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EGFRVIII-POSITIVE IDH-WILDTYPE LEFT FRONTAL GLIOBLASTOMA: AN ILLUSTRATION OF BIOMARKER-GUIDED THERAPY AND CLINICAL TRIAL INVOLVEMENT

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ABSTRACT

Glioblastoma (GBM), a WHO Grade 4 astrocytic tumour, remains the most aggressive primary malignant brain tumour in adults, with limited survival despite multimodal therapy. Molecular profiling has become essential for guiding prognosis, individualized treatment, and clinical trial eligibility. This case report illustrates the role of biomarker-driven management in a 70-year-old male diagnosed with left frontal glioblastoma, characterized by IDH-wildtype, MGMT-unmethylated, and EGFRvIII-positive status. The patient presented with subacute headache, mild expressive aphasia, behavioural changes, and right-arm weakness. MRI revealed a 4.2 × 3.8 cm ring-enhancing lesion with necrosis and vasogenic edema. Stereotactic biopsy confirmed glioblastoma with pseudo palisading necrosis and a Ki-67 index of 35%. Given the molecular profile, the patient underwent maximal safe resection followed by standard chemoradiation (Stupp protocol). He was enrolled in an EGFRvIII-targeted peptide vaccine clinical trial, aimed at inducing a selective cytotoxic immune response against tumour-specific neoantigens. Over 10 months of follow-up, the patient demonstrated stable neurological function and partial radiological response (40% reduction in enhancing lesion volume). This case underscores the importance of

integrating molecular diagnostics, precision immunotherapy, and multidisciplinary management in glioblastoma, particularly for EGFRvIII- positive tumours where targeted approaches may enhance clinical outcomes.

KEYWORDS: Glioblastoma multiforme (GBM); EGFRvIII mutation; IDH- wildtype; MGMT promoter unmethylated; Precision oncology; Biomarker- guided therapy; Targeted immunotherapy; Peptide vaccine; Clinical trial participation; Molecular profiling; Neuro-oncology; High-grade glioma; Stupp protocol; Stereotactic biopsy; EGFR-targeted therapy.

INTRODUCTION

- Glioblastoma multiforme (GBM) is the most common as well as the most aggressive primary malignant brain tumours of adult anatomy and that is why it is classified as the worst type of brain tumor according to WHO because of its rapid growth, extensive infiltration, microvascular proliferation, and necrosis.
- The prognosis is still grave even when the most effective treatment is given. By using molecular markers such as EGFR/EGFRvIII mutations, MGMT promoter methylation, and IDH status, the clinical trial eligibility and personalized therapy are determined.
- In this case, a 70-year-old male patient with a left frontal EGFRvIII-positive glioblastoma is shown to benefit from precision-guided treatment based on a combination of clinical, radiological, histological, and genetic findings.

PRESENTATION OF THE CASE

Patient demographics: 70-year-old male right-hander

Filing Complaints: A subacute headache that worsens for a week, Difficulty finding words (mild expressive aphasia); behavioural changes, such as increased anger and social disengagement.

The Present Illnesses

Previous the headache was intermittent at first, then chronic.

- No injuries to the head,
- Visual issues, seizures, diplopia, or vomiting

Past Medical History

- His blood pressure is well-controlled with amlodipine treatment.
- No previous history of cancer or other co morbid conditions.

Drug Use and Family History

No antiplatelet or anticoagulant drugs Family history is irrelevant.

Neurological Evaluation and Symptom Localization Correlation

Mental state: Responsive, not distracted, and completely engaged.

- **Motor activity:** The left primary motor cortex takes part in the mild weakness shown in the right arm (MRC 4+/5).
- **Language**: Fewer words per minute and interruptions for finding the right one → implicating Broca's area assigned to the left frontal lobe.
- **Mood**: Greater impatience and normal participation → implying frontal lobe defect that has to do with the social conduct and executive planning.
- **Nerves of the skull:** Intact normal giant and coordination

Status of Performance

ECOG: 0–1>70

Karnofsky Performance Score. >70

Vital signs: steady

Clinical Perception: Focal neurological signs associated with subacute headache and cognitive-linguistic deficits were suspicious of the cerebral mass lesion.

