

[CASE REPORT]

Bicytopenia in Primary Lung Melanoma Treated with Nivolumab

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Abstract:

A 73-year-old man who was a current smoker complained of weakness in his limbs and slow movement and was diagnosed with primary lung melanoma with brain metastases. Following stereotactic brain radiotherapy, nivolumab was administered. After the first cycle of nivolumab, his blood neutrophil count and hemoglobin levels started to decline. Excluding other possible causes, nivolumab was considered the most probable cause of bicytopenia. Nivolumab was not restarted, and the bicytopenia gradually recovered with no corticosteroid administration for this event. While serious hematological adverse events regarding immune checkpoint inhibitors have been assumed to be rare, severe neutropenia and anemia should be considered in patients receiving immune checkpoint therapy.

Key words: immune checkpoint inhibitor, nivolumab, neutropenia, anemia, hematological adverse event

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Introduction

Immune checkpoint inhibitors are emerging therapeutic agents for various types of tumors that restore the antitumor immune response suppressed during tumor progression (1-3). Monoclonal antibodies targeting programmed cell death (PD)-1 or PD-ligand 1 (PD-L1) have outperformed, with milder toxicities, conventional cytotoxic chemotherapies in clinical trials of solid tumors, including non-small cell lung cancer (NSCLC). It has been assumed that immune checkpoint therapy less frequently induces hematological adverse events than cytotoxic chemotherapy because of its mechanism of action. Indeed, clinical studies of immune checkpoint inhibitors have shown that hematological adverse events are rare, especially severe adverse events (4-7). Nivolumab is the first approved immune checkpoint inhibitor antibody targeting PD-1 and was approved for melanoma, followed by NSCLC.

We herein report a rare case of severe neutropenia and anemia after nivolumab therapy in a patient with primary lung melanoma.

Case Report

A 73-year-old man who was a current smoker consulted Aichi Medical University Hospital in December 2015 complaining of weakness in his limbs and slow movement. Brain magnetic resonance imaging showed three enhanced lesions (Fig. 1A and B). Chest X-ray and computed tomography showed a 35-mm mass in the lower lobe of the right lung (Fig. 1C and D). A transbronchial biopsy specimen of the right lung tumor revealed atypical cells positive for S-100 and melanoma-associated antigen HMB-45 (Fig. 2) and negative for thyroid transcription factor-1, Napsin A, p 40, and pan-cytokeratin AE1/AE3, suggesting melanoma. There were no skin or gut lesions indicative of melanoma. A final diagnosis of primary lung melanoma

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Figure 1. Brain magnetic resonance imaging (MRI), chest X-ray and computed tomography (CT) findings at the first visit. Brain MRI showed an enhanced 25-mm nodule in the right frontal lobe, a 31-mm mass in the left temporal lobe and a 15-mm nodule in the left putamen (A, B). Chest X-ray and CT showed a 35-mm mass in the lower lobe of the right lung (C, D).

with brain metastases was reached, and stereotactic brain radiotherapy was performed.

Nivolumab (3 mg/kg) therapy was started in February 2016. After nivolumab administration, his blood neutrophil count and hemoglobin (Hb) levels started to decline (Fig. 3). The nadir neutrophil count at day 16 of nivolumab administration was $456/\mu\text{L}$ and increased without granulocyte colony-stimulating factor injection. Thirty days after the administration, Hb dropped to 7.1 g/dL with a blood reticulocyte count in the normal range (5%). Serum ferritin (882.4 ng/mL), iron (335 mg/dL) and haptoglobin (type 2-2, 97 mg/dL) levels did not decrease, and the serum bilirubin (0.64 mg/dL) level was not high. Upper gastrointestinal tract endoscopy showed no bleeding lesions, and no apparent tarry or bloody feces were observed. Bone marrow aspiration resulted in dry-tap. A bone marrow biopsy showed hypoplasia of hematopoietic cells and no tumor cell infiltration (Fig. 4). With regard to drug-induced hematological disorders, the patient had been regularly taking dexamethasone for brain edema along with trimethoprim-sulfamethoxazole, vitamin K and proton pump inhibitors to prevent adverse effects from corticosteroids since December 2015. Dexamethasone had been started at 3.3 mg/day and was gradually tapered to 2 mg/day 3 weeks before nivolumab administration. Trimethoprim-sulfamethoxazole, vitamin K and proton pump

inhibitors were also continued with no dose modifications. The patient received red blood cell transfusions 30 and 34 days after nivolumab administration. Thirty-seven days after administration, the Hb level and reticulocyte count rose to 9.0 g/dL and 29%, respectively, and anemia gradually improved.

