













Pembrolizumab associated hypereosinophilia in locally advanced triple-negative breast cancer

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Abstract

The advent of immunotherapy has revolutionized the therapeutic landscape of breast cancer. The immune checkpoint inhibitor drug, pembrolizumab, a monoclonal antibody targeting programmed cell death protein 1 (PD-1), was recently approved by the Food and Drug Administration (FDA) as a neoadjuvant treatment in combination with traditional chemotherapy in locally advanced triple-negative breast cancer (LA-TNBC). This manuscript aims to highlight an uncommon adverse event of immune checkpoint inhibitors (ICIs): hypereosinophilia (HE). Herein, we report the case of AW, a 49-year-old female patient, who was treated for triple-negative breast cancer (TNBC) with pembrolizumab, achieving a complete response. After undergoing surgery, pembrolizumab was reintroduced as adjuvant therapy, at which point an abnormal increase in eosinophil count was observed. Hence, treatment was interrupted, and after glucocorticoid administration, the eosinophil count reverted to normality. Our findings underscore the necessity for vigilant monitoring of blood eosinophil levels during pembrolizumab therapy and provide insights into the management of such immunotherapy-related adverse events.

Keywords

Breast cancer, hypereosinophilia, immune-checkpoint inhibitors, pembrolizumab, programmed cell death protein 1 (PD-1)



Introduction

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies (mAbs) that block inhibitory molecules involved in the regulation of immune pathways, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), or its ligand programmed cell death protein ligand 1 (PD-L1) in the tumor microenvironment, which leads to systemic immune cell activation [1]. Pembrolizumab, a humanized IgG4 kappa anti-PD-1 mAb, has been extensively investigated in several malignancies, including melanoma, non-small cell lung cancer (NSCLC), and lymphomas [2]. PD-1 is a cell surface receptor expressed on T cells, B cells, and macrophages after they have been activated [3]. The primary ligands for PD-1 are PD-L1 and PD-L2, which both belong to the B7 family. When PD-1 binds to its ligands, it inhibits the proliferation of T cells, reduces cytokine production, and can lead to the apoptosis of antigen-specific T cells while promoting the survival of regulatory T (Treg) cells [4]. This interaction is an essential component of the immune response that helps prevent tissue damage during inflammation and maintain tolerance to self-antigens. However, many cancer cells exploit this regulatory pathway to evade immune detection and consequent destruction [5].

Immunotherapy strategies targeting the PD-1/PD-L1 axis have been developed to block this interaction, thereby enhancing the immune system's ability to fight cancer [6]. Pembrolizumab has shown promising results in locally advanced triple-negative breast cancer (LA-TNBC). Recently, the Food and Drug Administration (FDA) approved its use in combination with chemotherapy as a neoadjuvant treatment, followed by adjuvant monotherapy post-radical surgery in patients with high-risk LA-TNBC [7, 8]. Despite its efficacy, pembrolizumab is associated with a spectrum of immune-related adverse events (irAEs) [9, 10] among which hypereosinophilia (HE) remains rare but significant [11, 12]. This case report highlights the critical need for awareness and understanding of such irAEs to optimize patient care.