1. **Advanced Imaging and Surgical Planning**

- Among the high-tech MRI methods employed were diffusion tensor imaging (DTI) and functional MRI (fMRI), which facilitated mapping of the cortical areas crucial for language and thus planning of a resection that would be safest limit-wise.
- Neuronavigation made the exact tumours localization without affecting important language and motor skills. The surgical plan was formed by preoperative imaging and, as a result, there was a reduction in neurological deficits after operation.

2. Radiology Findings

MRI Brain contrast enhanced

INTERPRETATION: High grade glioma

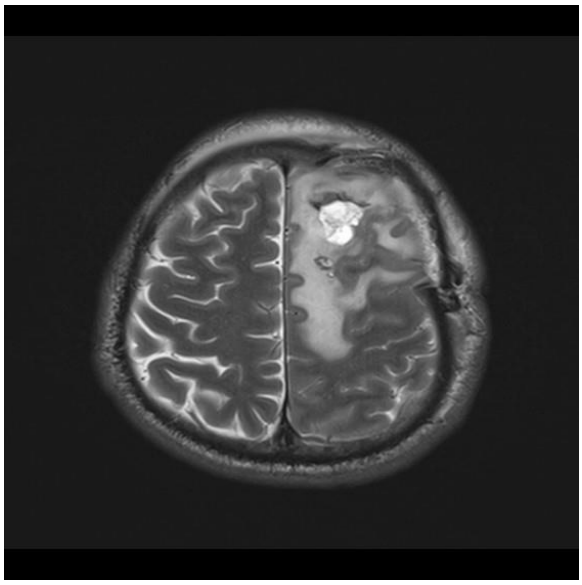

FIG. 1: MRI Brain contrast enhanced.

After I requested and reviewed a contrast-enhanced MRI, an abnormal ring- enhancing lesion of approximately 4.2 × 3.8 cm was found in the left frontal lobe of the brain.

- The main necrotic area and the surrounding vasogenic oedema caused a midline shift of around 4 mm. The lesion was seen as having a differential signal intensity on T2-weighted and FLAIR sequences, and there was an area of restricted diffusion at the enhancing borders.
- These characteristics very much indicated a high-grade glioma. Complete blood count and serum chemical analysis tests were all within normal limits. Imaging studies of the thorax and abdomen ruled out the presence of metastases or the existence of a systemic cancer.
- I executed a stereotactic biopsy under neuronavigational guidance. During the procedure, enough representative tissue samples were obtained, and the patient had an uneventful recovery.

3. Differential and Provisional Diagnosis: Provisional Diagnosis

- At the patient's first clinical assessment, a subacute headache, a slight case of expressive aphasia and a slight degree of weakness in the right arm were the clinical signs found.
- The above-mentioned signs were suggestive of a lesion located in the left frontal region.

- The initial diagnosis was high-grade glioma, most probably glioblastoma, which was based on the MRI findings and the neurologic tests performed.

Differential diagnosis

The following were considered:

1. **Brain abscess**

Although the brain abscess was due to ring-enhancing lesions with core necrosis, there was no indication of a widespread infection.

2. **Metastatic tumours:** Often found near the Gray-white matter border, the metastatic tumours did not correspond to any primary cancer on either systemic or imaging scans.
3. **WHO Grade III anaplastic astrocytom**a, which may enhance with contrast but does not have necrosis or microvascular proliferation.
4. **Primary CNS lymphoma:** The imaging characteristics were inconsistent with the typical periventricular location and progressive enhancement of primary CNS lymphoma.

