

Anti-PD-1 immune checkpoint blockade-based therapy using pembrolizumab in a patient with high-grade glioblastoma

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ABSTRACT

Background: Glioblastoma is a grade IV glioma tumor, and is the most frequent neoplasia in the central nervous system. Patients with glioblastoma have a very low overall survival rate and poor prognosis. Their major therapeutic challenges are the limited penetration of therapeutic agents through the blood-brain barrier, increased treatment resistance, and tumor heterogeneity. **Case presentation:** Anti-programmed cell death 1 (PD-1) immune checkpoint blockade-based therapy using pembrolizumab achieved good stability and non-recurrence in a Kurdish patient with high-grade glioblastoma who was refractory to first-line therapy. **Conclusion:** It appears that after the failure of routine and standard treatments in patients with glioblastoma, an immunotherapy-based therapeutic strategy is suitable for improving their clinical outcomes and creating antitumor effects. **Key words:** Glioblastoma, Pembrolizumab, Anti-PD-1 immunotherapy, Immune checkpoint

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INTRODUCTION

Glioma is a general term used to describe tumors originating from glial cells in the supporting tissue of the brain or primary brain tumors¹. Glioblastoma multiform (GBM) is the most common malignant type of central nervous system (CNS) tumor, with about 48.6% of malignant tumors arising in this region². These tumors are frequently formed in the brain hemispheres, and less often in the cerebellum, brain stem, and spinal cord³. The World Health Organization (WHO) grading system categorizes gliomas as grades I to IV based on histopathological criteria reflecting their malignancy⁴. Glioblastomas are graded based on their response to treatment, malignancy type, and potential for proliferation as (I) the lowest proliferative power and response to surgical treatment, (II) diffuse astrocytoma, (III) anaplastic astrocytoma, (IV) GBM⁵.

Regarding epidemiology, GBM has a low prognosis and can occur at any age. However, it occurs often in those aged 55–60 years and is more frequent in men. In addition, the post-diagnosis survival rate is 14–15 months⁶. Moreover, complete and accurate information about its causes remains unavailable, and its specific carcinogens have not been identified. The only known risk factor is exposure to high doses of ionizing radiation⁷. However, genetic predisposition has been reported in 5%–10% of all cases⁸.

The treatment response will differ based on the glioma grade. However, GBMs do not respond well to stan-

dard treatments such as surgery and chemotherapy due to the limited penetration of therapeutic agents through the blood-brain barrier and increased drug resistance. Previous studies have shown that immunotherapy targeting the pathway involving programmed cell death 1 (PD-1) and its ligand (PD-L1) can be used to treat GBM⁹. In this case report, we present a patient with grade IV glioblastoma who was unresponsive to routine treatments but showed promising results with anti-PD-1 immune checkpoint blockade-based immunotherapy.

CASE PRESENTATION

In July 2022, a 67-year-old Kurdish woman without a medical history was referred to Kermanshah Hematology and Oncology Clinic for headache, confusion, and numbness. The patient had no relevant clinical history. Following a physical examination, the physician requested a magnetic resonance imaging scan of her head. It showed a right parietal brain lesion, 45 × 40 mm in size. Since these findings indicated a glioma tumor, we performed an open biopsy for a definitive diagnosis. Microscopic evaluation of the biopsy sample revealed an infiltrative, diffuse growth pattern of glioma cells, and the immunohistochemistry (IHC) findings for glial fibrillary acidic protein (GFAP) were positive. Based on these results, the patient was diagnosed with grade IV GBM. Therefore, the patient was concomitantly treated with radiation therapy (30 sessions) and chemotherapy with temozolomide (250

