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Case Report

Oncolytic Virotherapy for Relapsed, IDH-Mutant, Grade 3 Astrocytoma: A New Promising Approach – A Case Report

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Keywords

Astrocytoma · IDH-mutant · CNS WHO grade 3 · Oligodendroglioma · Oncolytic virotherapy · Immunotherapy · Radiology

Abstract

Introduction: IDH-mutant astrocytomas are high-grade gliomas with a poor prognosis. Transformation to glioblastoma multiforme is common, which further shortens overall survival and frequently renders the tumor inoperable. Oncolytic viruses (OVs) have been shown to be safe and effective agents for the treatment of some malignant brain tumors. Intra-tumoral application may further enhance their therapeutic potential. ***Case Presentation:*** This report presents a case of a 37-year-old female patient with advanced relapsed grade 3 astrocytoma, with multiple foci, including one along the rim of the left fronto-parietal post-op cavity, who was treated with a one-shot OV regimen via an Ommaya reservoir (IO-OV), with the catheter tip placed intra-tumorally. Adjunct electro-hyperthermia therapy was also provided. No evidence of disease (NED) was achieved after the first cycle of IO-OV and was maintained for 9 months until the non-vaccinated patient contracted COVID-19, after which aggressive and refractory relapse occurred. ***Conclusion:*** OV therapy proved to induce significant clinical improvements and radiological NED for this incurable astrocytoma. This promising modality should be evaluated as an adjunct to first-line therapy for inoperable brain tumors.

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Introduction

IDH-mutant astrocytomas are diffuse infiltrating astrocytic tumors lacking an identifiable border between the tumor and the healthy brain tissue. Transformation to glioblastoma multiforme (GBM) is common and is associated with a shorter median overall survival. While surgical resection and radiation prolong survival, the efficacy of chemotherapy, including temozolomide, remains controversial [1]. Considering the poor prognosis despite aggressive treatments, clinicians focus on supportive and palliative care to maintain quality of life (QoL). While cancer patients undergoing current therapies may show a systemic T-cell-mediated anti-tumor immune response in blood and bone marrow, the tumor microenvironment (TME) can prevent effective anti-tumor immunity [2]. This localized absence of anti-tumor immune function is a typical feature of high-grade gliomas [3–5]. Thus, chemotherapy and radiation are insufficiently effective and can suppress immune functions, highlighting the need for alternative therapies.

Oncolytic viruses (OVs) selectively infect and replicate in tumor cells, which leads to cell lysis, after which tumor cell fragments can induce potent secondary immune activation, even in immune-suppressed hosts. These processes have been linked to control metastatic lesions and prevent tumor recurrence. OVs have shown promising therapeutic effects for various cancers, including brain tumors [2, 4–8]. For example, Newcastle disease viruses (NDVs) displayed oncolytic and immune-stimulating activities, including for GBM. Similar effects have been observed with reoviruses [2]. Based on the reported effects of NDV and reovirus, there is a clear rationale for combination virotherapy [2, 9].

Local or intra-tumoral injection of OVs improves their primary oncolytic effect [10] and efficiently stimulates innate and adaptive TME immunity, whereby immunologically quiet "cold" tumors are transformed into "hot" tumors [2]. In this process, activated memory T cells counteract the immunosuppressive TME and can offer protection against tumor recurrence. The insertion of an Ommaya reservoir with its tip close to the tumor is a novel OV delivery approach for the induction of local oncolytic effects and activation of TME immune functions. Intra-Ommaya OV (IO-OV) injections also provide the crucial advantage of bypassing the blood-brain barrier (BBB), which significantly improves intracranial OV bioavailability compared to peripheral intravenous (IV-OV) and intra-arterial (IA-OV) injections. Consequently, IO-OV dosages are markedly lower than those used for systemic administration and systemic side effects of therapy are milder. Finally, if increased intracranial pressure develops secondary to tumor growth or due to IO-OV-induced peritumoral edema, the Ommaya catheter provides a readily available means of draining cerebrospinal fluid for pressure relief. Samples collected through this access port can also be used for immunological analyses. Molecular diagnostics and recognition of immunological response patterns will help guide oncolytic virotherapy (OVT) in the future and contribute to individually tailored treatment approaches [2, 5, 6]. Based on this rationale, we present the treatment course and remarkable response to IO-OV of a 37-year-old patient with relapsed astrocytoma and multifocal MRI lesions who presented with severe clinical deterioration.