4. **Stereotactic-guided brain biopsy**

- To identify the lesion type, the patient had a stereotactic-guided brain biopsy carried out on the left frontal tumours.
- The neuronavigation-based targeting was performed during the general anaesthetic procedure to accurately sample the tumours margin getting bigger and at the same time to avoid damaging the neighbouring eloquent brain areas.
- Several tissue core samples were taken for histological and molecular investigations; the surgery was well tolerated, and no problems occurred during or after the procedure.

5. **Histopathology and Molecular Findings**

I assessed biopsy tissue using histopathology (H&E staining).

- Glial cells that are widely infiltrating and exhibit notable nuclear atypia.
- Quick mitotic action.
- The growth of microvascular tissue. Necrosis that is pseudopalisadic.

These traits aligned with glioblastoma, a WHO grade 4 astrocytic tumours.

6. **Immunohistochemistry (IHC) and Molecular Profiling**

- **IDH1 R132H: IDH-wildtype** → Negative.
- **Methylation of the MGMT promoter:** Unmethylated → indicates reduced temozolomide sensitivity.

- **EGFR mutation or amplification:** Positive → qualified for a clinical trial that targets Egeria.
- **ATRX:** Maintained: Astrocytic lineages of the IDH wildtype are supported.
- **P53:** non-mutant pattern, weakly positive.
- **A Ki-67** index of about 35% denotes significant proliferation activity.

1. **H&E Strain (40x)**

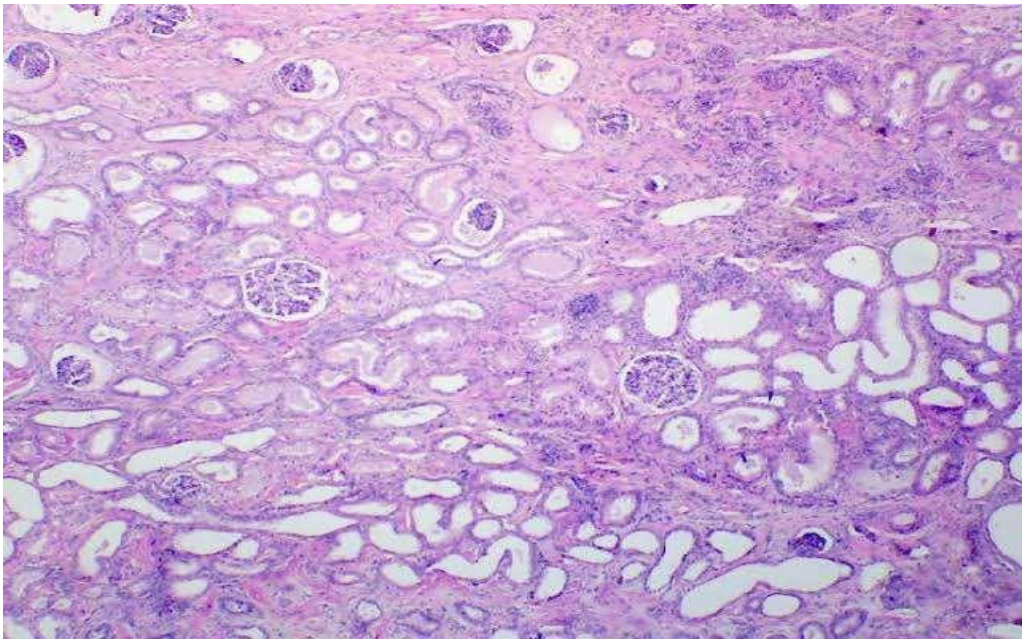

FIG. 1: Nuclear atypia and pseudo palisading necrosis in diffusely infiltrating glial cells.