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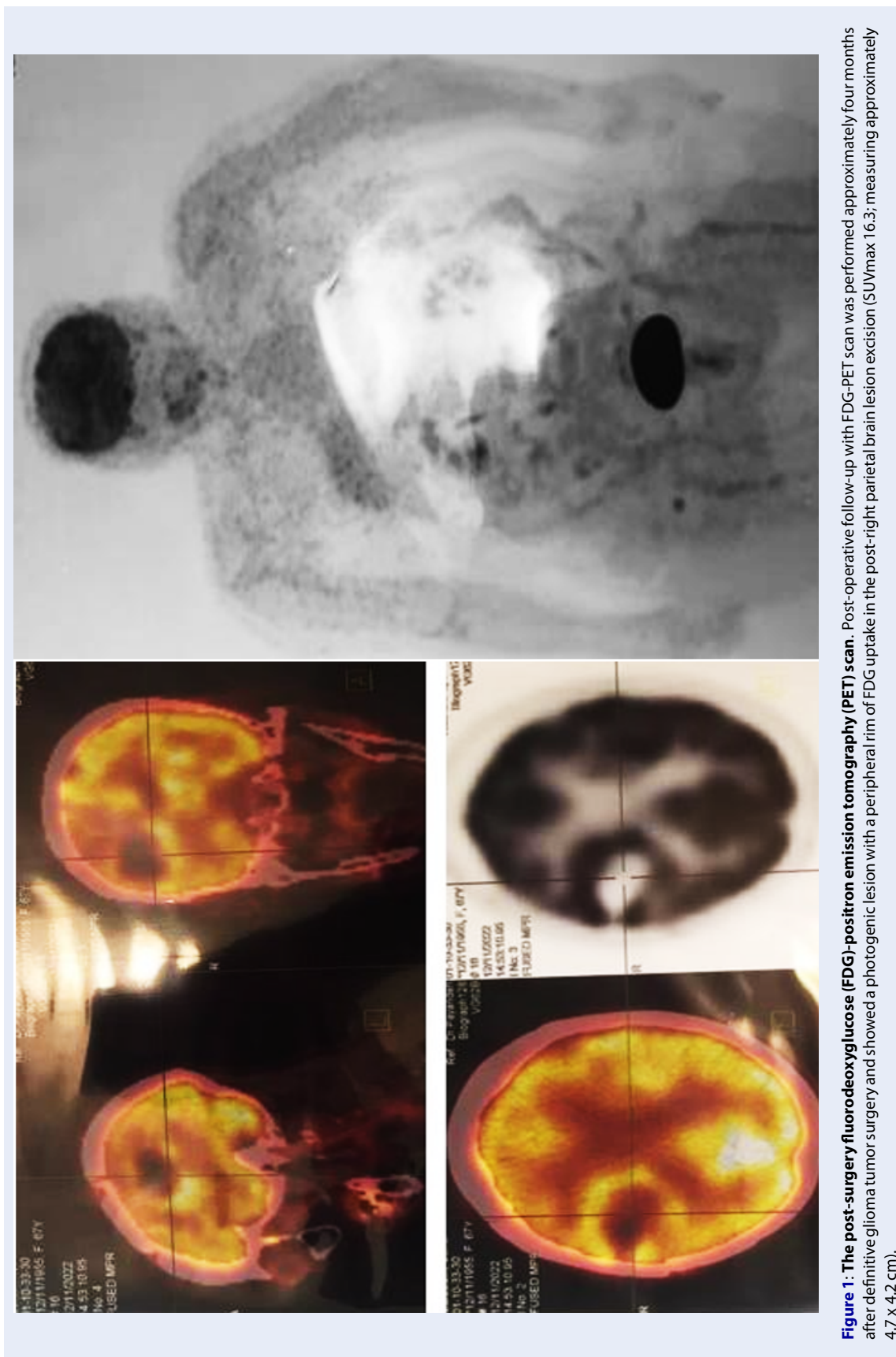


Figure 1: The post-surgery fluoro-deoxyglucose (FDG)-positron emission tomography (PET) scan. Post-operative follow-up with FDG-PET scan was performed approximately four months after definitive glioma tumor surgery and showed a photogenic lesion with a peripheral rim of FDG uptake in the post-right parietal brain lesion excision (SUVmax 16.3; measuring approximately 4.7 x 4.2 cm).