Nivolumab was not restarted, and the tumor remained in a stable disease status for six months until disease progression. After disease progression, the patient declined any active treatment and died of primary lung melanoma nine months after starting nivolumab administration.

Discussion

In the present case, neutropenia and anemia progressed after a single nivolumab administration. Considering his stable use of medications except for nivolumab, we speculated that drug-induced bicytopenia independent of nivolumab was unlikely. Excluding other possible causes of simultaneous anemia and neutropenia, nivolumab was considered the most probable cause of bicytopenia. Bone marrow findings and peripheral blood results suggested hematopoietic hypoplasia. Although the precise mechanism remained unclear, a nivolumab-induced immune related anaplastic mechanism might have been involved.

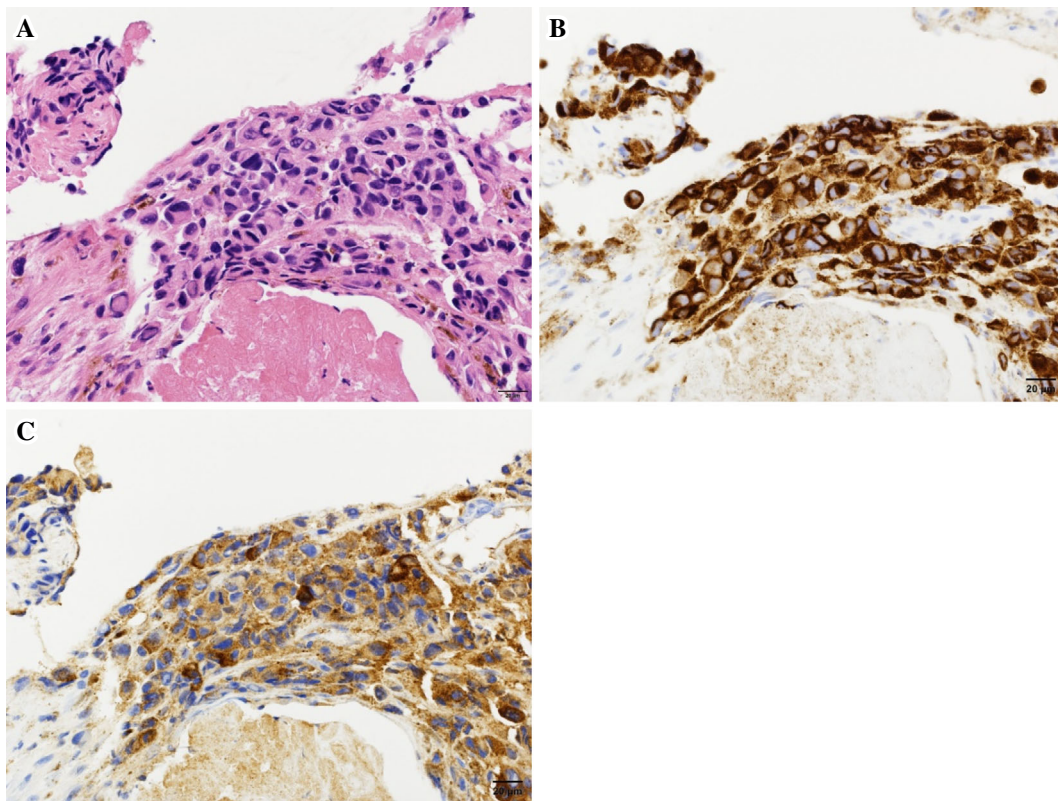


Figure 2. Pathological findings in the transbronchial biopsy specimen. Hematoxylin and Eosin staining showed tumor cells with large amounts of acidophilic cytoplasm and large polymorphic nuclei in the subepithelial region of the bronchiole (A) ($\times 400$ magnification). Tumor cells were positive for S-100 (B) and HMB-45 (C) ($\times 400$ magnification).