2. **IDH1 R132H**

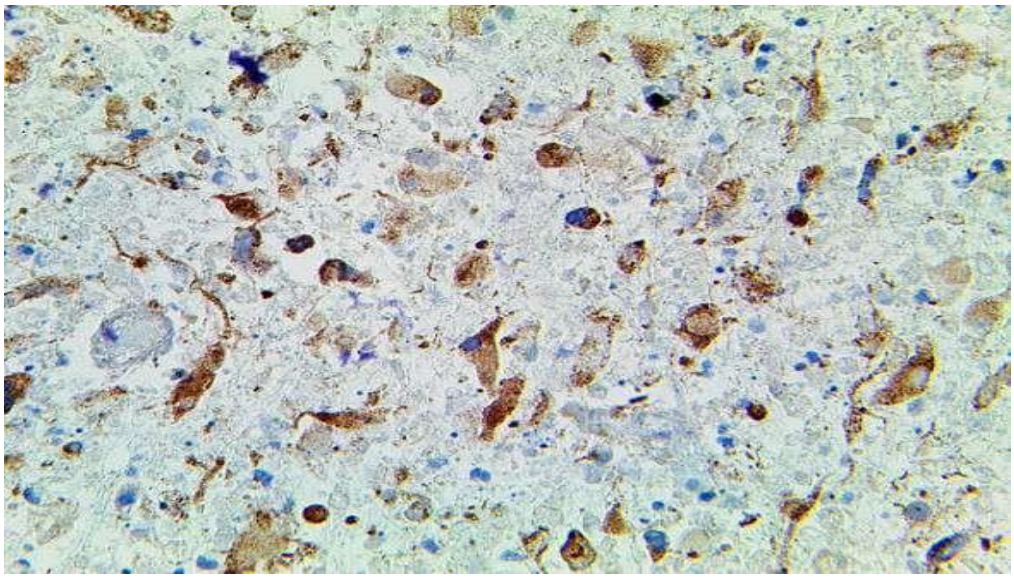

Fig. 2: IDH-wildtype is confirmed by a negative staining pattern.

3. Ki 67

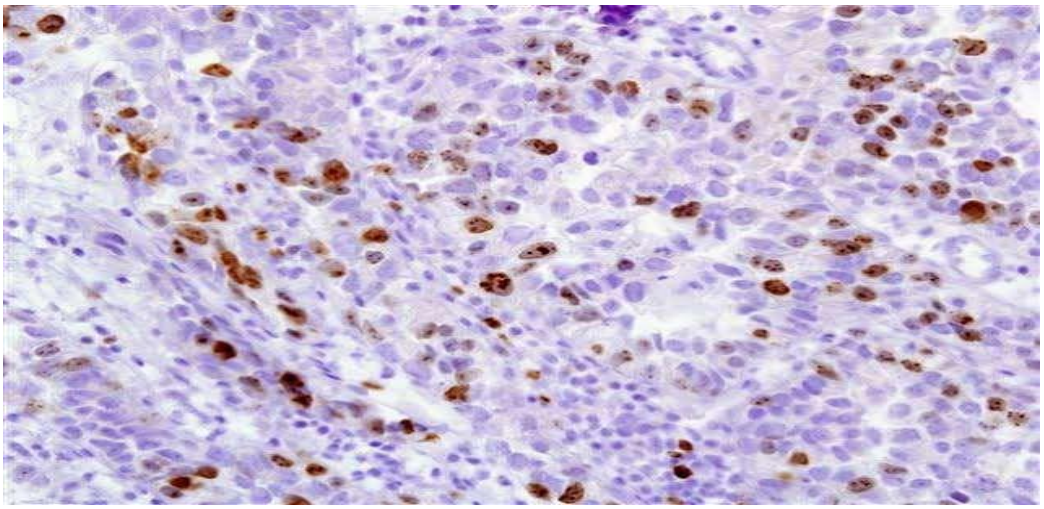

Fig. 3: ~35% nuclear positivity indicating high proliferation.

- Following stereotactic biopsy, histology and molecular profiling verified the final diagnosis of left frontal glioblastoma, IDH-wildtype, MGMT-unmethylated, EGFRvIII-positive (WHO Grade 4).

