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Case Report

Durable Response to Programmed Death 1-Directed Antibodies in a Hypermutated Triple-Negative Breast Cancer: A Case Report

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Keywords
Triple-negative breast cancer · Programmed death 1 · Microsatellite instability-high · Immune-oncology · Hypermutated tumor · Next-generation sequencing · Case report

Abstract
Introduction: The advent of immune checkpoint inhibitors marks significant progress in the evolution of cancer treatment. Recent clinical trials have demonstrated the success of immune-oncologic (IO) agents like pembrolizumab (Keytruda™) in combination with chemotherapy against triple-negative breast cancer (TNBC) [Ann Oncol. 2017 Jun 1;28(6): 1388–1398]. There is less literature investigating pembrolizumab in monotherapy and in cases of rare tumor mutational burden. ***Case Presentation:*** Here, we report the case of a 65-year-old Native American and African American woman with previous incomplete lines of therapy diagnosed with recurrent TNBC and pulmonary metastases. Next-generation sequencing of the metastatic nodules demonstrated a significantly hypermutated tumor with rare polyploidy. The patient had a durable (14 months) response and ongoing remission of the metastatic lesions after administering the programmed cell death 1 inhibitor pembrolizumab. No serious immune checkpoint inhibitor-related toxicities or disease progression was observed during the treatment. ***Conclusion:*** Our report describes recurrent TNBC with a rare amount of hypermutation and the successful use of an IO agent as a treatment.

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Introduction

Immunohistochemical analysis is used to determine the breast cancer subtype, which allows the determination of the level of expression of receptors on the surface of tumor cells, including estrogen receptors (ERs), progesterone receptors (PRs), and oncoprotein human epidermal growth factor receptor 2 (HER-2/neu – the second epidermal growth factor receptor). One of the most challenging subtypes to treat is triple-negative breast cancer (TNBC), in which ER, PR, and HER-2/neu are absent or detected in deficient concentrations. TNBC makes up 10–20% of diagnoses and warrants complex treatment and invasive measures [1]. The main components of combined treatment are varied types of surgical removal of the tumor and areas of metastasis and topical treatment with radiation therapy and nonspecific chemotherapy in neoadjuvant and adjuvant regimens. The notably aggressive features of TNBC include but are not limited to early onset age, lack of durable therapeutic targets, and higher likelihood of recurrence and metastasis. Identification of accurate biomarkers is being researched, seeing as a relatively small amount of TNBCs are responsive to immune-oncologic (IO) agents or IO antibody-drug conjugates [2].

Recently, IOs have been trialed with patients who have TNBC and had limited success as a monotherapy option [3]. Little information is available regarding the response of TNBC to IO agents, let alone hypermutated recurrent metastases [4]. In this report, we discuss the use of pembrolizumab, a specific humanized IgG4 kappa monoclonal antibody that inhibits the programmed cell death 1 (PD-1) receptor [5]. PD-1 is a critical element in regulating immune checkpoints within the tumor microenvironment [4, 5].

African American (AA) and Native American women are most likely to be diagnosed with TNBC, indicating a disproportionate burden of TNBC in this population [6, 7]. However, there are no documented differences in the tumor microenvironment among ethnic groups [6, 7]. This case exemplifies the use of PD-1 monotherapy in an AA/AI woman with extremely high tumor mutational burden (TMB) and microsatellite instability (MSI) status, indicating that monotherapy IOs could be an efficacious first-line treatment in patients with similar alterations. The authors have completed the CARE Checklist for this case report, which is attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000535743).

Case Presentation

A 65-year-old AA and Native American woman was diagnosed with right breast ER negative, PR negative, HER-2 equivocal by immunohistochemistry, and positive by fluorescence in situ hybridization (ratio: 3.1) invasive carcinoma pT2N0 in 2013 (Fig. 1). She underwent a right partial mastectomy and SLNB at the time of diagnosis (2013) and initially received adjuvant treatments with vinorelbine (Navelbine™) and trastuzumab (Herceptin™). In September 2019 (6 years after initial diagnosis), a right breast core-needle biopsy for a palpable abnormality in the lumpectomy bed revealed invasive ductal carcinoma grade three TNBC by immunohistochemistry and fluorescence in situ hybridization (ratio: 1.4). In November 2019, the patient received two cycles of neoadjuvant doxorubicin hydrochloride (Adriamycin™) and cyclophosphamide (AC) with cumulative doses of 244 mg and 2,440 mg, respectively. AC was discontinued owing to diastolic heart failure, fatigue, and electrolyte imbalance.