Case Presentation

The 27-year-old previously completely healthy female patient presented in 2011 with bilateral blurred vision, frontal headaches, bilateral tremors, short-term memory deficit, slightly slurred speech and right-sided focal as well as grand-mal seizures. Radiological studies showed a brain lesion in the left frontal lobe, which was surgically resected. Histopathology demonstrated neoplastic cells with mostly astrocytic appearance with nuclear

atypia and elevated mitotic rate, then compatible with anaplastic astrocytoma; however, the presence of cells with rounded nuclei and perinuclear halos raised the diagnosis of oligodendroglial components. Molecular diagnosis was not available. Postoperative treatment included external beam radiotherapy; chemotherapy was rejected by the patient. Various anti-epileptic drugs were given to control seizures. Follow-up evaluations revealed relapsing radiological lesions, which were surgically removed and treated with radiotherapy and several rounds of Temodal. The patient continued her anti-epileptic regimen, and no further seizures were experienced. She remained overall stable with good QoL.

Eleven years after the initial diagnosis, the patient suffered a sudden deterioration (3/2022) with grand-mal seizures, right-sided hemiparesis and blurred right-eye vision. Consecutive T1-weighted post-gadolinium MRI images (Fig. 1A1, 2A1) revealed a severe relapse with multiple enhancing foci, including one along the rim of the left fronto-parietal post-op cavity. FLAIR imaging showed patchy hyperintensities in these regions. These radiological findings showed the tumor to be inoperable, and therefore, palliative temozolomide chemotherapy was suggested.

Given her end-stage condition and the poor prognosis with palliative chemotherapy, the patient signed consent for experimental OV treatment, which was administered in Germany on a compassionate-use basis ("Individueller Heilversuch"). After insertion of an Ommaya reservoir (05/2022), with its tip in the affected region, a single low dose of IO-OV with NDV1 and REO3 (10^2 pfu each) was injected. Supportive electro-hyperthermia therapy (EHT) in a 60-min EHT session was added and was later repeated 2 times within the same week. The EHT consisted of short radiofrequency waves of 13.56 MHz applied by capacitive coupling technique while maintaining the skin surface temperature at about 20°C. The applied power ranged between 40 W and 150 W, with heating stepped up with each EHT session. The patient showed gradual clinical improvement with no further seizures and slow resolution of hemiparesis over the subsequent 3 months, with regained fine motor skills and clear vision. She eventually returned to her former independent lifestyle, including regular physical workouts, with no clinical complaints.

MRI indicated an excellent treatment response, with full disappearance of the enhancing lesions. PET-FET-MRI was also performed to exploit the unique unmasking effect of residual tumor tissue by OV in which solitary focal uptake was detected in the region of the left globus pallidus, which was not visible with standard MRI. In follow-up MRIs on Days 50 (Fig. 1D2), 101 (Fig. 1D3), 139 (Fig. 1D4) after initial OVT, the tumor was markedly smaller and displayed reduced metabolic activity. 3D volume rendering techniques clearly distinguished between the shrinking tumor and the surrounding halo of active immune-mediated inflammatory edema (Fig. 1F2–F4, G2–G4, 2C1–C4, D1–D4).

Post-OVT PET-FET-MRIs showed no evidence of disease (NED) (Fig. 1A4, B4, D4). Day 50 MRI confirmed NED, while later imaging on Days 101 and 139 revealed increased SUV PET signals, consistent with minor residual disease. A second dose of IO-OV equal to the first was administered on Day 154, with consecutive removal of the Ommaya reservoir due to persistent skin irritation. The increased SUV PET signals disappeared by Day 187. More specific 3D-VR imaging ascribed the gradual tumor shrinkage observed during Days 101-139-187 to tumor degradation in parallel to an increased immune response, which is typical for cancer immunotherapy. In contrast to radiological NED determined by conventional MRI and PET-FET-MRI on Day 187, minor residual findings were still detected with 3D-VR (Fig. 1C4–G4). The IO-OV treatments were tolerated without any severe side effects, and the patient's clinical condition remained well overall.