7. WHO CNS 2021 Grading System

Astrocytic tumours	**I**	**II**	**III**	**IV**
Pilocytic astrocytoma	*			
Diffuse astrocytoma		*		
Anaplastic astrocytoma			*	
Glioblastoma				*
Oligodendroglial tumours				
Oligodendroglioma		*		
Anaplastic oligodendroglioma			*	
Oligoastrocytic tumours				
Oligoastrocytoma		*		
Anaplastic oligoastrocytoma			*	
Ependymal tumours				
Ependymoma			*	
Anaplastic ependymoma				*
Meningeal tumours				
Meningioma	*			
Atypical meningioma		*		
Anaplastic meningioma			*	

8. Clinical Interpretation

- The patient was confirmed to have the most aggressive type of brain cancer (WHO Grade 4) the same as glioblastoma, IDH-wildtype, MGMT-unmethylated, and EGFRvIII-positive. An MRI scan indicated a left frontal tumour with necrosis and edema that was ring-enhancing.
- Neoplastic tissue examination revealed the presence of diverse astrocyte-like cells, the formation of micro vessels, and the occurrence of necrosis with the typical "pseudopalisading" feature.
- Through molecular analysis, the tumours were characterized as IDH-wildtype (de novo, poor prognosis), EGFRvIII (targetable), and MGMT (unmethylated, resistance to temozolomide).
- A 35% Ki-67 index was a pointer to extremely high proliferation of cells.
- All these features pointed to an aggressive glioblastoma subtype which would theoretically benefit from EGFRvIII-targeted immunotherapy.

9. Final Diagnosis

The right frontal lobe has been diagnosed with a glioblastoma with wildtype IDH, unmethylated MGMT, EGFRvIII positive, and a grade of WHO 4.

10. Enrollment in Clinical Trials and Treatment

I oversaw the treatment and administered it. The management plan was as follows:

I. Surgical Resection: I removed the lesion in the left frontal lobe using the safest method possible. Postoperative MRI confirmed near-total excision with minimal enhancing tissue left.

II. Adjuvant Therapy (Stupp Protocol): 30 fractions of 60 Gy of external beam radiation administered over six weeks Concurrent temozolomide: 75 mg/m² daily during radiation therapy. Adjuvant temozolomide at 150–200 mg/m² for five days every 28 days for six cycles.

III. Surgical Care: To accomplish the safest possible resection, a left frontal craniotomy was performed. Postoperative MRI verified near-total excision with minimal residual enhancement.

IV. Clinical Trial Design and Justification

i. The patient participated in a phase II clinical trial that evaluated a peptide vaccine that targets EGFRvIII in patients with EGFRvIII-positive glioblastoma who had just received

a diagnosis.

ii. The trial aims to generate an immune response specific to the tumours while minimizing off-target damage. Individuals who meet the eligibility requirements typically have tumours of the IDH wildtype with unmethylated MGMT, a subgroup that reacts poorly to standard therapy.

iii. Every three weeks for three cycles, 500 µg of the vaccine and the adjuvant temozolomide were administered subcutaneously. Participating in the trial allowed for the integration of precision immunotherapy with standard care while upholding stringent safety regulations.

11. The mechanism, immune response, and integration of EGFRvIII- targeted immunotherapy with conventional therapy

1. EGFRvIII Vaccine's Mode of Action

i. The tumours-specific EGFRvIII mutation, which is only expressed on glioblastoma cells and not in healthy brain tissue, is the target of the EGFRvIII peptide vaccine.

ii. Antigen-presenting cells process synthetic peptides resulting from the mutation and deliver them to T lymphocytes. CD8+ cytotoxic T cells are then activated to destroy Egeria-positive tumours cells only.

iii. Long-term immunological memory development and antibody generation are both supported concurrently by CD4+ helper T cells. By accurately targeting the cancerous cells and sparing the non-affected areas of the brain, this selective strategy reduces off-target toxicity and significantly lowers the risk of treatment-related neurologic complications.