She underwent a right partial mastectomy with axillary lymph node dissection in November 2019 (6 years post-initial diagnosis), which confirmed recurrent TNBC. She received 18 fractions of radiation, 45 Gy, and she elected for medical monitoring rather than further lines of therapy.

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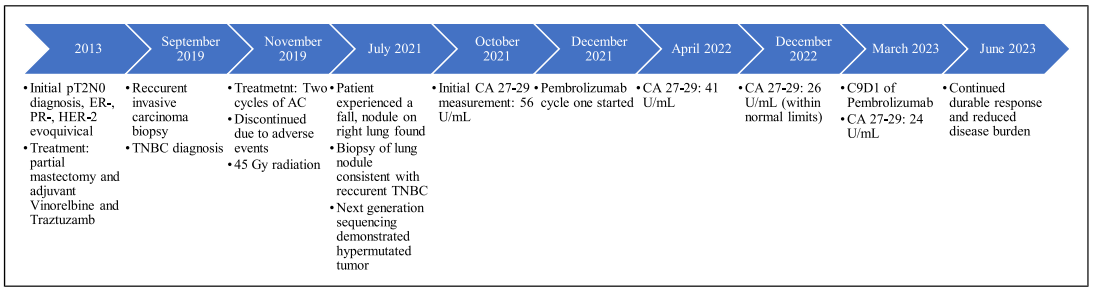

Fig. 1. Case report timeline.

In July 2021 (8 years post-initial diagnosis), the patient fell and sustained a humoral head and several rib fractures. A chest computed tomography (CT) scan obtained during the hospitalization revealed a 1-cm nodule in the right lower lobe of her lung, new from prior imaging from August 2020. Positron emission tomography/CT demonstrated a 1.4-cm FDG-avid pulmonary nodule and FDG-avid nodular soft tissue thickening in the right breast and axilla (Fig. 2). CT-guided biopsy of the pulmonary nodule showed two cores of poorly differentiated carcinoma, consistent with invasive ductal carcinoma (ER 0%, PR 0%, and HER2 negative). Subsequent next-generation sequencing showed a TMB of 59 muts/mb and MSI-high status of the metastatic tissue.

The hypermutated tumor was notable for multiple copy gains, including MSI-high status and amplifications in programmed cell death ligand 1 (PD-L1), CD274, programmed cell death ligand 2, neurofibromatosis type 1, myelocytomatosis oncogene amplification, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha amplification, BRCA2-interacting transcriptional repressor EMSY (C11orf30) amplification, Raf-1 proto-oncogene, serine/threonine kinase amplification, and telomerase RNA component amplification. Notable alterations and missense matches included missense match EGFR ring finger protein 43 alteration, cyclin-dependent kinase inhibitor 1A alteration, cyclin-dependent kinase inhibitor 2B alteration, checkpoint kinase 1 alteration, cAMP response element-binding protein alteration, DNA methyltransferase 3 alpha alteration, inhibitor of DNA binding 3 alteration, Janus kinase 1 alteration, Janus kinase 2 alteration, parkin RBR E3 ubiquitin-protein ligase alteration, protein regulator of cytokinesis 1 alteration, Tet methylcytosine dioxygenase 2 alteration, and transformation-related protein 53 alteration.

The MSI-high status, TMB of 59 muts/mb, and copy gain mutations indicated that the patient could have a durable response to immunotherapy. She began pembrolizumab on 29 December 2021 (8 years post-initial diagnosis) (Fig. 1). Her CA 27–29 was measured before cycle one, on 13 October 2021, and was 56 U/mL. Six months after treatment, on 11 April 2022, CA 27–29 fell to 41. At 1 year, it fell to 32 U/mL. CA 27–29 fell to 26 U/mL within the normal limits C9D1 on 21 December 2022 and has continued to fall to 24 U/mL as of 6 March 2023. She responded exceptionally to pembrolizumab with a reduced disease burden (Fig. 2, 3). She did not experience typical adverse events such as acute pneumonitis and cytokine release syndrome, which are usually associated with IO agents. Her initial success with pembrolizumab indicated a durable response, as patients with initial disease burden reduction exhibit durable disease reduction in other disease groups [2, 8]. The metastatic pulmonary lesions demonstrated a drastically reduced 18F-FDG uptake, stabilizing for 14 months (Fig. 3).