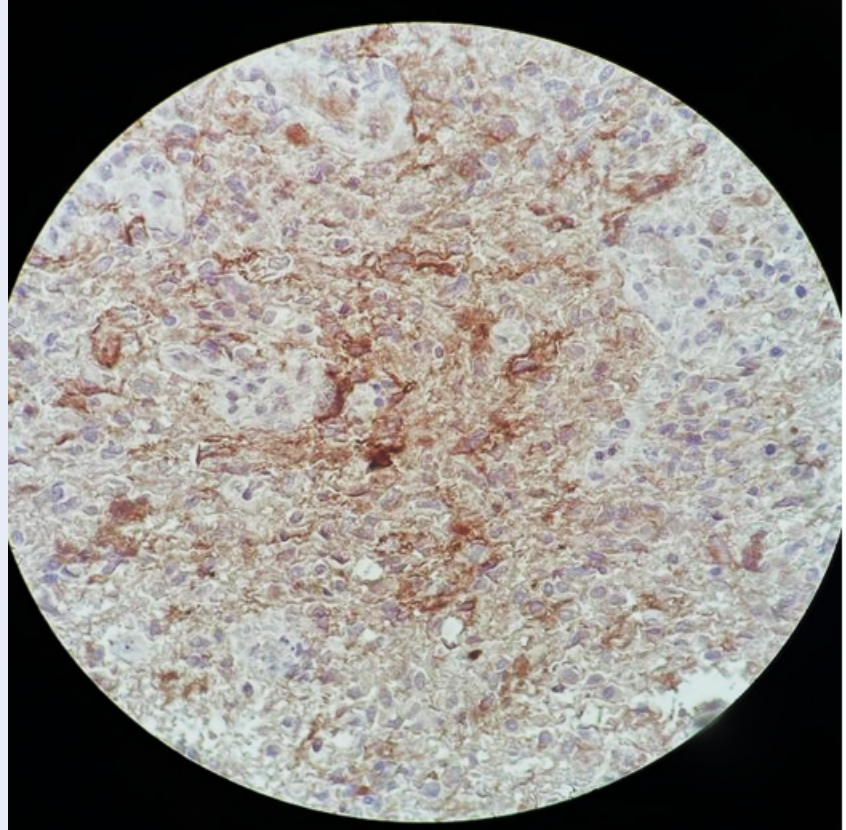


Figure 2: IHC analysis of patient tumor cells. Immunohistochemical analysis of PD-L1 expression in glioma lesions specimen demonstrated that PD-L1 was positive in more than 50% of the patient's tumor cells. It is noteworthy that PD-L1 staining is shown by the brown chromogen.

mg). Then, a surgical procedure was performed in the parietal brain region to remove the lesion. A fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan performed four months after surgery showed disease progression and worsened symptoms (**Figure 1**). Tumor regrowth was not inhibited, and a second open biopsy was performed. The IHC analysis of PD-L1 was positive, indicating an ideal candidate for immunotherapy (**Figure 2**). Therefore, the patient underwent immunotherapy with pembrolizumab (200 mg) and a combination of bevacizumab (400 mg) and irinotecan (300 mg) at three-week intervals. After the third immunotherapy cycle, the patient was stable and is being monitored regularly.

DISCUSSION

GBM is an aggressive tumor and the most common cancer of the CNS. It is thought to be caused by genetic abnormalities that affect neuroglial stem or progenitor cells¹⁰. Grade IV is the aggressive GBM stage,

characterized by microvascular proliferation, necrosis, or both¹¹. Therapeutic options for these patients include surgery, combination chemotherapy, and radiotherapy. However, their effectiveness is decreased due to the tumor's metastatic and aggressive nature¹². Nevertheless, immunotherapy using immune checkpoint inhibitors has opened a new window for treating these patients. As modulators of the immune response, immune checkpoints control immune system function by balancing inhibitory and stimulatory signals. In addition to preserving immune homeostasis, they also prevent autoimmunity¹³. Moreover, checkpoint inhibitors have been successfully approved to treat 12 types of cancerous tumors¹⁴.

