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Case Report

Exploring Immune-Related Adverse Events: A Case of Febrile Neutropenia in a Melanoma Patient Receiving Immunotherapy

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Abstract
Introduction: The introduction of immune checkpoint inhibitors (ICIs) has opened a new chapter in cancer treatment. Nevertheless, their use may result in immune-related adverse events (irAEs) with multifactorial determinants, complex mechanisms, and varying clinical implications. In specific cancer types, like melanoma, irAEs exhibit a complex relationship with patient outcomes. ***Case Presentation:*** We present a case of febrile neutropenia following ICI therapy in a patient with metastatic melanoma, underscoring the intricate clinical landscape associated with irAEs in the context of cancer immunotherapy. More specifically, a 68-year-old man was diagnosed with metastatic malignant melanoma and administered a combination of nivolumab and ipilimumab. However, after a single dose, the patient was hospitalized due to febrile neutropenia. The patient eventually recovered, but a diagnosis of myelosuppression related to prior immunotherapy led to treatment discontinuation. Subsequently, the patient transitioned to a second-line therapy. ***Conclusion:*** This case contributes to our comprehension of rare yet potentially severe hematological irAEs and their influence on immunotherapy outcomes. Such insights will guide future diagnostic and therapeutic strategies in the field of immunotherapy.

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Introduction

The introduction of immune checkpoint inhibitors (ICIs) has presented a groundbreaking advancement in cancer therapy. ICIs have significantly enhanced the survival rates of cancer patients and have emerged as the primary treatment option for various tumor types. Nonetheless, the utilization of ICIs is commonly linked to immune-related adverse events (irAEs), which have the potential to impact various organs [1]. These irAEs manifest across a range of severity levels and tolerance, frequently requiring interruptions or discontinuation of treatment and the implementation of immunosuppressive treatments [1–3]. Although they can occur at any point during the treatment regimen, most frequently, these adverse events manifest within the first few weeks after the initiation of ICI therapy. In some instances, autoimmune toxicities may even emerge many months after treatment cessation [1]. While irAEs can impact virtually any organ in the body, they most commonly affect the skin, gastrointestinal tract, endocrine organs, and lungs [1–3].

The mechanisms underlying irAEs are not fully understood, but several hypotheses exist. One theory proposes that ICIs disrupt self-tolerance and encourage pre-existing autoimmunity by targeting programmed cell death protein 1 (PD-1) and cytotoxic T-cell antigen 4 (CTLA-4), which are crucial for preventing autoimmunity [4–6]. The shared antigen theory posits that self-antigens in both tumors and healthy organs trigger an immune response in non-tumor tissues. Similarly, the antigen mimicry hypothesis suggests that T cells targeting tumor neoantigens mistakenly target normal antigens in other organs [1–3]. Another theory involves immune cell-released inflammatory mediators causing tissue damage, leading to autoimmunity. Furthermore, irAEs may result from off-target ICI effects on non-blood cell types that express immune checkpoints. The microbiome is also thought to influence irAE development, with specific bacteria either promoting or protecting against irAEs and modulating cytokine production. These mechanisms likely interact with genetic and environmental factors [1].

Melanoma is an aggressive malignancy that originates from the malignant transformation of melanocytes, primarily found in the basal layer of the epidermis. This specific location renders cutaneous melanoma the most prevalent form of the disease [7]. Nonetheless, melanoma can manifest in less obvious locations, including the uvea, gastrointestinal tract, genitourinary tract, and meninges. During the course of their disease, up to 60% of patients with advanced melanoma develop brain metastases, significantly worsening their prognosis. Before the introduction of novel therapies, survival in these cases rarely exceeded 6 months [7, 8].

During the past decade, we have witnessed substantial progress in the development of advanced melanoma treatment strategies. Immunohistochemistry and genetic tumor analysis have gained importance in diagnosis. Melanoma stands out for its immunogenicity and high mutational burden, with molecular profiling playing a crucial role in management [7]. To date, over 20 genes implicated in melanoma pathogenesis have been identified, with the most frequent mutations occurring in BRAF, NRAS, and KIT oncogenes [8, 9]. Presently, two primary categories of systematic therapy are available for melanoma. The first encompasses the use of ICIs, targeting CTLA-4 and PD-1. The second approach includes drugs targeting key protein kinases involved in melanoma pathogenesis, such as BRAF and MEK [9, 10].