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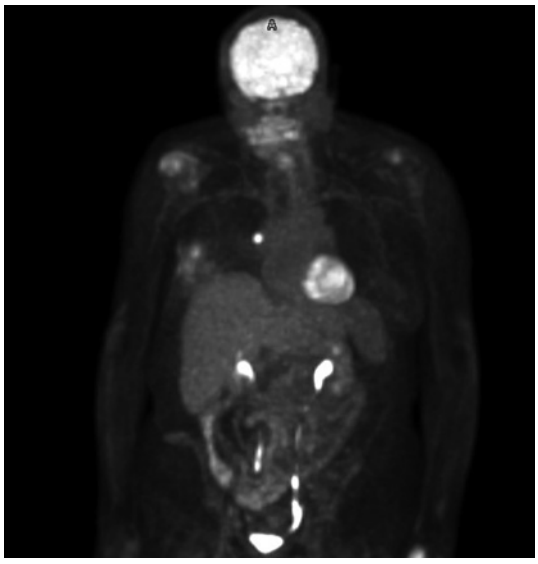

Fig. 2. Initial staging ^{18}FDG-PET scan of the patient showing region of ^{18}FDG uptake in the right lung, right breast, and axilla. PET, positron emission tomography.

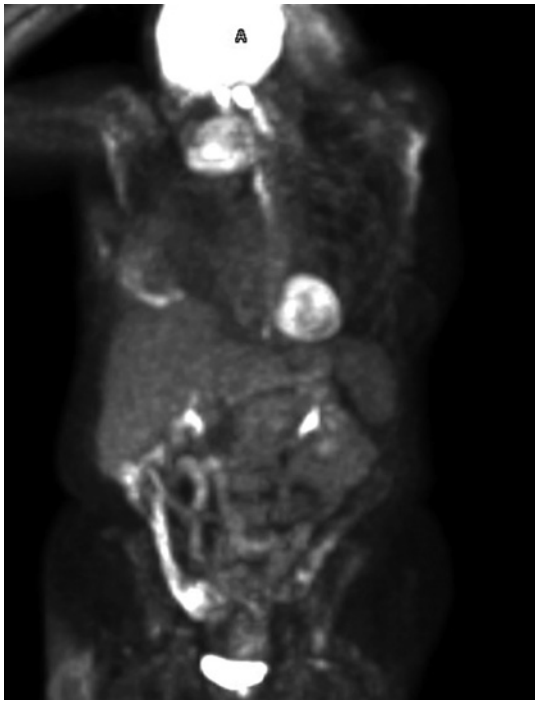

Fig. 3. Staging scan from December 2022, ^{18}FDG-PET scan of the patient showing region of ^{18}FDG uptake in the right breast and axilla, minus left lung lesion. PET, positron emission tomography.

Discussion

This patient presented with clinical challenges, given her performance score and significant comorbidities, including heart disease, hypertension, diabetes mellitus type one, lung disease, and non-healing foot ulcers, which prevented her from receiving further cytotoxic therapy. Moreover, an extremely high TMB and MSI-high status indicated that an IO agent would be effective [1–4, 7, 9, 10]. Extensive genomic findings from next-generation sequencing, including amplifications and alterations, suggest the presence of polyploidy. Breast cancer typically has a median TMB of 2.6 muts/mb, which is lower than other cancers for

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which immunotherapy is commonly used [9, 11]. For example, the median is 7.2 mut/mb in lung cancer and 13.5 mut/mb in melanoma [12, 13]. Commonly, high TMB is defined as ≥10 mut/mb, of which approximately 5% of all breast cancer cases (including all breast cancer subtypes) are considered TMB-high [14]. In addition, 10% of TNBC cases are PD-L1-positive (defined as ≥ 1% tumor or immune cell expression) [11, 14–16]. This patient's hypermutated tumor is remarkable for areas of mutation like parkin RBR E3 ubiquitin-protein ligase and MSI-high status not typically seen in TNBC, especially given the compounding of MS-high, high TMB, and extensive polyploidy [12, 15, 17, 18].

