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CASE REPORT

Successful Treatment of Steroid-Refractory Immune Thrombocytopenia in a Patient Developing Multiple Myeloma While on Immune Checkpoint Inhibitor Therapy for Lung Cancer: A Case Report

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Abstract: Immune checkpoint inhibitor-related thrombocytopenia (irTCP) is a relatively rare immune-related adverse event (irAE); however, overall survival may worsen when it occurs. Prolonged use of high-dose steroids can diminish the effectiveness of immune checkpoint inhibitor (ICI) therapy on the primary disease because of T lymphocyte suppression, thus early tapering is necessary. We experienced a rare case of a 79-year-old male who concurrently developed irTCP and multiple myeloma (MM) during treatment with ICIs for lung adenocarcinoma. The patient exhibited severe thrombocytopenia and elevated serum IgA levels. Based on various tests, we diagnosed MM and irTCP. Despite administering the standard bortezomib plus dexamethasone (Bd therapy) treatment for MM, there was no response and the irTCP was steroid-resistant. Consequently, we administered a regimen including daratumumab (DPd therapy) for steroid-resistant irTCP and refractory MM, which resulted in a response. As a result, we were able to avoid prolonged use of high-dose steroids and the patient is stable without exacerbation of lung adenocarcinoma for 1 year and 5 months after the onset of MM. To our knowledge, there are no cases of MM developing during ICI treatment and this is the first case report in which daratumumab was effective for the treatment of irTCP.

Keywords: immunotherapy, immune-related adverse event, multiple primary cancer, immune-mediated hematologic toxicity, monoclonal antibody

Introduction

Immune checkpoint inhibitors (ICIs) are becoming a standard treatment for various cancers, such as malignant melanoma, lung cancer, gastric cancer, and colorectal cancer. Consequently, various side effects known as immune-related adverse events (irAEs), such as diabetes, colitis, and myocarditis, have been identified. The importance of managing these side effects has become increasingly recognized.[1,2] Immune checkpoint inhibitor-related thrombocytopenia (irTCP) is relatively rare among irAEs.[2] For differentiating thrombocytopenia during cancer treatment, numerous factors must be considered. These include 1) drug-induced thrombocytopenia associated with chemotherapy including ICIs, 2) hemophagocytic syndrome caused by ICIs,[3,4] 3) disseminated intravascular coagulation or marrow carcinosis resulting from cancer, 4) hematologic disorders, such as secondary myelodysplastic syndromes, 5) anti-HLA antibodies resulting from transfusions, and 6) liver diseases, such as cirrhosis or liver failure. Therefore, diagnosing irTCP is often more challenging compared with immune thrombocytopenia (ITP). The coexistence of irTCP may result in a worsening of overall survival (OS).[5] Factors contributing to the deterioration of OS include severe bleeding due to thrombocytopenia, limited treatment options for primary disease due to the impact of irAEs, including irTCP, and the inability to resume chemotherapy because of a poor response to irTCP treatment. Severe cases have resulted in fatalities,[6] and reports suggest that irTCP has a higher risk of reaching grades 3–4

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compared with other hematologic irAEs.[7] Moreover, there is no evidence indicating that ICIs cause secondary cancers, including hematologic diseases, and there are no established treatment protocols for complications arising from the coexistence of irTCP and secondary cancers. In the present case, during the treatment of lung adenocarcinoma with ICIs, the patient developed multiple myeloma (MM) and irTCP. We successfully managed the disease and its complications with daratumumab, which indicates that this approach represents a new treatment strategy.