In this case report, we present a patient with metastatic melanoma who received the first cycle of nivolumab-ipilimumab. The patient was hospitalized due to febrile neutropenia as a side effect of immunotherapy. In addition, the CARE Checklist has been completed for this case report, which is included as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000536288).

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Case

A 68-year-old man was diagnosed with metastatic malignant melanoma on May 30, 2023, after surgical excision of a mass in the right axillary region. In his past medical history, the patient reported hypertension, diabetes mellitus, dyslipidemia, and peripheral vasculopathy. He was a smoker and a frequent alcohol consumer. There was also a positive family history of cancer; his father had been diagnosed with lung cancer. Following biopsy results, computed tomography (CT) staging revealed brain metastases, lung metastasis in the right lower lobe, lymphadenopathy in the area of the right bronchus, and two other metastases in the right perinephric space and the left rectus abdominis muscle. The patient underwent whole brain radiation therapy with the last session taking place on June 8, 2023. The molecular profile of the tumor revealed a BRAF V600E mutation.

As a next step, we decided to initiate combined immunotherapy with nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) eventually commencing on June 26, 2023. His blood test results were as follows: white blood count (WBC) at 6,880/μL with neutrophils (NEU) at 3,230/μL, hemoglobin (Hb) at 10.8 g/dL, and platelets (PLT) at 375,000/μL. However, after a single dose, the patient was hospitalized due to febrile neutropenia.

Specifically, on the first day of his hospitalization, July 17, 2023, his WBC was 1,600/μL, with NEU = 50/μL. His Hb level was 9.2 g/dL. He presented with a fever that had started 24 h prior to his hospitalization, reaching a maximum temperature of 39.1°C, without other symptoms. He remained in good clinical condition. Other blood tests revealed an elevated C-reactive protein (CRP) level of 146 mg/L (normal upper limit 6 mg/L). Blood and urine cultures were obtained, and we initiated antibiotics (meropenem 2 g × 3) and granulocyte-colony stimulating factor (G-CSF) as a precautionary measure.

On the second day of hospitalization, July 18, the patient remained in good clinical condition but continued to experience fever episodes, with WBC at 1,620/μL and NEU at 50/μL. Additionally, there was a deterioration of anemia (Hb = 8.2 g/dL, hematocrit [Ht] = 27.5%), necessitating a blood transfusion. Due to the persistent fevers, an infectious disease specialist recommended a comprehensive virus test, a complete polymerase chain reaction (PCR) test for respiratory pathogens, and CT scans to rule out abscesses. Vancomycin was also added to his treatment (1 g × 2).

Over the next 2 days, July 19–20, we observed a significant decrease in WBC (WBC = 1,630/μL, NEU = 20/μL). On July 20, the patient experienced difficulty swallowing and hoarseness. An otorhinolaryngologist examination revealed throat redness with mycosis, leading to the addition of antifungal medication (fluconazole).

On July 21, we decided to perform a bone marrow biopsy. While awaiting the biopsy results, we initiated corticosteroid treatment with methylprednisolone 40 mg × 2 (1 mg/kg/d) as indicated by ESMO guidelines. The bone marrow report indicated no stem cell infiltration but an absence of a medullary series.

From July 23 to July 27, we observed a significant improvement, with a decline in CRP and stabilization of WBCs. Notably, procalcitonin remained negative throughout hospitalization. Blood and urine cultures were also negative. The patient remained clinically stable and afebrile from July 28 until his discharge, with WBCs at 44,840/μL and NEU at 38,760/μL (due to G-CSF).

On August 1, 2023, the bone marrow biopsy results became available. The report indicated complete maturation arrest and lymphocytic infiltration (15–20% by small T-cells with an interstitial pattern), suggesting myelosuppression related to prior immunotherapy. The patient was finally discharged on August 3, with a corticosteroid therapy prescription (methylprednisolone with gradual dose tapering) for 2 months. Online supplementary Table 1 shows the summarized values of the patient's blood tests from start of treatment until recovery.

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Due to the serious side effects of immunotherapy, we decided to discontinue nivolumab and ipilimumab and initiate BRAF and MEK inhibitor combination. The first cycle commenced on September 6, 2023, with a scheduled CT restaging during the upcoming appointment.