Case report

AW, a 49-year-old woman with a history of hypothyroidism, bronchial asthma, and allergic rhinitis, was diagnosed with LA-TNBC in March 2022. From 17 August 2022 to 6 March 2023, she underwent neoadjuvant chemotherapy with carboplatin and paclitaxel on weekly administrations for 12 cycles, supplemented by pembrolizumab (200 mg e.v. every 3 weeks), followed by 4 cycles of epirubicin and cyclophosphamide in addition to pembrolizumab. In April 2023 she underwent a left total mastectomy with left axillary lymph node dissection, achieving pathological complete response (ypT0N0). From 29 June 2023 to 18 July 2023, the patient underwent adjuvant radiotherapy. Concurrently, the medical treatment plan incorporated the prosecution of nine cycles of immunotherapy with pembrolizumab. Table 1 represents a timetable in which are displayed radiological findings and biopsy reports from the time of disease detection through neoadjuvant medical treatment, surgery, and adjuvant radiotherapy. Pembrolizumab administration was halted on August 14th, 2023, following the identification of persistent and progressive eosinophilia (initial eosinophil count: 0.4×10^3 cell/ μ L; peak value 5.6×10^3 cell/ μ L), as illustrated in Figure 1. Therefore, she was admitted to the Clinical Immunology Division of the University of Naples Federico II on December 4th, 2023, where further diagnostic tests were performed to rule out primary and secondary causes of HE. The patient was apparently asymptomatic except for worsening of her diagnosed bronchial asthma. Furthermore, there was no evidence of systemic involvement on physical examination.

Immunophenotype and genetics for *FIP1L1-PDGFR*A were performed, both resulting in negative; stool test and parasitological fecal examination on three specimens for eggs and parasites were also negative. Serum IgG for *Strongyloides stercoralis*, serum antigen of *Cryptococcus neoformans*, *Aspergillus* galactomannan antigen, and serum Quantiferon test ruled out infectious causes of HE. Liver function tests, cortisol levels, and vitamin B12 levels were also normal. A cardiac ultrasound, cardiac enzymes, and electrocardiogram revealed no abnormalities. The patient also underwent bone marrow aspiration and biopsy, which showed trilinear, normo-cellular marrow with a prominent proportion of eosinophilic granulocytes. During hospitalization, the eosinophil blood count value was consistently elevated despite discontinuation of pembrolizumab. Given the negativity of all the diagnostic and instrumental tests

Table 1. Timetable of radiological imaging and biopsy reports over the time from disease detection

Date	Imaging/Procedure	Summary
17/03/2022	Breast US	Dense glandular tissue, fibrocystic mastopathy. Suspicious left axillary lymph node (22 × 20 mm).
18/03/2022	Mammography	Dense parenchyma with nodular aspects, no pathological calcifications. Axillary lymph nodes present.
07/04/2022	Axillary core biopsy	Poorly differentiated carcinoma with squamous features.
19/04/2022	Breast MRI	Large heterogeneous lesion in left breast (> 42 mm), enlarged left axillary lymph node (> 45 mm), BIRADS 5.
19/04/2022	Full-body CT scan	Enlarged left axillary lymph nodes, small liver and ovarian cysts, mild left pleural effusion.
18/05/2022	PET scan	Pathological hyperaccumulation in left breast (SUV _{max} 6.3), bilateral lymph node involvement. Indeterminate pelvic lesion.
20/05/2022	Abdomen US	Hepatomegaly with small angioma (5 mm), distended gallbladder, no peritoneal fluid.
01/06/2022	Mammary and axillary biopsy	High-grade invasive carcinoma (ER ⁻ /PR ⁻ /HER2 ⁻ , Ki-67 40%). Lymph node involvement confirmed.
14/08/2022–06/03/2023	Neoadjuvant chemotherapy	Carboplatin/paclitaxel + pembrolizumab (12 cycles), followed by epirubicin/cyclophosphamide + pembrolizumab (4 cycles).
12/12/2022	Mammography	Reduction in left breast mass (19 mm vs 33 mm), persistent axillary lymphadenopathy.
09/12/2022	Full-body CT scan	Stable mammary and lymph node lesions. Ascending aortic aneurysm (42 mm).
13/03/2023	Abdomen US	Small gallbladder adenomyoma (5 mm).
14/03/2023	Breast US	Left fibroadenoma (15 mm), reactive axillary lymphadenopathy bilaterally.
27/03/2023	PET scan	Stable left breast lesion improved axillary lymph nodes.
29/03/2023	Breast MRI	Persistent left breast nodules (12 mm vs 15 mm), BIRADS 6.
14/04/2023	Left total mastectomy and axillary dissection	Fibrocystic changes. Negative margins. 10 lymph nodes disease-free. Pathological stage: ypT0N0.
29/06/2023–18/07/2023	Radiotherapy	42.56 Gy to left breast, supraclavicular/subclavian nodes, and internal mammary chain. Mild skin toxicity (G1).
29/06/2023–04/08/2023	Immunotherapy	Pembrolizumab.
14/10/2023	Breast US	Post-mastectomy changes. Right breast with cystic and dysplastic nodules. Normal lymph nodes.
24/10/2023	Full-body CT scan	Mild pulmonary changes, left mastectomy without recurrence, hepatomegaly.