Case Presentation

A 79-year-old Asian male was diagnosed with lung adenocarcinoma stage cT3N2M1a in August 2021. At diagnosis, CYFRA was 1.3 ng/mL (normal upper limit: 3.5 ng/mL) and SCC was 1.8 ng/mL (normal upper limit: 2.0 ng/mL). First-line treatment was initiated with nivolumab plus ipilimumab (Nivo + IPI) and the patient has since maintained a partial response. In April 2022, after the 11th course of Nivo + IPI, the patient developed adverse events with a white blood cell count of 1,600/μL (Grade 3), a neutrophil count of 550/μL (Grade 3), and a platelet count of 50,000/μL (Grade 2), resulting in the discontinuation of chemotherapy; however, the cytopenia progressed even after the postponement of Nivo + IPI treatment. The patient had a creatinine level of 2.42 mg/dL, indicating renal impairment, total protein of 9.6 g/dL, albumin of 2.6 g/dL, indicating total protein-albumin dissociation, and elevated serum immunoglobulins with IgA at 4,469 mg/dL (normal range: 93–393 mg/dL), IgG at 983 mg/dL (normal range: 861–1,747 mg/dL), and IgM at 134 mg/dL (normal range: 33–183 mg/dL). Physically, the patient presented with anemic conjunctiva and pain in both rib areas. Immunoelectrophoresis revealed M-protein. Bone marrow examination showed a nucleated cell count of 8.5×10^4 μ/L (normal range: 10–25 × 10^4 μ/L), megakaryocyte count of 51.0 μ/L (normal range: 50.0–15.0 μ/L), plasma cells at 10.0% (normal range: 0.2–2.0%) (Figure 1), and megakaryocytes at 0.4% (normal