Discussion

The hematological irAE is a rare immunological side effect. In recent years, the expanded approvals of novel ICI products and their increased clinical applications have led to a gradual increase in associated incident reports [5]. In the context of hematological toxicity linked to ICIs, anemia and thrombocytopenia are the predominant adverse events, whereas neutropenia is considered a rare occurrence among hematological irAEs. The median onset of neutropenia is observed at 10.5 weeks after the initial ICI treatment, with a range spanning from 2.2 to 25.4 weeks [3–6].

Here, we present a case report of neutropenia occurring after the first dose of ICIs (4 weeks after administration) and recovery within 11 days. The diagnostic principles and underlying mechanisms for neutropenia associated with ICIs remain unclear. To exclude other causes of neutropenia, a bone marrow biopsy was conducted to reach a diagnosis. Therapeutically, we administered both corticosteroids and G-CSF, resulting in a rapid patient recovery. Unfortunately, following this complication, it became necessary to discontinue immunotherapy and switch to a second-line treatment.

A particularly intriguing aspect of ICI-induced irAEs is their association with improved patient survival. This is supported by several systematic reviews and meta-analyses. This association appears particularly strong in certain cancer types, such as melanoma. Patients who develop ICI-induced irAEs tend to experience enhanced overall survival and progression-free survival and a reduced risk of death [1–3]. Low-grade irAEs and specific types of irAEs, such as dermatological and endocrine irAEs, exhibit a more pronounced association with improved survival [1, 2]. Cancer patients receiving ICIs frequently develop two or more irAEs. In this context, a recent study has demonstrated that the more irAEs a patient experiences, the better their survival. However, it is essential to note that not all irAEs are associated with improved survival. High-grade (G3-5) and more severe irAEs, including pneumonitis, hepatitis, neurotoxic effects, and myocarditis, are typically not linked to improved survival [1–3]. A rare side effect that is not commonly mentioned is myelosuppression, which can clinically manifest as febrile neutropenia [3–6].

We conducted a review of previously published case reports focusing on neutropenia diagnosed through bone marrow testing. Our search identified 19 cases involving patients with lung cancer or melanoma. In 16 cases, immunotherapy was discontinued due to toxicity. Concurrent thrombocytopenia and/or anemia were diagnosed in 10 cases. The majority of bone marrow tests indicated hypoplastic bone marrow. Treatment strategies included G-CSF and corticosteroids, with intravenous immunoglobulin deemed necessary in some instances. Additionally, 1 case involved the administration of cyclosporine as a treatment. Among these cases, 5 individuals experienced persistent neutropenia without a positive response to therapy. An extensive summary of the 19 cases can be found at the following link: https://doi.org/10.5281/zenodo.10475685 [11–29].

Numerous investigations have suggested a link between irAEs and the therapeutic effectiveness of anti-PD-1 treatment across various tumor types, including non-small cell lung cancer, melanoma, and gastric cancer [1]. The findings indicate that individuals in the non-irAE group independently experienced an unfavorable prognosis. Conversely, the presence of low-grade irAEs predicted improved treatment efficacy. However, in cases where side effects are severe and discontinuation of immunotherapy is mandatory, the prognosis is worse [1–3].

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Therefore, it is essential to understand which patients are more likely to benefit from immunotherapy in order to make treatment decisions more precise [1–3]. Specifically, various factors can influence the effectiveness of immunotherapy, including age, immune system status, and the presence of tumor-infiltrating lymphocytes. These factors suggest that the use of multifactor predictive models, rather than single markers, would provide enhanced prognostic capabilities. An in-depth understanding has the potential to improve our ability to manage adverse effects and further advance the field of immunotherapy [1, 2].

Conclusion

In summary, this case illustrates that grade 4 neutropenia, a rare but potentially severe adverse event associated with ICIs, often leads to infectious complications. While some limitations were apparent in our approach, such as the timing of glucocorticoid therapy and the potential benefits of combining intravenous immunoglobulin treatment, our experience highlights the importance of early intervention. This case contributes to the growing body of knowledge regarding the hematological immune-related adverse effects of ICIs, providing additional insights and experiences to guide future diagnostic and treatment strategies in the area of immunotherapy.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of General University Hospital of Ioannina (protocol code 1.046/16-11-2023).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.Y., N.T., A.-L.A., F.K., E.K., G.Z., and D.M. contributed equally to the study as well as to the preparation of the manuscript for publication.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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