On Day 242, the unvaccinated patient suffered COVID-19 infection, with high fever and mild respiratory symptoms for 7 days. PET-FET-MRI on Day 262 (Fig. 1D5) found progressive disease, with no signs of immune response at the tumor site. Signs of nasopharyngeal

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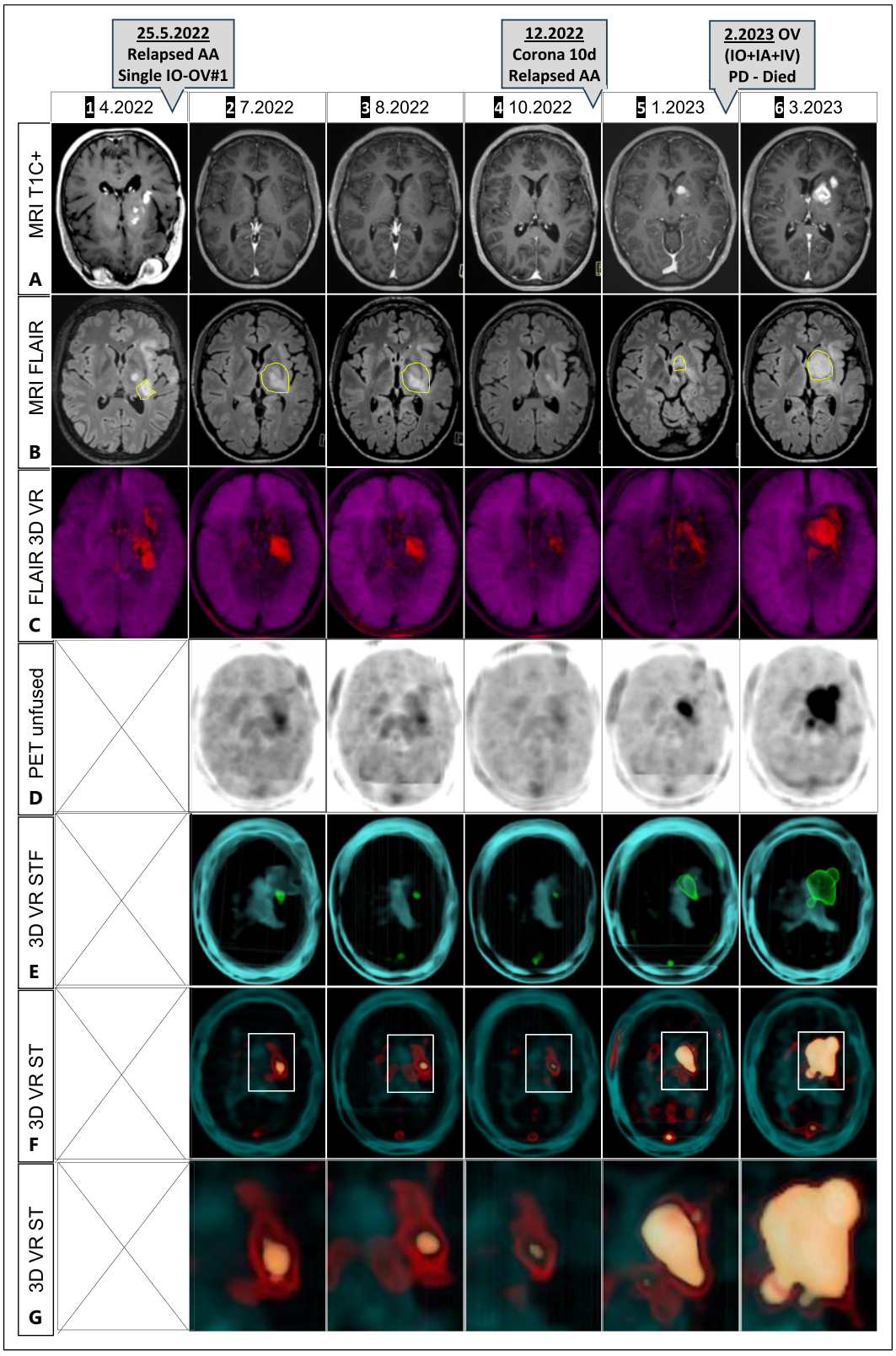