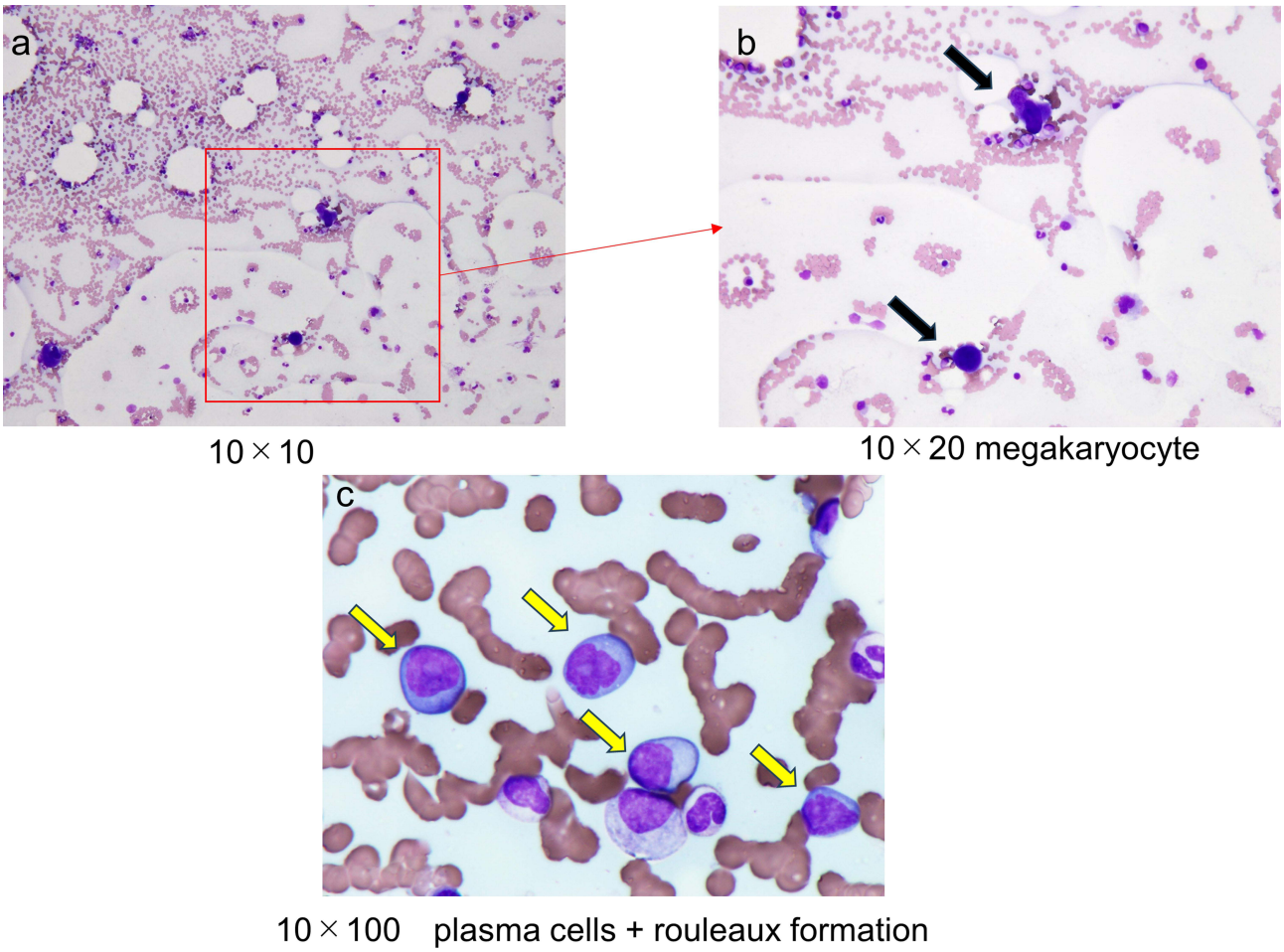

Figure 1 The bone marrow aspiration. (**a** and **b**) The bone marrow is hyperplastic, with an increase in megakaryocytes. Cells at various stages of maturation in all three lineages are observed. No obvious atypical epithelial cells are noted. (**c**) There is an increase in plasma cells.

range: 0–0.2%). Flow cytometry revealed a profile of CD19- CD20- CD38+ CD56+ CD138+ cyλ. Magnetic resonance imaging (MRI) revealed abnormal signals and postcontrast enhancement, predominantly in the vicinity of the left jugular foramen, near the sternum of the right middle cranial fossa, and at the anterior arch of the C1 cervical spine at the base of the skull. Bone scintigraphy revealed heterogeneous abnormal uptake in the sternum, cervical-thoracic-lumbar-sacral vertebrae, left and right ilia, and right ischium, along with multiple uptakes in the left and right ribs (Figure 2). MRI showed bone lesions in the head, and bone scintigraphy revealed accumulations in the ribs and spine, confirming bone lesions in two or more locations in MM. The patient was diagnosed with MM based on the presence of 10% plasmacytes in the bone marrow showing clonality by FCM, IgA M-protein (4,469 mg/dL) and three myeloma defining events; 1) renal impairment (CrCL 24.8 mL/min < 40 mL/min, serum creatine 2.42 mg/dL > 2 mg/dL), 2) anemia (hemoglobin 9.3 mg/dL < 10 mg/dL) and 3) hypercalcemia (serum calcium 12.5 mg/dL > 11 mg/dL), along with myeloma defining biomarkers; the presence of 2 or more bone lesions measuring 5 mm or more in size on MRI study. β2-microglobulin was 13.8 mg/L and LDH was 244 U/L. FISH was negative for P53 deletion, IgH-FGFR translocation, and IgH-MAF translocation. The diagnosis was IgA λ-type MM, classified as R-ISS Stage III. With respect to thrombocytopenia, the bone marrow megakaryocyte count was 51.0 μ/L (normal range: 50.0–15.0 μ/L) and the immature platelet fraction (IPF) was high at 6.8%, suggesting that the thrombocytopenia was not attributable to MM. Pathological examination of the bone marrow clot revealed all three blood cell lineages and no overt atypical epithelial cells, negating the possibility of thrombocytopenia resulting from bone marrow carcinosis of lung adenocarcinoma. TSH was 2.82 μIU/mL, FT4 was 1.16 ng/dL, with no thyroid dysfunction. Thrombocytopenia resulting from disseminated intravascular coagulation or other drug-induced causes was ruled out. Instead, thrombocytopenia in this case was diagnosed as irTCP. Computed tomography scan showed maintenance of shrinkage in the primary lesion of the lung with obliteration of the right middle lobe and multiple right pleural metastatic layers. There was no significant change in the size of the bilateral hilar and mediastinal lymph nodes, or the multiple lymph nodes in the right supraclavicular fossa, thus maintaining stable disease.

To prioritize the treatment of MM, first-line therapy was initiated with bortezomib (BOR 1.3 mg/m2 on days 1, 8, 15, 22) plus dexamethasone (oral DEX 20 mg on days 1, 8, 15, 22), which is referred to as Bd therapy; however, posttreatment, high serum IgA levels maintained, and bone marrow examination revealed a poor response. Furthermore, the steroid component of the therapy was ineffective against irTCP, resulting in a dependence on transfusions.