US: ultrasound; BIRADS: breast imaging reporting and data system

performed, she was discharged with a diagnosis of pembrolizumab-related HE and an indication to start therapy with prednisone 25 mg per day with progressive tapering into 2 weeks. Monthly peripheral blood eosinophil counts were performed after the discontinuation of the glucocorticoid therapy and showed a normalization of blood eosinophil levels from one month after hospital discharge, with collateral improvement in the symptoms of bronchial asthma.

Discussion

ICIs provide clinical benefit in a percentage of patients with advanced cancer, but they are usually associated with a remarkable spectrum of irAEs [9, 10, 13]. Although any organ system can be involved, hematological irAEs such as anemia, thrombocytopenia, and neutropenia are less frequently observed [14]. Nevertheless, some cases of ICI-induced HE have been documented across different malignancies, underlining the need for vigilance [15]. Most irAEs resolve either pharmacologically or after discontinuation of ICIs, but some appear to be persistent. Glucocorticoids are the mainstay of irAEs management [16]. However, other immunosuppressive drugs can be used to treat refractory irAEs [17].

Eosinophilia is defined as a peripheral blood eosinophil count above the upper limit of normal, which typically represents 3–5% of peripheral leukocytes, translating to an absolute eosinophil count (AEC) of 0.35–0.5 × 10⁹/L [18]. The severity of eosinophilia is stratified into mild (AEC up to 1.5 × 10⁹/L), moderate