Two critical immune checkpoints identified are cytotoxic T lymphocyte antigen-4 (CTLA-4) and PD-1/PD-L1. PD-L1 is encoded by the *PDCDL1* gene located at p24.1 on chromosome 9. PD-L1 is a type I membrane protein activated by binding to the PD-1 receptor¹⁰. They play an essential role in tumor cells escaping the immune system¹⁵ because PD-1 is

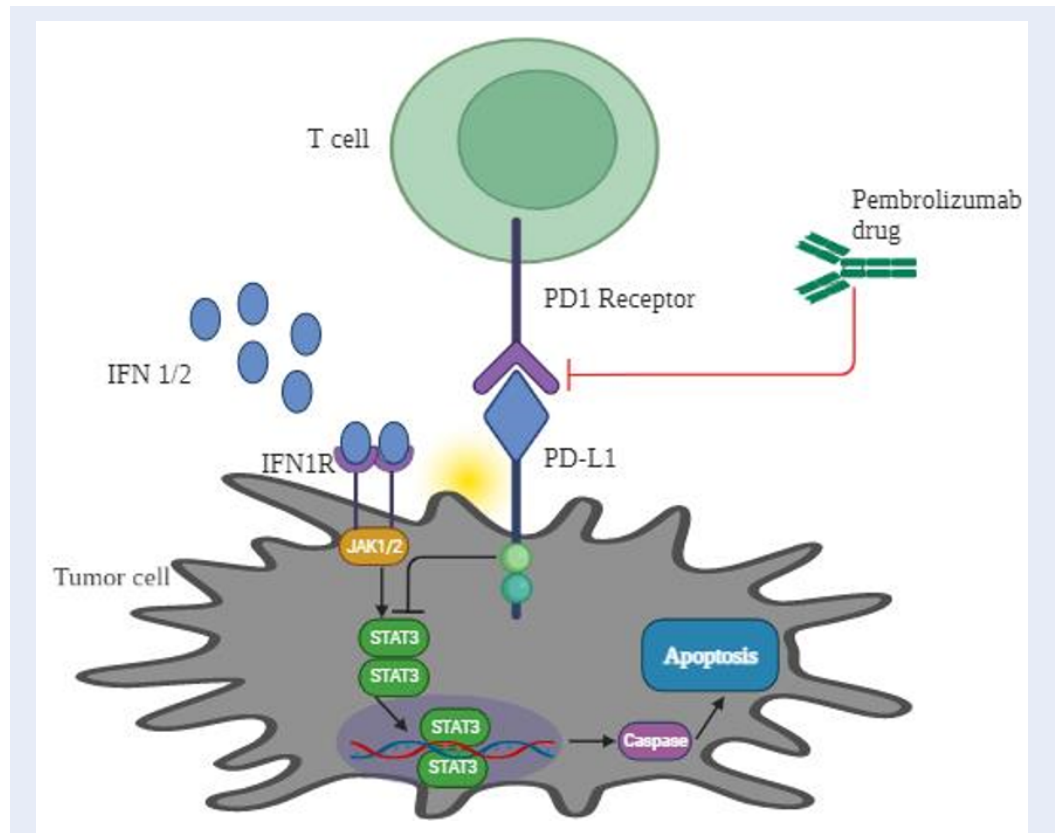


Figure 3: Mechanism of inhibitory effect of pembrolizumab against tumor cells. As a PD-1 inhibitor, pembrolizumab allows T cells to identify and remove tumor cells in the tumor microenvironment by binding to the PD-1 receptor and blocking its interaction with PD-L1. **Abbreviations:** IFN: interferon, IFN1R: Type 1 interferon receptor, PD-1: Programmed cell death 1, PD-L1: Programmed cell death-ligand 1, JAK: Janus kinase, STAT: Signal transducer and activator of transcription.