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inflammation were detected, compatible with persistent SARS-CoV-2 upper respiratory tract infection (Fig. 2E5). There were no neurological deficits. Given these findings, an OV-rescue therapy regimen of IV-OV with both viruses on day 264 (5×10^3 pfu each) and IA-OV via the left carotid artery on day 266 (5×10^3 pfu each) was delivered. Mild symptoms, including chills, fever and arthralgia, occurred after OV administration, and fully resolved within a few days. Despite rescue therapy, the patient deteriorated gradually both clinically and radiologically (Fig. 1D6) and died on Day 360. An overview of the treatment course is provided in Figure 3.

Discussion

To the best of our knowledge, this is the first report radiologically documenting an immunotherapeutic response in PET-FET-MRI of relapsing progressive astrocytoma with NED after only a single IO-OV dose. Of note, this anaplastic astrocytoma tumor was diagnosed before molecular and genetic brain tumor pathology tools were available, and may have been classified differently with contemporary tumor profiling protocols. Notwithstanding the limited tumor characterization data, the treatment response was remarkable, considering the patient's end-stage condition and poor prognosis. OVs can induce prolonged and efficient oncolytic effects with powerful immune activation. Our patient's clinical course following experimental OV immunotherapy, including the deterioration after SARS-CoV-2 infection, provides important insights that may have a significant impact on future perspectives and on the management of astrocytoma and other malignant brain tumors.

OV for Cancer

Various natural and engineered OVs and combinations have shown positive therapeutic effects on multiple tumor types, with good safety profiles [2, 4–6, 8]. Treatment efficacy can be augmented by rational genetic engineering of the OVs with enhanced tumor selectivity and anti-tumor activities [2, 4]. Their efficacy can be further improved by IO administration, as direct injection into the tumor site initiates a focused oncolytic effect without the need to overcome the BBB and the tumor's immune defenses [6, 10]. The immunologically "cold" TME turns "hot," enabling the host's immune system to efficiently attack the tumor tissue and potentially make it more susceptible to conventional oncologic treatment regimens [2]. IT-OV

Fig. 1. Initial response to a single IV-OV and subsequent disease progression. Contrast-enhanced MRI shows foci of distinct lesion enhancement (A1) with multifocal tumoral edema on FLAIR (B1), presented with 3D volume rendering (C1). The absence of pretreatment PET is left blank (D1–G1). With the first IT-OV dose, there was resolution of contrast enhancement on A2 with an alteration in the edema pattern to inflammatory type with hazy margins on FLAIR (B2 and C2). The first post-treatment PET-FET shows the "melting" nature of the treatment response with decreasing uptake and inflammatory "flaring" of margins on the unfused (D2), mildly prominent nodularity of the inflamed tumor on STF VR (E2) and in 3D on ST-VR (red halo in E2–G2). While there was persistent non-enhancement (A2–A4), MRI FLAIR (B2–B4 and C2–C4) showed decreasing edema. PET findings correlated by showing decreasing PET uptake (D2–D4 and E2–E4) – tumor shrinkage and F2–F4 and G2–G4 – minimal residual tumor and an active inflammatory halo. After COVID, multifocal enhancing foci (A5–A6) and edema (B5–B6 and C5–C6) reappeared and rapidly progressed, matching a spiking uptake from recurrence on D5–D6, E5–E6, F5–F6, and G5–G6, with the characteristic absence of an inflammatory halo. Thereafter, a rapidly enlarging enhancing mass (A6) with satellite extensions, extensive peritumoral edema (B6 and C6), intense conglomerated uptake of the FET-PET (D6–G6) confirmed uncontrolled disease progression. In addition, the characteristic inflammatory halo (F6–G6) seen in earlier response to treatment on the VR-ST images was no longer observed.

