

Case Report

# Nivolumab Induced Lethal Aplastic Anemia in a Patient with Metastatic Melanoma

Keren Rouvinov<sup>a</sup> Karen Nalbandyan<sup>b</sup> Victor Kozlov<sup>c</sup> Nir Peled<sup>a</sup>  
Alexander Yakobson<sup>a</sup>

<sup>a</sup>Department of Oncology, Soroka University Medical Center, Faculty of Health Sciences, Ben Gurion University of the Negev, Beer Sheva, Israel; <sup>b</sup>Department of Pathology, Soroka University Medical Center, Faculty of Health Sciences, Ben Gurion University of the Negev, Beer Sheva, Israel; <sup>c</sup>Department of Hematology, Soroka University Medical Center, Faculty of Health Sciences, Ben Gurion University of the Negev, Beer Sheva, Israel

## Keywords

Nivolumab · Immunotherapy · Melanoma · Aplastic anemia · Programmed death 1 inhibitor

## Abstract

Nivolumab is an active treatment in patients with metastatic melanoma. We report a case of a patient with metastatic malignant melanoma who was given nivolumab as an advanced-line treatment. She received nivolumab 3 mg/kg every 2 weeks for 4 cycles and developed aplastic anemia. To the best of our knowledge, there are only three published case reports that have shown aplastic anemia in patients who have been treated by immunotherapy. This is the first report of a lethal aplastic anemia during nivolumab monotherapy in a metastatic melanoma patient.

© 2019 The Author(s)  
Published by S. Karger AG, Basel

## Introduction

Nivolumab is an effective treatment option for programmed death 1 (PD-1) inhibitor-naïve patients with metastatic melanoma [1, 2].

A randomized, open-label, phase 3 study (CheckMate 066) of nivolumab, an anti-programmed death antibody inhibitor versus dacarbazine in 418 patients with untreated melanoma without BRAF mutation, showed longer overall survival and fewer grade 3 or 4 adverse events with nivolumab than with dacarbazine [1]. Another trial, CheckMate 037, of nivolumab versus investigator's choice in 272 patients previously treated with ipilimumab, showed higher and more durable responses with nivolumab but no difference in survival [2].

The more common side effects of nivolumab include fatigue, pruritus, nausea, diarrhea and skin rash. The less common include endocrine toxicities, elevation in ALT and AST levels and pneumonitis. Isolated cases of neurologic, ocular, renal toxicities and anemia have been reported [1–3]. To our knowledge, only two cases have been published that showed lethal aplastic anemia caused by immunotherapy [4, 5].

We present a case of a patient with metastatic melanoma given nivolumab monotherapy as an advanced-line treatment who developed lethal aplastic anemia.

### Case Report

A 74-year-old woman, generally healthy, presented to the emergency room with abdominal pain. Computed tomography (CT) imaging of the chest and abdomen revealed a right ovarian mass, right adrenal mass, multiple soft tissues and lung metastases. She underwent tru-cut biopsy from the retroperitoneal mass in April 2012. Pathologic study revealed metastatic malignant melanoma. Immunostaining for s-100 and HNB-45 were positive. BRAF mutation was wild type. She refused dacarbazine treatment due to the possibility of alopecia. The patient started vinblastine 6 mg/m<sup>2</sup> administered every two weeks in May 2012. Partial response was seen in September 2012. In February 2013 she refused to continue chemotherapy and stayed in follow-up. In May 2013 computed tomography revealed new multiple retroperitoneal masses. Second-line systemic therapy with temozolomide 200 mg/m<sup>2</sup> for 5 consecutive days per 28-day treatment cycle was initiated. Stable disease was seen in July 2013 with subsequent progressive disease in November 2013.

Immunotherapy was initiated with ipilimumab 3 mg/kg every 3 weeks. After 3 cycles near complete response was seen. The patient declined to continue treatment due to side effects such as fatigue grade 3 and liver enzyme elevation grade 2. All subsequent computed tomographic scans were stable.

In June 2016 she had progressive disease with appearance of new retroperitoneal, lung and bilateral adrenal metastases. Nivolumab 3mg/kg every two weeks was initiated. After the fourth treatment cycle she developed pancytopenia (hemoglobin level 6.9 g/dL, absolute neutrophil count was 1,000 uL, platelet count 13,000 uL). She started prednisone 1.5 mg/kg orally without any improvement. She was treated by blood transfusions and repeated platelet transfusions. Bone marrow biopsy has been performed. Pathology revealed severe hypoplasia of bone marrow with only isolated erythroblastic islands and almost complete absence of myeloid lineage. The stroma was “empty,” with only partial replacement by fatty tissue. No evidence of metastatic melanoma was found in the examined biopsy. Immunostainings for melanoma cocktail and S100 were negative. CD 20 was positive in isolated cells and CD3 highlighted small T-cell aggregates, composed of CD4 and CD8 positive cells. Alcian blue staining confirmed a picture of serous degeneration (Fig. 1). As per the recommendation of the consulting hematologist revolade 50mg/day was initiated with subsequent increased dose to 100mg/day. Despite treatment the patient continued to deteriorate and died.

## Discussion

Nivolumab is a fully human immunoglobulin G4 programmed death 1 (PD-1) immune-checkpoint inhibitor antibody that selectively blocks the interaction between PD-1 and PD-1 ligand 1 (PD-L1) and 2 (PD-L2) [2].