expressed as a co-inhibitory receptor on the surface of activated CD4⁺ or CD8⁺ T cells, and PD-L1 is expressed by various cells, including tumors. Therefore, their interaction allows tumor cells to survive in the natural physiological environment of the body¹⁶. Studies have shown that *PD-L1* expression in glioma cells correlates with glioblastoma grading under the WHO criteria and can be considered a diagnostic biomarker for glioma cells¹⁷. It can also be very useful in targeted treatments and disease management. Anti-PD-1 immune checkpoint inhibitors enhance the antitumor immune response in patients¹⁸. This new immunotherapy-based therapeutic strategy has been investigated in various preclinical- or clinical-stage cancers, such as melanoma, Hodgkin's lymphoma, breast cancer, and non-small cell lung cancer (NSCLC)¹⁹⁻²¹. Therapy resistance and tumor heterogeneity are considered key challenges for the clinical application of this strategy since previous studies showed that only about 50% of patients with

PD-L1 overexpression might respond adequately to it²². However, monoclonal antibodies against PD-1 (nivolumab, pembrolizumab, and cemiplimab) or PD-L1 (atezolizumab, durvalumab, and avelumab) have been approved by the US Food and Drug Administration (FDA) to treat different cancers²³. The goal of using PD-1/PD-L1 inhibitors is to disrupt the interaction between PD-1 and PD-L1, preventing immune system escape and normalizing the induction of the apoptotic pathway in tumor cells (**Figure 3**).

Our patient was diagnosed with high-grade glioblastoma. After the failure of the first-line treatment (surgery combined with temozolomide and bevacizumab chemotherapy), IHC analysis showed PD-L1 positivity, making her a potential candidate for immunotherapy. Therefore, she underwent anti-PD-1 immunotherapy using pembrolizumab (Keytruda), which showed very promising results. Pembrolizumab is a humanized anti-PD-1 monoclonal antibody that has shown favorable anti-cancer

activity. The FDA has approved it to treat resistant and metastatic tumors and those with microsatellite instability²⁴. In addition, it has shown a long-term response advantage and a high overall survival rate during five-year follow-up compared to chemotherapy for some cancers, such as PD-L1 positive metastatic NSCLC²⁵. Furthermore, studies have shown that patients with glioblastoma who received neoadjuvant pembrolizumab after surgery had increased OS, overexpressed interferon- γ , and induced PD-L1 in the tumor microenvironment²⁶.

It is crucial to note that our patient had the following distinctive characteristics:

- 1- High-grade glioblastoma (IV)
- 2- Older age (67 years)
- 3- Kurdish ethnicity
- 4- A positive response to treatment with an appropriate pembrolizumab dose (200 mg)
- 5- High *PD-L1* expression after the failure of first-line therapy with surgery and chemotherapy

CONCLUSIONS

Our study provides important evidence of pembrolizumab's efficacy in patients with high-grade glioblastoma overexpressing *PD-L1*. After the failure of first-line treatment or resistance to therapy in these patients, pembrolizumab appears useful for improving clinical outcomes and creating relatively long-lasting antitumor effects. Therefore, our results highlight the importance of further prospective studies with larger volumes.

ABBREVIATIONS

CNS: Central nervous system, **CTLA-4:** Cytotoxic T lymphocyte antigen-4, **FDA:** Food and drug administration, **FDG:** Fluorodeoxyglucose, **GBM:** Glioblastoma, **GFAP:** Glial fibrillary acidic protein, **IHC:** Immunohistochemistry, **MSI:** Microsatellite instability, **NSCLC:** Non-small cell lung cancer, **OS:** Overall survival, **PD-1:** Programmed cell death protein-1, **PD-L1:** Programmed cell death-ligand1, **WHO:** World health organization.

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AUTHOR'S CONTRIBUTIONS

Mehrdad Payandeh & Noorodin Karami: Literature search, Clinical studies, Data acquisition, Data analysis, Guarantor; Noorodin Karami, Mahboobeh Jafari: Manuscript review, Figure design; Afshin Karami:

Concepts, Design, Definition of intellectual content, Manuscript preparation; Samira Asadollahi & Sareh Bakhshandeh Bavarsad: Manuscript editing, Referencing by EndNote, Manuscript preparation, Literature search. All authors read and confirmed the final manuscript.

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AVAILABILITY OF DATA AND MATERIALS

None.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The procedures have been reviewed and approved by the ethics committee. All procedures were in accordance with the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards. Written informed consent was obtained from the patient to publish this case report and any accompanying images.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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