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Pembrolizumab-Induced Pancytopenia: A Case Report

O. Lamsyah[1*], S. Lkhoyaali[1], Y. Al Harrak[1], A. Kouanga[1], S. Boutayeb[1], H. ER-Rihani[1], N. Badrane[2], R. Soulaymani Bencheikh[2,3]

[1]Department of Medical Oncology, National Institute of Oncology, Rabat, Morocco
[2]Moroccan Anti Poison and Pharmacovigilance Center, Rabat, Morocco
[3]Mohammed V University, Rabat, Morocco

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***Corresponding author:** O. Lamsyah
Department of Medical Oncology, National Institute of Oncology, Rabat, Morocco

Abstract **Case Report**

***Introduction*:** Immunotherapy is increasingly acknowledged as an effective treatment for metastatic melanoma. Hematological immune-mediated adverse events are rarely reported. In this article, we report a case of a patient who developed pancytopenia following administration of pembrolizumab. ***Case Report*:** A 63 -year-old woman, followed for a scalp melanoma with pulmonary metastasis developed severe pancytopenia after receiving 4 cycles of pembrolizumab. ***Outcome and Management*:** Following the appearance of the adverse effect, Pembrolizumab was stopped. A series of blood tests were performed in order to get the reasons of this event. The patient received high-dose of corticosteroids with tapering the dose over 6 weeks, and blood transfusion was required. ***Discussion*:** Checkpoint inhibitors (ICI) stimulate both humoral and cellular immune responses against tumor antigens, potentially resulting in immune-related adverse effects, including hematological issues like pancytopenia. Due to the substantial morbidity and mortality linked to ICI-induced pancytopenia, further data is essential to formulate evidence-based management guidelines.

Keywords: Metastatic melanoma, Immunotherapy, Pembrolizumab, Pancytopenia.

INTRODUCTION

The medical world has witnessed the emergence of immunotherapy to Combat cancer since the mid-90s. Checkpoint inhibitors (ICI) are a type of monoclonal antibodies specifically designed to target immune checkpoints, allowing anti-tumor lymphocyte stimulation. These treatments have significantly improved the prognosis of many cancer patients, but have a new spectrum of immune-related toxicity.

Hematological toxicity is rare and its mechanism is uncertain ; it can vary from anemia, thrombocytopenia to leukopenia and rarely pancytopenia. For this reason, management is often based on the experience gained from the use of these ICI, the imperative being to maintain effective treatment against the cancer or to interrupt it as little as possible [1, 2]. We report a case of pembrolizumab-induced pancytopenia in a patient followed for a metastatic scalp melanoma.

CASE PRESENTATION

A 63 -year-old woman followed for a scalp melanoma with pulmonary metastasis, for which she received an immunotherapy based treatment, she was receiving Pembrolizumab 200mg every three weeks. The patient presented to her follow up during her 4th cycle of Pembrolizumab with a one week history of worsening physical weakness and dyspnea initially on exertion and then at rest. Standard routine laboratory analyses indicated a hemoglobin reading of 8.3 g/dL, a white blood cells count of 2.5 x G/L and thrombocytopenia of 37 x G/L. The fourth cycle of pembrolizumab was suspended following suspicion of pancytopenia induced by immunotherapy. Her absolute reticulocyte count was normal, her anemia was normocytic and no spherocytic hemolysis was visible on the smear. A vitamin assay showed a vitamin B12 level of 352 pg/ml, a vitamin B9 level of 14.94 nmol/l, and a ferritin level of 4042 ng/ml. Bone marrow biopsy revealed no cancer cells infiltration and all lineages were present and mature, a myelogram revealed multilineage dysplasia. Cytogenetic study was negative revealing a diploid karyotype with 46 chromosomes without abnormalities. Anti-platelet antibodies and autoimmune antibodies were not detected

during testing. Toxicological screening of drugs, illégal drugs, pesticides and herbals performed by liquid chromatograhy and gaz chromatography coupled to mass spectometry was negative. Prednisone at a dose of 1 mg/kg per day orally was quickly initiated with tapering the dose over 6 weeks. The patient needed transfusions of both packed red blood cells and platelets to aid in her recovery. The pancytopenia improved after suspension of pembrolizumab, at the end of her prednisone treatment, her neutrophil count was 5.8 x G/L, her hemoglobin was 13.6 g/dL, and her platelets were 259x G/L.