The progression of this patient to a hypermutated tumor and high level of genetic mutations may be associated with resistance to previous incomplete systemic therapy, which included a genotoxic agent, failure to complete longitudinal radiation, and the development of metastases. The lesion's differentiation into TNBC may be caused by the instability of cells in metastatic lesions and the compounding of mutations over time with cell division at new sites [15]. MSI-high status is observed in less than 5% of TNBC cases [15, 18]. However, this does correspond to the idea that the prevalence of hypermutation can be significantly higher in metastatic tumors than in primary tumors [4, 10]. The limitations associated with this report include a need for access to initial tumor biopsy samples. Therefore, we could not use next-generation sequencing to compare the original primary and recurrent tumors' genetic makeup. In addition, as this patient was initially diagnosed and began treatment at an outside facility, a complete picture of the electrolyte imbalance that contributed to AC discontinuation could not be determined.

The results of the KEYNOTE-119 study suggest that early-line treatment of PD-L1/2-positive TNBC with pembrolizumab monotherapy may have durable antitumor activity, as exhibited by this patient [5, 7, 8, 19]. There was a positive association between TMB and response to pembrolizumab (overall response rate, $p = 0.154$, progression-free survival, $p = 0.014$) [4, 7]. PD-L1-positive TNBC is associated with higher TIL counts and response rates to anti-PD-1 therapies [9, 10].

EGFR, p53, and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha amplifications may drive malignancy, but in the context of TNBC, they are unlikely to be relevant for treatment [1, 15, 17]. As described above, NF1 alterations are typically enriched in metastatic invasive lobular carcinoma. While myelocytomatosis alteration cannot be directly targeted, prognostically, it could be combined with the MF1 amplification. The longevity of response demonstrated by this patient to pembrolizumab suggests that in the context of breast cancer, the duo may be pointing toward IO efficacy.

This study highlights a remarkable response with unique genetic features typically not seen in TNBC [4, 7]. We hope this case serves as an example of effective monotherapy IO use in patients who commonly may not be treated with IO agents. The extensive mutations, like TMB and MSI-high status, are prognostic, but other mutations characterized by next-generation sequencing remain unclear if they served as targets for IO in this case. We hope that as IO use is explored in cancer types and stages, like this case, lesser understood genes and mutations can become more predictive of potential IO success. Our case report demonstrates the importance of completion of prior lines of therapy, as this patient's incomplete lines likely contributed to her recurrent BC and subsequent TNBC status. We hope this case supports the growing literature discussing using IO agents in TNBC subtypes. Even with notable advancements in the diagnosis and treatment of breast cancer, TNBC continues to pose a challenge due to its aggressive nature, heterogeneity of subtypes, and the absence of specific targeted therapies. We acknowledge that the TNBC disparity seen in AA/AI people is multifactorial, including factors like socioeconomic status enforcing barriers to preventative care and treatment [6]. We hope this report identifies an innovative approach to addressing disparities seen in TNBC affecting AA/AI women and contributes to future clinical discussions on using IOs in TNBC.

Conclusion

Here, we described an AA/AI woman patient with refractory pulmonary metastases of hypermutated TNBC who demonstrated a rapid and durable remission of the metastatic lesions after administering a PD-1 inhibitor. Positively, she did not experience the common adverse events associated with IO. Our report highlights the importance of next-generation sequencing and the use of IO agents in refractory metastatic cancers, adding to the literature regarding the frequency and number of genetic mutations in TNBC in AA/AI women.

Statement of Ethics

This research was conducted in accordance with the World Medical Association Declaration of Helsinki. Ethical approval is not required for this study in accordance with local guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors declare conflicts of interest or funding to report.

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No institutional or external funding was used to write this report.

Author Contributions

Emilie Platteter, B.S., conducted the conception, analysis, investigation, interpretation, and drafting of this case report and is guarantor of the submission. Gerburg Wulf, M.D., Ph.D., was the treating physician, responsible for reviewing, editing, and supervising the case report.

Data Availability Statement

All relevant data are within the paper. Further inquiries can be directed to the corresponding author.

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