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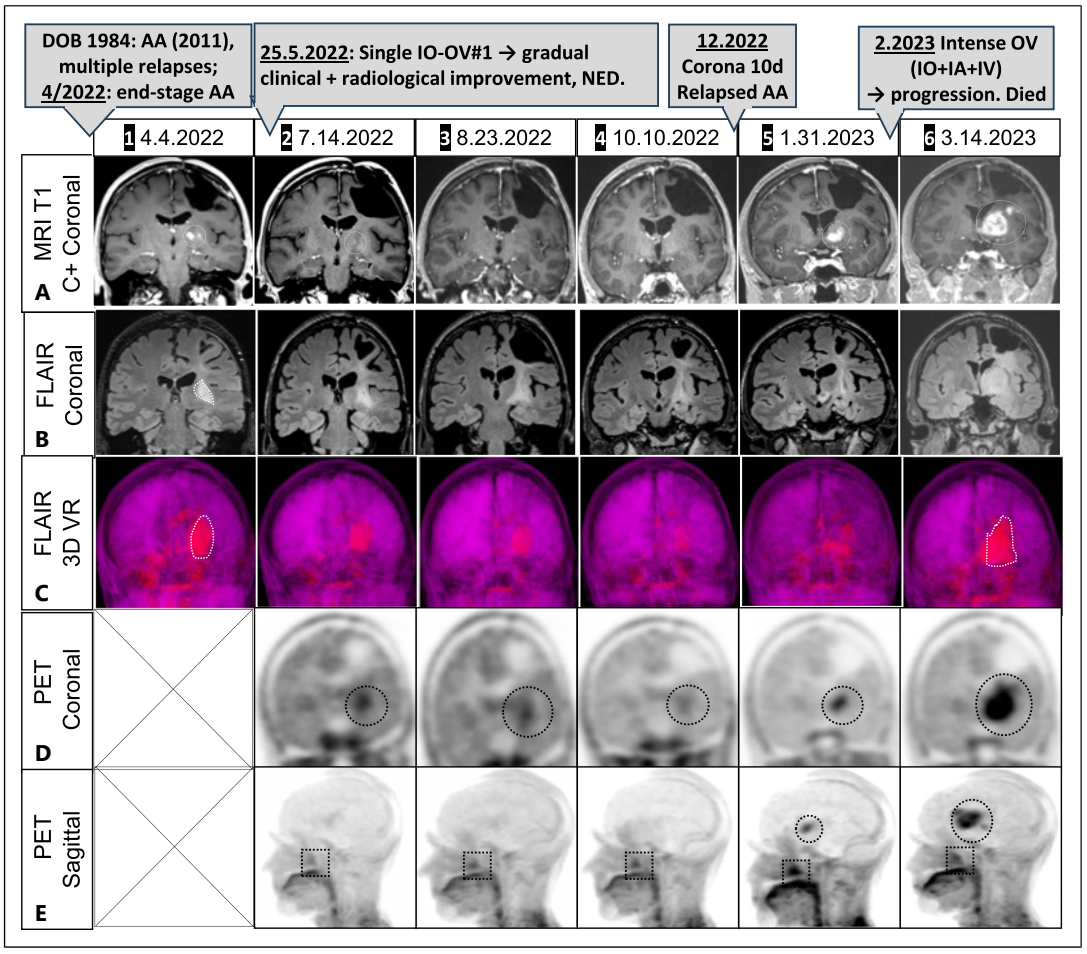

Fig. 2. Coronal overview of the initial immune response to a single IO-OV and subsequent progression after SARS-CoV-2 infection. Coronal T1 contrast-enhanced MRI showing a lesion in the left internal capsule (A1), which disappeared after a single IO-OV (A2–A4), with a progressive relapse after SARS-CoV-2 infection (A5–A6). Coronal FLAIR images show multifocal lesions with edema (B1) with 3D volume rendered presentation (C1). PET-FET was not acquired pretreatment; hence, coronal and sagittal unfused PET images are left blank (D1–G1). After IO-OV treatment, reformatted images show absence of enhancement (A2–A4) and improving decrease in inflammatory patterns of the tumoral environment (B2–B4, C2–C4) with decreasing uptake (D2–D4). A5–A6 show aggressive disease progression with recurring enhancing lesions, and a reappearance of tumoral edema (B5–B6, C5–C6), confirmed by multifocal neoplastic grade uptake (D5–D6). Sagittal PET shows pre-COVID baseline uptake in the nasopharynx (E2–E4) and increased uptake in the nasopharynx compatible with coincidental clinical corona infection (black boxes in E5–E6) in parallel to rapidly progressing relapse of the intracranial tumor (D5–D6 and E5–E6).

induces systemic activation of the endogenous immune system, leading to degradation of both the primary tumor and metastatic lesions, known as the abscopal effect [8]. Side effects of systemic OV administration are reduced with IT-OV.