After consulting a hematologist, it was concluded that pembrolizumab caused pancytopenia through an autoimmune reaction.

No other serious adverse effects were encountered, no other agents than Pembrolizumab were administered.

Table 1: Chronology of relevant laboratory test results

	Hemoglobin (g/dL)	***White blood cells (G/L)***	***Platelets (G/L)***
30/05/2022	13.9	4.63	278
19/10/2022	8.3	2.5	37
31/10/2022	7.3	2.1	36
04/11/2022	7.2	3	35
16/01/2023	13	6.7	212
17/03/2023	13.6	10	259
17/04/2023	12.7	6.5	179

DISCUSSION

Hematological toxicity of immune checkpoint inhibitors is relatively rare (< 5%) but may be associated with significant mortality. Occurrences have been reported subsequent to the administration of anti-CTLA4 (cytotoxic T-lymphocyte-associated antigen 4) and anti-PD-1 (programmed cell death-1) agents, either individually or in combination. Among patients with significant hematological toxicity, more than 90% of those treated with the anti-PDL-1 and anti-CTLA-4 combination had grade 3 toxicity, compared with 70% of patients treated with one of them. The combination therapy showed a shorter median time to the onset of hematological toxicity compared to monotherapy, with 12 weeks versus 25 weeks, respectively [3].

The mechanisms responsible for pembrolizumab-induced pancytopenia remain unclear. Therapies targeting PD-1 or PD-L1 block inhibitory signals to cytotoxic CD8 and helper T lymphocytes, thereby suppressing the activation of Tregs (CD4 and CD25). Additionally, they disrupt inhibitory signals to B lymphocytes, macrophages and natural killer cells. Thrombocytopenia, anemia, neutropenia, and bone marrow failure induced by immunotherapy are associated with mechanisms involving CD8 T lymphocyte cytotoxicity and B cell autoantibody production. The activity of macrophages can be significantly influenced by PD-1 and PD-L1 blockers, potentially resulting in excessive cytokine production. This heightened cytokine release has been associated with the development of hemophagocytic syndrome and venous thromboembolism [4].

Few reports have described pancytopenia as a major side effects.

A study included patients with grade 2 or more severe hematological immune-related adverse events (IRAEs) following treatment with anti-PD-1 or anti-PD-L1, as documented in three French pharmacovigilance databases. Among 948 patients, 35 were identified with hematological IRAEs. Furthermore, the Registry of Severe Adverse Events of Immunomodulatory Monoclonal Antibodies in Cancer (REISAMIC), a multicenter registry of patients treated with anti-PD-1 or anti-PD-L1, found 4 hematological IRAEs in 745 patients, with a frequency of 0.5%. Thrombocytopenia, autoimmune hemolytic anemia, and neutropenia were the most frequent hematological immune-related adverse events (IRAEs) among the 35 patients, accounting for 26% of cases. Pancytopenia or aplastic anemia followed closely, representing 14% of cases [5].

One study based on the 19 clinical trials of ICI, the frequency of hematological toxicity induced by ICI was 3.6 % for all grades and 0.7 % for grade III or IV. The frequency were found to be higher with anti PD-1 (4.1 %) than with anti- CTLA-4 (0.5 %). Of the 63 documented cases with hematological toxicity, the occurrences were distributed as follows: thrombocytopenia (29%), pancytopenia (12 %), neutropenia (11%), hemolytic anemia (10%), and bicytopenia or pure red cell aplasia (5 %).The more severe were pancytopenia or aplastic anaemia. The mortality rate was 14% [6].