To treat refractory MM, the regimen was switched to daratumumab (Dara 1800 mg on days 1, 8, 15, 22) + pomalidomide (Pom 2 mg daily on days 1–21) + dexamethasone (DEX 16.5 mg on days 1, 8, 15, 22), which is known as DPd therapy. This resulted in an improvement in IgA levels (Figure 3a), indicating a response to MM. At the time of diagnosis, the creatinine level

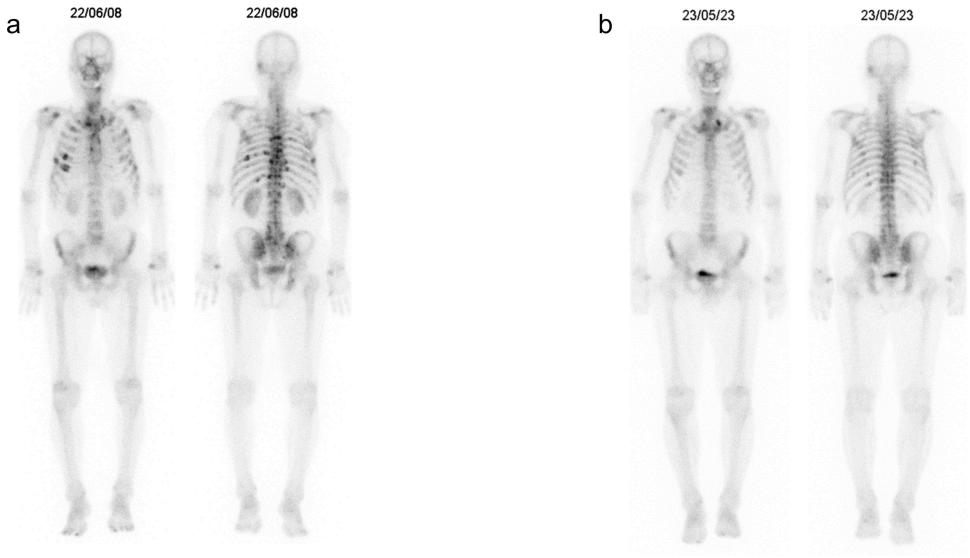

Figure 2 Bone scintigraphy (**a**) At the time of MM diagnosis. Abnormal accumulations are noted in the right sternum, left temporal bone, sternum, cervical-thoracic-lumbar-sacral vertebrae, left and right ilia, and right ischium. (**b**) After the completion of nine courses of DPd therapy. 1 year after the initiation of MM treatment. Although some residual accumulations are noted, the multiple abnormal accumulations observed previously have improved, suggesting that they were associated with pathological fractures caused by MM, rather than MM lesions themselves.