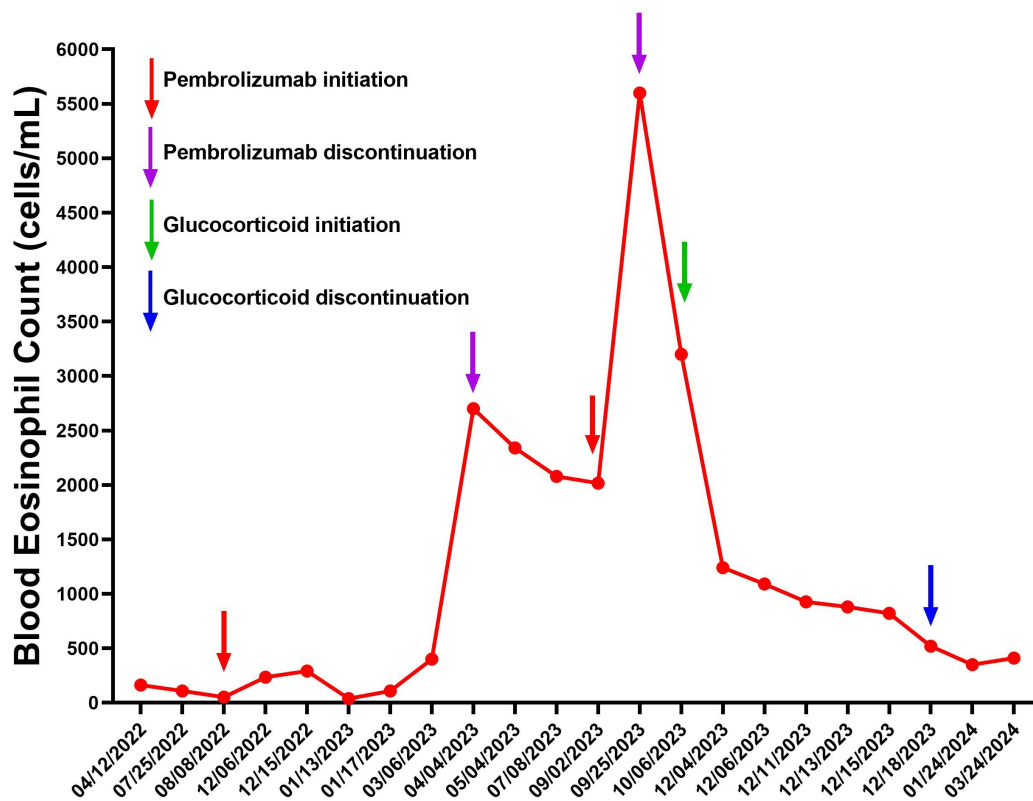


Figure 1. Peripheral blood eosinophil count before, during, and after pembrolizumab therapy

(AEC $1.5\text{--}5 \times 10^9/\text{L}$), and severe (AEC $> 5 \times 10^9/\text{L}$). HE is, therefore, clinically established upon detection of an AEC exceeding $1.5 \times 10^9/\text{L}$ on two distinct occasions, separated by a minimum time frame of one month [18]. HE includes a broad range of non-hematologic (secondary or reactive) and hematologic (primary or clonal) disorders with the potential for end-organ damage. Essentially, all organ systems can be susceptible to prolonged eosinophilia [19]. Dermatological involvement is the most common clinical manifestation reported in 69% of patients, followed by pulmonary (44%) and gastrointestinal (38%) manifestations. Cardiac disease unrelated to hypertension, atherosclerosis, or rheumatic disease has been identified in 20% of patients [20]. In a study involving 146 patients receiving various ICIs, including pembrolizumab, eosinophilia developed in 22% of patients during treatment [21]. Few cases of eosinophilia associated with pembrolizumab administration have been described in the literature. Baroz et al. [22] highlighted that pembrolizumab, used as a first-line systemic therapy in patients with NSCLC, can lead to high blood eosinophil counts. Furthermore, Soto and collaborators [23] described a case of eosinophilia associated with severe asthma and sarcoidosis one month after starting pembrolizumab for metastatic nasopharyngeal carcinoma, successfully treated with interleukin-5 (IL-5) inhibition. Harada et al. [24] have recently reported a case of asthma exacerbation with HE and elevated serum IL-5 in a patient undergoing pembrolizumab therapy for endometrial cancer. Khoja et al. [25] also observed eosinophilia in association with eosinophilic fasciitis and acute encephalopathy toxicity due to pembrolizumab used for the treatment of metastatic melanoma. HE can occur even months after the start of pembrolizumab treatment, as reported in this case.

To our knowledge, this report is the first documentation of pembrolizumab-induced HE in the context of LA-TNBC. This case underlines the imperative for clinicians to maintain a high index of suspicion for this rare but significant adverse effect.

The pathophysiological mechanisms underlying pembrolizumab-associated HE remain largely unknown, but several hypotheses have been proposed. One potential explanation involves the disruption of immune homeostasis due to PD-1 blockade, leading to an unregulated activation of eosinophils. PD-1 plays a critical role in maintaining immune tolerance, and its inhibition may result in excessive T-cell activation,

particularly Th2-mediated immune responses, which promote eosinophil recruitment and activation. Additionally, pembrolizumab-induced HE may be linked to increased levels of IL-5, a key cytokine in eosinophil proliferation and survival, as observed in prior reports of pembrolizumab-related eosinophilic complications. The tumor microenvironment, particularly in highly immunogenic cancers such as TNBC, may also contribute to this phenomenon by altering the immune landscape following neoadjuvant chemotherapy and immunotherapy. Changes in cytokine profiles and immune cell infiltration, including shifts in tumor-infiltrating lymphocytes (TILs), may play a role in the development of HE as an irAE. Future studies investigating cytokine signatures and immune cell dynamics in patients receiving ICIs could provide further insight into the mechanisms responsible for pembrolizumab-induced HE.