In 2019, Dan Ni *et al.*, reported the case of a 67-year-old patient with metastatic melanoma and a medical history of chronic lymphocytic leukemia who developed pancytopenia after the 8th cycle of pembrolizumab [7].

Ueki *et al.*, reported a case of a patient with squamous cell carcinoma of the lung who developed

grade 3 pancytopenia during pembrolizumab treatment that naturally improved within 6 months of pembrolizumab suspension, corticosteroid administration was suggested but the patient declined due to the risk of steroid-related adverse events [8].

In 2017, a case study by Dinesh Atwal *et al.*, documented a 52-year-old patient with rectal melanoma. After the 18th cycle of pembrolizumab, the patient developed severe grade 4 pancytopenia. However, the situation improved after receiving high dose corticosteroids and intravenous immunoglobulin (IVIG) [1].

Le Roy *et al.*, documented two cases of severe pancytopenia induced by pembrolizumab, which resolved following treatment with corticosteroids and intravenous immunoglobulin (IVIG) [9].

Table 2: Hematological Adverse Events after treatment with Pembrolizumab or Nivolumab

Author	PD-1 Inhibitors	Hematological Toxicity	Treatment
Nair *et al.,* (2016) [10]	Pembrolizumab	Autoimmune hemolytic anemia	Corticosteroids
Le Roy *et al.*, (2016) [9]	Pembrolizumab	Thrombocytopenia	Corticoteroids, IVIG
Kong *et al.,* (2016) [11]	Nivolumab	Autoimmune hemolytic anemia	Corticosteroids
Inadomi *et al.,* (2016) [12]	Nivolumab	Anemia, thrombocytopenia	Corticosteroids
Michal *et al.*, (2017) [13]	Nivolumab	Pancytopenia	Corticosteroids hematopoietic growth factors
Atwal *et al.*, (2017) [1]	Pembrolizumab	Pancytopenia	Corticosteroids, IVIG
Ueki *et al.*, (2020) [8]	Pembrolizumab	Pancytopenia	Nothing
Dani *et al.*, (2019) [7]	Pembrolizumab	Pancytopenia	Corticosteroids

In the KEYNOTE-021 study, a randomized phase II trial of pemetrexed and carboplatin with or without pembrolizumab in advanced non small cell lung cancer, no occurrences of pancytopenia were reported [14].

In contrast to anti-PD-1 therapies, pancytopenia is commonly observed with anti-CTLA-4 like Ipilimumab. Rusquec *et al.,* presented a case study of a patient with metastatic melanoma who developed grade 4 pancytopenia after receiving ipilimumab. The patient received IVIG, corticosteroids, and hematopoietic growth factors, and required transfusions of packed red blood cells and platelets. The blood count subsequently improved, but the pancytopenia recurred few weeks later, another dose of ipilimumab was given and required administration of hematopoietic growth factors and IVIG [15].

Hematological toxicity is rare but can be fatal. These studies demonstrate the hematological side effects of immunotherapy and stress the need for increased patient safety monitoring. They also emphasize the importance of healthcare providers being familiar with rescue therapy for managing pancytopenia induced by anti-PD1 treatment. Immediate consultation with a hematologist for diagnosis and management is recommended. A bone marrow biopsy should be considered, especially to exclude other causes of pancytopenia, such as marrow infiltration, secondary myelodysplastic syndrome or plasma disease, or aplastic anemia.The management of hematological toxicity depends on the severity but includes symptomatic treatment, such as blood transfusion, administration of growth factors and corticosteroids [3].

In one series, 70% of hematological toxicities responded to corticosteroids, with second-line immunosuppressants, such as intravenous immunoglobulin, rituximab, and cyclosporine, in refractory cases. Eltrombopag, an oral thrombopoietin receptor agonist (TPO-RA), has shown efficacy in managing thrombocytopenia that does not respond to IVIG and corticosteroids [3, 16]. Consequently, discontinuation of immunotherapy is recommended. Subsequent continuation of ICI therapy should take into account the benefits and risks, noting that 20% of affected patients may have persistent cytopenias, and that continued or reintroduced therapy may carry a significant risk of exacerbation of symptoms [17].