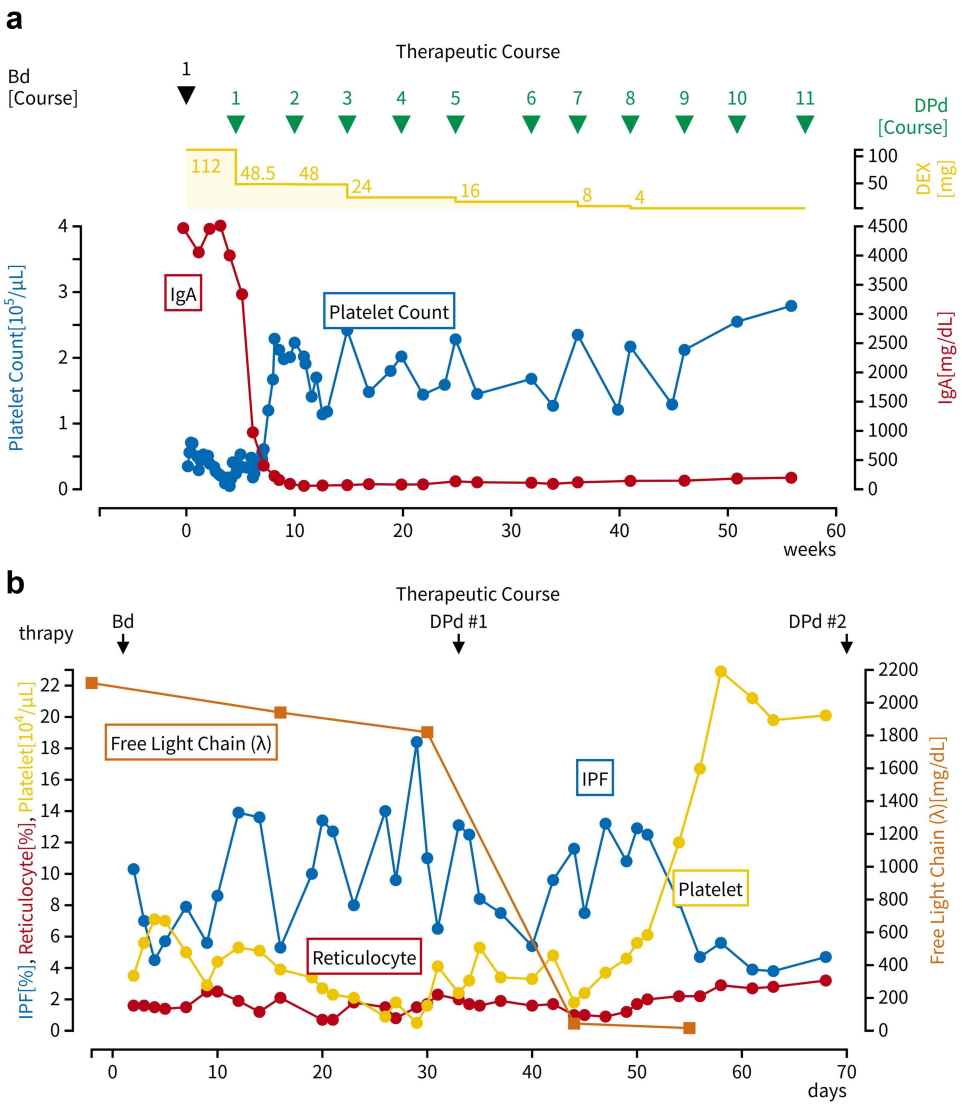

Figure 3 Therapeutic course. (**a**) Created with September 9th, the start date of the first course of Bd therapy, as day 1. (**b**) Before DPd treatment, reticulocyte generally remained within the normal range of 0.7–2.3% (normal range: 0.8–2.0%), with no decline observed, and the IPF has consistently remained high. After DPd treatment, a decrease in IPF and an increase in platelet count were observed.

was 2.42 mg/dL, which later increased to 4.18 mg/dL. However, after DPd therapy, the creatinine level improved significantly to 0.70 mg/dL, suggesting the presence of myeloma kidney. In addition, following DPd therapy, a decrease in IPF and an increase in platelet count were observed, which eliminated the need for transfusions (Figure 3b). After achieving a response with DPd therapy for MM, steroid administration was rapidly reduced early in the course of treatment. As of August 2023, the patient had undergone 12 cycles of outpatient DPd therapy. Computed tomography scans revealed that shrinkage was maintained in the primary lesion of the right middle lobe obliteration and multiple right pleural metastatic layers in the lung. There was also no significant change in the size of the bilateral hilar and mediastinal lymph nodes, or the multiple lymph nodes in the right supraclavicular fossa, indicating a progression-free status. Furthermore, the accumulations in the ribs and spine observed in the bone scintigraphy before treatment were improved one year after the start of treatment, suggesting through clinical progression that they were associated with pathological fractures caused by MM, rather than MM lesions themselves (Figure 2).

Discussion

Thrombocytopenia can occur as an irAE; however, it is rare.[2] The coexistence of irTCP may worsen OS.[5] To diagnose irTCP, it is essential to differentiate thrombocytopenia during ICI therapy by ruling out other causes, such as bone

marrow infiltration by cancer, hematologic diseases including secondary myelodysplastic syndromes or acute myeloid leukemia, and other drug-induced effects, which make diagnosis challenging.[8] Although there are cases of concurrent lung cancer and MM,[9] to our knowledge, there have been no examples of another cancer developing during ICI treatment. Therefore, it is unclear whether the MM was secondary to the ICI therapy or occurred coincidentally. The case was further complicated in its diagnosis of irTCP because of the severe thrombocytopenia and concurrent MM during ICI therapy for lung adenocarcinoma.