In the CheckMate 066 trial, which included only previously untreated melanoma patients without BRAF mutation, Robert et al showed a superior response rate in the nivolumab arm versus dacarbazine arm (40 vs. 13.9%), longer 1 year overall rate of survival (72.9 vs. 42.1%) and less grade 3 or 4 drug-related adverse events (11.7 vs. 17.6%) [1]. In the CheckMate 037 trial which included patients with advanced melanoma who experienced disease progression with ipilimumab, Larkin et al showed a benefit in overall response rate in the nivolumab arm versus ICC (27 vs. 10%), duration of response (32 vs. 13 months) and fewer grade 3 and 4 treatment-related adverse events (14 vs. 34%), but no difference in overall survival [2]. Treatment related anemia in the nivolumab group was 8% (any grade), but only 1% of patient had grade 3 or 4 anemia.

Several reports of nivolumab-induced autoimmune hemolytic anemia and a case of pure red cell aplasia were described [6–8]. However, to the best of our knowledge, only three case reports have been published that showed aplastic anemia. Helgadottir et al published case of aplastic anemia caused by dual immune checkpoint blockade with PD-1 and CTLA-4 inhibitors in a patient with metastatic melanoma [4]. Meyers et al. reported second case of aplastic anemia in melanoma patients to dual immune checkpoint blockage [9]. Comito et al described a patient with glioblastoma multiforme who developed aplastic anemia one month after her second dose of nivolumab [5].

In our case we recommended treatment with nivolumab in a heavily pretreated metastatic melanoma patient. In addition, the patient was treated by 3 cycles of ipilimumab in a previous line of treatment with near complete remission.

To the best of our knowledge, this is the first report of a lethal aplastic anemia during nivolumab monotherapy in a metastatic melanoma patient.

## Conclusion

We report a rare case of lethal aplastic anemia in a patient with metastatic malignant melanoma treated by nivolumab as an advanced treatment line. Some published cases of immunotherapy-induced aplastic anemia were lethal; therefore close follow up of the complete blood count is very important in patients on immunotherapy.

## Acknowledgement

The authors thank David B. Geffen, MD for his critical review of the manuscript.

## Statement of Ethics

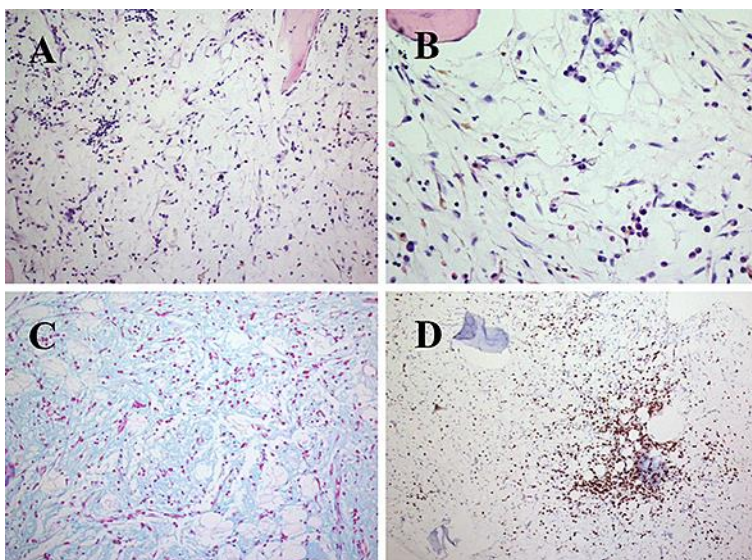
The authors have no ethical conflicts to disclose.

## Disclosure Statement

The authors declare no conflict of interest.

## References

- 1 Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med*. 2015 Jan;372(4):320–30.
- 2 Larkin J, Minor D, D'Angelo S, Neyns B, Smylie M, Miller WH Jr, et al. Overall survival in patients with advanced melanoma who received nivolumab versus investigator's choice chemotherapy in CheckMate 037: A randomized, controlled, open-label phase III trial. *J Clin Oncol*. 2018 Feb;36(4):383–90.
- 3 Naidoo J, Page DB, Li BT, Connell LC, Schindler K, Lacouture ME, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. *Ann Oncol*. 2015 Dec;26(12):2375–91.
- 4 Helgadottir H, Kis L, Ljungman P, Larkin J, Kefford R, Ascierto PA, et al. Lethal aplastic anemia caused by dual immune checkpoint blockade in metastatic melanoma. *Ann Oncol*. 2017 Jul;28(7):1672–3.
- 5 Comito RR, Badu LA, Forcello N. Nivolumab-induced aplastic anemia: a case report and literature review. *J Oncol Pharm Pract*. 2019 Jan;25(1):221–5.
- 6 Palla AR, Kennedy D, Mosharraf H, Doll D. Autoimmune hemolytic anemia as a complication of nivolumab therapy. *Case Rep Oncol*. 2016 Nov;9(3):691–7.
- 7 Schwab KS, Heine A, Weimann T, Kristiansen G, Brossart P. Development of hemolytic anemia as a nivolumab-treated patient with refractory metastatic squamous cell skin cancer and chronic lymphatic leukemia. *Case Rep Oncol*. 2016 Jun;9(2):373–8.
- 8 Yuki A, Takenouchi T, Takatsuka S, Ishiguro T. A case of pure red cell aplasia during nivolumab therapy for cardiac metastatic melanoma. *Melanoma Res*. 2017 Dec;27(6):635–7.
- 9 Meyers DE, Hill WF, Suo A, Jimenez-Zepeda V, Cheng T, Nixon NA. Aplastic anemia secondary to nivolumab and ipilimumab in a patient with metastatic melanoma: a case report. *Exp Hematol Oncol*. 2018 Mar;7(1):6.



**Fig. 1.** Microscopic section. Hematoxylin and eosin stained section of the bone marrow showing hypoplasia,  $\times 20$  (A). Hematoxylin and eosin stained section of the bone marrow showing hypoplasia,  $\times 40$  (B). Alcian blue staining demonstrates serous degeneration,  $\times 20$  (C). Immunostaining for CD8,  $\times 20$  (D).