European Society For Medical Oncology (ESMO) has published guidelines regarding the management of toxicity after immunotherapy:

- Early involvement of a haematologist is recommended, and Immunotheray should be withheld. Obtaining a bone marrow aspirate and trephine biopsy should be prioritized for diagnostic purposes, with a readiness to proceed even with a low suspicion threshold.
- Blood product and growth factor support in addition to corticosteroids 1 mg/kg should be initiated as first-line treatment.
- For patients who do not respond to standard therapies, eltrombopag or alternative oral thrombopoietin receptor agonists (TPO-Ras) should be considered [3].

Rechallenging patients after hematological toxicity is feasible in three scenarios. Firstly, a switch between anti-PD -L1 and anti-CTLA-4 therapy, or vice versa, may be considered if both classes are clinically relevant in the disease. Secondly, reintroducing the same

class of agent after resolving the immune-related adverse event (IRAE) is an option. Thirdly, resuming ICI alongside immunosuppressive therapy is also a possibility. However, certain studies suggest a deficiency in dependable predictive and prognostic factors for severe recurrent or distinct immune-related adverse events following the readministration of immunotherapy. In cases where severe initial IRAEs occur and therapeutic alternatives are limited, resuming ICI may be considered. Patients with severe IRAEs are frequently chosen for permanent ICI discontinuation in routine practice. Only patients with non-life-threatening, immunosuppression-sensitive, and resolved initial IRAEs should be considered for a single agent ICI rechallenge [18].

One group has provided a algorithm for reintroducing treatment to patients. Specifically for hemolytic anemia, they suggest a waiting period of several months before considering restarting treatment. Additionally, they recommend restarting treatment only when anti-CD-20 therapy is administered synchronously, either with or without high-dose intravenous immunoglobulin (IVIG). No indication is provided for other hematological toxicities. In small case series, the recurrence rates after rechallenge with ICI were : Hemolytic anemia: 1 in 2, Immune thrombocytopenia: 1 in 3, neutropenia 4 in 6, there is no information on the rate of recurrence after changing the class of ICI [4].

Future studies should focus on finding predictive biomarkers of immune-related hematologic adverse events and defining the optimal management algorithm.

CONCLUSION

As immunotherapy becomes increasingly common in treating metastatic melanoma and other cancers, physicians face new challenges. Learning from shared experiences is crucial in this unexplored territory. It's vital to recognize and manage the various immune-related adverse events that may occur during treatment. Close monitoring of blood counts is essential, and severe cytopenias (grade 3 or 4) should prompt immediate treatment cessation, with early administration of high-dose corticosteroids and immunoglobulins if necessary [1].

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Anonymization

« We confirm that exhaustive attempts have been made to contact the patient or their family, and that the document has been sufficiently anonymized to prevent any potential harm to the patient or their family. »

- ***Naranjo Adverse Drug Reaction Probability Scale***

Question	**Yes**	**No**	**Do Not Know**	**Score**
1. Are there previous conclusive reports on this reaction ?	+1	0	0	+1
2. Did the adverse event appear after the suspected drug was administered ?	+2	-1	0	+2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered ?	+1	0	0	+1
4. Did the adverse event reappear when the drug was re-administered ?	+2	-1	0	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction ?	-1	+2	0	+2
6. Did the reaction reappear when a placebo was given ?	-1	+1	0	0
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic ?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased ?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure ?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence ?	+1	0	0	0
TOTAL SCORE:				**6**

TOTAL SCORE: 6 (5-8): Probable. The reaction (1) followed a reasonable temporal sequence after a drug, (2) followed a recognized response to the suspected drug, (3) was confirmed by withdrawal but not by exposure to the drug, and (4) could not be reasonably explained by the known characteristics of the patient's clinical state.