2. Targeting and Immunological Reaction

i. The tumour-specific immune response is induced after immunization. The helper T cells are responsible for the activation of the B cells and the ensuing production of antibodies, and the cytotoxic T cells through their direct interaction with the tumour's cells multiply the ones with EGFRvIII and eliminate them.

ii. The vaccination acts as a continuous supply of tumours antigens to the body and it not only keeps the memory of the immune system but also possibly prevents the coming back of the tumours. This specifically directed immune response in eloquent cortical areas, where the function of the nervous system is critically dependent, is especially important for the preservation of the neurological function.

12. Treatment and Overview

Treatment	Intervention	Duration	Outcomes
Surgical Resection	Near-total excision following a left frontal craniotomy.	First step	Minimal residual MRI enhancement following surgery.
Radiotherapy	Therapy with external beams	30 halves of 60 Gy spread over six weeks	In addition to temozolomide
Concurrent Therapy	Temozolomide	75 mg/m² every day while receiving radiation	Well tolerate
Adjuvant Therapy	Temozolomide	150–200 mg/m² for five days every 28 days × six cycles	The typical Stupp regimen
Targeted therapy	Peptide vaccination for EGFRvIII	Subcutaneous injection of 500 µg every three weeks × three cycles	Good tolerance and mild local reactions

13. Patient counselling and recommendations

- The aggressive nature of left frontal glioblastoma (WHO Grade 4, IDH-wildtype, EGFRvIII-positive) and its treatment implications were explained to the patient and family.
- Adjuvant chemoradiotherapy (Stupp protocol), maximal safe surgical resection, and participation in a clinical trial for an EGFRvIII-targeted peptide vaccine were all part of the suggested treatment strategy.
- Regular MRI follow-up, supportive care (e.g., corticosteroids for edema, antiepileptic prophylaxis, physiotherapy/speech therapy), and preserving general health were emphasized.
- To help the patient and family deal with the emotional effects of the diagnosis, psychological support and counselling were also suggested.

Results and Follow-Up

- I carried out several neurological and radiological follow-ups:
- Three months: The RANO criteria state that stable illness Half a year: Partial radiological response (40% reduction in contrast-enhancing volume)
- Ten months later, the patient has no new MRI abnormalities, is ambulatory, self-sufficient in daily activities, and is clinically stable (ECOG 1; KPS 80).

DISCUSSION

- In the case of left-sided frontal glioblastomas, they are often found in the preference area of the brain and thus, expressed as problems in speech production, changes in behaviour,

and weakness of the muscles on the opposite side of the body.

- The treatment of the tumours was precision-targeted and based on the confirmation of histopathology that the tumours was a WHO Grade 4 astrocytic tumours which was Egeria-positive, IDH-wildtype, and MGMT-unmethylated.
- To maintain the neurological function, the combined use of EGFRvIII peptide vaccination, adjuvant chemoradiotherapy (Stupp protocol), and maximal safe resection was employed.
- At the follow-up, there was a partial radiological response and the patient continued to play her usual role functionally. This case highlights the importance of integrating molecular profiling, clinical features, and tumour's location in the management of glioblastoma.

CONCLUSION

- The case of a left frontal EGFRvIII-positive, IDH-wildtype, MGMT-unmethylated glioblastoma has demonstrated the necessity for integration of clinical evaluation, neuroimaging, histopathology, and molecular profiling in the individualized treatment path.
- Immunotherapy targeted at EGFRvIII, maximum safe surgery, and standard radiotherapy and chemotherapy together helped in getting a partial decrease in tumours size and preserving the function.
- It underlines the necessity of a multidisciplinary approach to ensuring the best possible outcomes alongside the preservation of life quality and the applicability of biomarker-based precision medicine in the management of gliomas, particularly in the brain areas that are functionally critical.

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