The management of pembrolizumab-induced HE requires its discontinuation as the first intervention. If eosinophilia persists despite discontinuation of the drug, treatment with glucocorticoids is necessary. As shown in our case, glucocorticoid therapy caused a rapid reduction of peripheral blood eosinophils. Published guidelines from the National Comprehensive Cancer Network (NCCN) [26], European Society for Medical Oncology (ESMO) [27], and American Society of Medical Oncology (ASCO) [28] outline recommendations for the management of immunotherapy-induced HE. These guidelines emphasize the importance of regular monitoring of eosinophil counts, early recognition of eosinophilia, and comprehensive evaluation to rule out secondary causes such as infections, hematologic malignancies, or autoimmune conditions. In cases of mild or asymptomatic HE, close observation is suggested, whereas moderate to severe eosinophilia, particularly if accompanied by organ involvement, necessitates immediate intervention with high-dose corticosteroids. In refractory cases, additional immunosuppressive therapies such as IL-5/IL-5R α inhibitors, including mepolizumab or benralizumab, may be considered. Reintroduction of pembrolizumab may be cautiously attempted following resolution of HE, but recurrence mandates permanent discontinuation. These recommendations align with our management approach, reinforcing the need for vigilance in monitoring immune-related hematological toxicities and the role of immunosuppressive therapies in mitigating these adverse effects.

TNBC is known for its high immunogenicity, which contributes to its responsiveness to immunotherapy and neoadjuvant chemotherapy. This is partly due to the presence of elevated TILs, which have been associated with improved clinical outcomes and a higher likelihood of achieving pathological complete response [29]. Neoadjuvant chemotherapy can induce modifications in the tumor immune microenvironment, potentially influencing both treatment efficacy and the development of irAEs. Although in our case TIL density and PD-1/PD-L1 expression were not assessed before or after treatment, future studies incorporating these biomarkers could provide valuable insights into the mechanisms underlying both treatment response and immunotherapy-related toxicities.

In conclusion, our case report illustrates a rare late onset of HE associated with pembrolizumab in the treatment of early LA-TNBC. This case highlights the need for awareness among clinicians regarding potential hematological side effects of ICIs. The lack of resolution of HE following discontinuation of pembrolizumab and the need of glucocorticoid therapy suggests a manageable approach to this adverse event. HE requires specific treatment, as it can be associated with cardiovascular, neurologic, and thrombotic events [30, 31]. Therefore, clinicians should consider HE as a possible side effect associated with pembrolizumab therapy. This report adds to the growing evidence on ICI safety profiles and calls for further research to elucidate the mechanisms underlying such immune-mediated adverse events.

Abbreviations

AEC: absolute eosinophil count

HE: hypereosinophilia

ICIs: immune checkpoint inhibitors

IL-5: interleukin-5

irAEs: immune-related adverse events

LA-TNBC: locally advanced triple-negative breast cancer

mAbs: monoclonal antibodies

NSCLC: non-small cell lung cancer

PD-1: programmed cell death protein 1

PD-L1: programmed cell death protein ligand 1

TILs: tumor-infiltrating lymphocytes

Declarations

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Author contributions

RP, AC, CGT, AdP, and GV: Conceptualization, Investigation, Writing—original draft, Writing—review & editing, Validation, Supervision. AdS, LS, ES, MTN, and MW: Conceptualization, Investigation, Writing—original draft, Writing—review & editing. All authors read and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

The research complies with the Declaration of Helsinki. This case report does not require ethical approval according to the requirements of the author's country or institution.

Consent to participate

Informed consent to participate in the study was obtained from the participant.

Consent to publication

Informed consent to publication was obtained from the participant.

Availability of data and materials

Datasets generated by this study are available upon request from the author (gildanet@gmail.com).

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