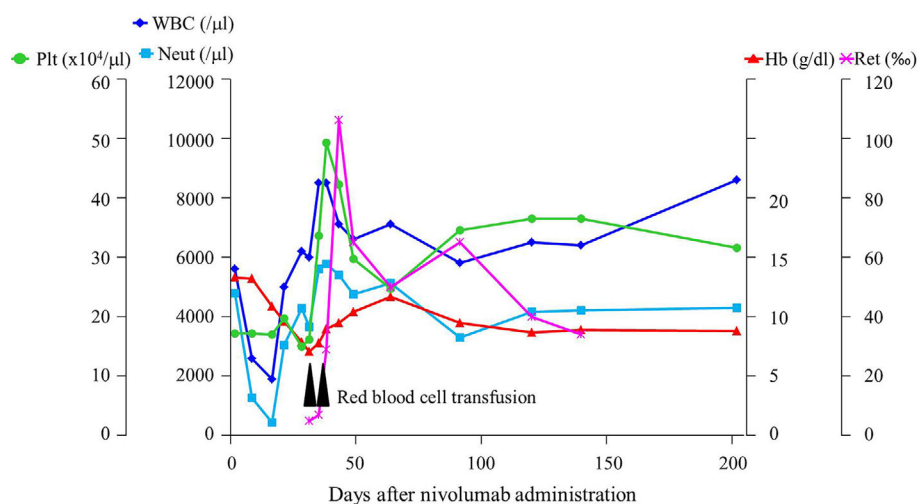


Figure 3. Changes in the peripheral blood cell counts after nivolumab administration. The blue diamond mark indicates white blood cell (WBC) counts ($/\mu\text{L}$). The sky blue square mark indicates neutrophil (Neut) counts ($/\mu\text{L}$). The red triangle mark indicates hemoglobin (Hb) levels (g/dL). The green circle mark indicates platelet (Plt) counts ($\times 10^4/\mu\text{L}$). The pink 'X' mark indicates the ratio of reticulocyte (Ret) (%).

Clinical studies for NSCLC have shown that hematological adverse events from nivolumab are less frequent than with cytotoxic chemotherapies. The frequency of anemia was 2-3% for any grade and <1% for grades 3 and 4 (4-6).

Furthermore, the frequency of neutropenia was <1% (4-6), and that of thrombocytopenia 1% (6) for any grade. Studies of nivolumab for urothelial carcinoma (7) and mucosal melanoma (8) have shown that anemia was more frequent

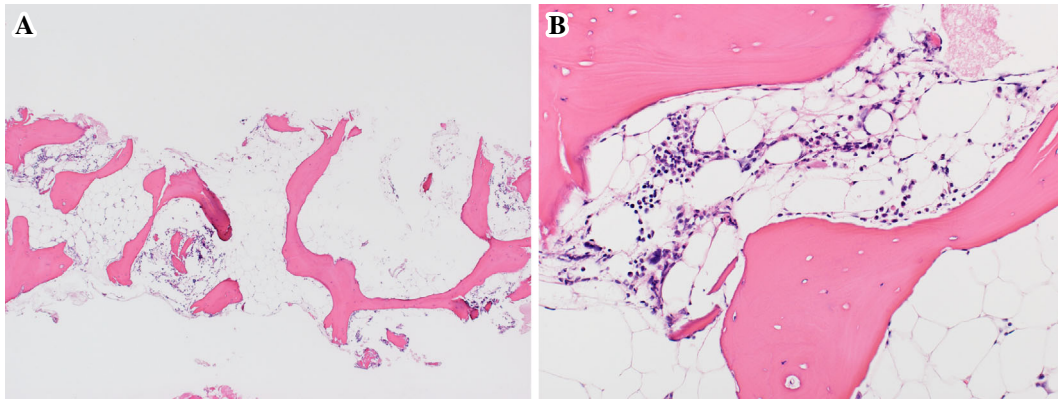


Figure 4. Pathological findings in the bone marrow biopsy specimen. Hematoxylin and Eosin staining showed hypoplasia of hematopoietic cells and no tumor cell infiltration (A: $\times 80$ magnification, B: $\times 400$ magnification).

(10% and 3.5%, respectively) than that in the studies for NSCLC, while the rate of severe anemia was 0% in both studies. In studies of pembrolizumab (9) and tremelimumab (10), other immune check point inhibitors, the rate of severe hematological adverse events was less than 2%.

Several case reports have described nivolumab-induced blood cell reduction (11-16), including a case with bicytopenia (15, 16). In those reports, cases of autoimmune hemolytic anemia (13, 14) and autoimmune neutropenia (16) were described. Hematological adverse events induced by ipilimumab, a monoclonal antibody targeting cytotoxic T-lymphocyte-associated antigen 4, were also reported, with red blood cell aplasia described (17, 18). In those reports, an immune related mechanism was assumed, and corticosteroids were administered to treat hematological disorders. Unlike previous reports, both neutropenia and anemia in our present case progressed relatively slowly and recovered over a short period of time with no additional corticosteroid administration, despite the severity of his bicytopenia. The patient had no symptoms due to bicytopenia. He continuously received low-dose dexamethasone for brain edema. This might have some effect on the course of bicytopenia. In such a case, additional corticosteroids might not necessarily be needed.

Conclusion

Although severe hematological adverse events are rare when immune checkpoint inhibitors are used, severe neutropenia and anemia should be considered when encountering such cases.

The authors state that they have no Conflict of Interest (COI).

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