irTCP and ITP are thought to have similar pathologies, suggesting the production of anti-platelet antibodies.[10,11] Therefore, steroid therapy was considered effective. However, in this case, there was no response to dexamethasone, leading to a dependence on platelet transfusions. Switching to DPd therapy resulted in a response to both the failure of induction therapy in MM and steroid-resistant irTCP. Before DPd treatment, reticulocyte generally remained within the normal range of 0.7–2.3% (normal range: 0.8–2.0%), with no decline observed. Thus, we concluded that there was no bone marrow suppression due to MM. Furthermore, if it were suppression from MM, the IPF should be low; however, the IPF has consistently remained high, and following DPd therapy, a decrease in IPF and an increase in platelet count were observed. It is difficult to distinguish between ITP caused by MM and irTCP. Instances of ITP related to MM are rare,[12] and the concurrent diagnosis of both conditions is even less common.[13] Interestingly, in cases where ITP is linked to MM, the M-protein is typically IgG.[13] In this case, ITP due to MM could not be excluded as a potential cause of the patient's thrombocytopenia. However, because the patient had previously undergone ICI treatment, was diagnosed with MM concurrently, and the M-protein was IgA, we determined that the thrombocytopenia was attributed to irTCP based on the course of the disease. To date, there have been no reports of successfully treating thrombocytopenia with pomalidomide caused by irTCP, suggesting that the effect may be attributed to daratumumab in the DPd regimen. Rituximab, which is indicated for refractory ITP, works by suppressing the production of anti-platelet antibodies from activated B cells.[14,15] Daratumumab is a monoclonal antibody that targets CD38,[16] an antigen expressed on normal activated T and B cells, NK cells, monocytes, and plasma cells. It is hypothesized that daratumumab improves irTCP, not only by acting on plasma cells, but also on activated B cells, thereby ameliorating the exacerbation of platelet destruction caused by autoantibody production.

Steroids are the standard treatment for irTCP, but they are not always effective against severe thrombocytopenia (grades 3–4). Furthermore, there are reports that irTCP can reduce OS.[5] Considering reports of decreased survival with high-dose steroid administration for irAEs,[17] this may be considered a contributing factor. This suggests that the worsening of OS is not only due to the severity of irAEs, which require high doses of steroids, but the use of steroids may have adversely affected the primary disease by suppressing the effect of ICIs on T lymphocytes. Indeed, there are reports of successful treatment with thrombopoietin drugs for steroid-resistant thrombocytopenia, following the initiation of pembrolizumab.[18] Guidelines recommend the use of IVIg, rituximab, or thrombopoietin agents for cases, in which thrombocytopenia as an irAE develops and the response to steroid therapy is inadequate.[19,20] In this case, daratumumab may be added to standard Bd therapy for refractory MM to successfully treat both MM and steroid-resistant irTCP. Furthermore, it was possible to reduce high-dose steroid dosages without long-term use. As a result, there was no worsening of the lung adenocarcinoma 1 year and 5 months after the onset of MM. We hypothesized that daratumumab may have less impact on T lymphocytes compared with high-dose steroids, thus sustaining the effectiveness of the ICIs. As the indications for ICIs expand, cases of irAEs, including irTCP, in combination with other cancer types, will likely increase. We demonstrated the importance of early management of irAEs, considering efficacy for the concurrent cancer (MM), and of maintaining awareness of treatment effectiveness for the target cancer (lung adenocarcinoma).

Conclusion

We encountered a rare case of concurrent MM and irTCP during ICI therapy for lung adenocarcinoma. By focusing on the common mechanisms of action in irTCP and MM, we successfully achieved a response with daratumumab. During the development of secondary cancers during ICI administration, it is necessary to consider not only the concurrent cancer, but also the treatment of the target cancer. Therefore, it is necessary to reduce steroid therapy promptly if a response is achieved for irTCP to avoid decreasing the efficacy of ICIs on the target cancer.

Ethics and Consent

The patient provided written informed consent for publication of the case report. Institutional approval was not required to publish the case details.

Disclosure

The authors report no conflicts of interest in this work.

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