAEs than in patients without irAEs.[10] We need to manage irAEs appropriately, particularly in MPM treatments, where the treatment options remain limited, compared with other types of malignancies.

Conclusions

We described a patient with MPM who developed an irAE of severe thrombocytopenia. We successfully treated nivolumab-induced ITP with steroids and TPO-R. The current case revealed that nivolumab could be readministered and continued as an MPM treatment, with careful management of irAEs.

CRediT Authorship Contribution Statement

Takaaki Tanaka: Conceptualization, Investigation, Writing—original draft preparation.

Shoji Asakura: Investigation.

Kazuya Hisamatsu: Writing—review and editing.

Nobukazu Fujimoto*:* Investigation, Supervision.

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