OV for Brain Tumors

Administration of a single IO-OV dose to a patient with relapsing advanced astrocytoma resulted in remarkable clinical and radiological improvement with NED by Day 50. IO injection of two low-dose OVs showed the powerful therapeutic efficacy of combined IO-OVs

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Fig. 3. Overview of treatment course.

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compared to repeated IV-OV or IA-OV with $>10^6$ pfu, which reflects a 10^4- to 10^5-fold reduction in dosage level.

Our end-stage palliative patient received OVT on an experimental compassionate-use basis. Treatment was guided by clinical observations and radiological monitoring. Future trials are needed to develop standardized protocols, which should define effective OV combinations, administration intervals, and optimal routes for IT-OV application. Clinical and radiological monitoring requires complementary laboratory investigations for immune markers, tumor metabolites, and viral loads, especially in the cerebrospinal fluid, to gain a better general understanding of the mechanisms of OV immunotherapy and, specifically, whether circulating tumor cell fragments activate and train the endogenous immune system to attack residual tumor cells [5, 6]. The latter has enormous clinical consequences as surgical resection of such astrocytomas and GBM almost never removes the entire tumor, and residual malignant cells usually invade the surrounding tissue. OVs have the ability to detect and destroy these residual tumor cells, thereby inhibiting relapse [11].

Diagnosis of IDH-Mutant Astrocytoma

In 2011, the patient's tumor was diagnosed as "anaplastic astrocytoma," based on the available histological findings, including nuclear atypia and elevated mitotic rate, the presence of oligodendroglial components and astrocytic features, which all highlighted the complexity of tumor classification even then. In 2021, the altered WHO Classification of Central Nervous System Tumors revolutionized the classification of brain tumors by incorporating molecular alterations alongside histopathological features. Molecular profiling of the tumor, which only became available at a later stage, showed loss of heterozygosity (LOH) of 1p/19q, along with IDH-1 mutation (G395A), strongly supporting an oligodendroglial lineage, and a weak EGFR amplification, suggesting astrocytic features. In addition, the MGMT methylation (25%), while not diagnostic, was an important prognostic factor. This mixed molecular profile reflects the often-seen heterogeneity of such tumors and is aligned with the histological findings. Under the 2021 WHO criteria, the best term to describe this tumor would be "astrocytoma, IDH-mutant, CNS WHO grade 3," instead of the historic term "anaplastic astrocytoma."

Relapse and Therapy-Refractory Tumor Progression after COVID-19 Infection

After achieving remarkable treatment success with a single OV dose, the non-vaccinated patient suffered a sudden relapse with rapid tumor progression after SARS-CoV-2 infection. Chronic sequelae after acute infection, known as "long COVID" (LC), are observed in up to 76% of hospitalized and up to 30% of community-managed COVID-19 cases. The symptoms of LC manifest systemically with severe relapsing fatigue, dyspnea, chest tightness, cough, brain fog and headache, the latter being a clear indication of central nervous system involvement. Immunologically, LC is associated with immune dysfunction and a sustained inflammatory response, which follows even mild-to-moderate acute COVID-19 [12]. Although the definitive impact of these observations on clinical oncology remains unclear, COVID-19-associated inflammation may generate a favorable microenvironment for tumor cell proliferation, particularly of dormant cancer cells [13]. We thus speculate that COVID-19-induced immune dysfunction and chronic inflammation triggered residual cancer cell proliferation [11], which led to sudden and refractory tumor growth. Our hypothesis is supported by the radiological finding of distinct new inflammation in the nasopharynx shortly after infection, which was accompanied by the sudden absence of immune response at the tumor site. Future studies should evaluate COVID-19 impact on the immune system of vaccinated and unvaccinated patients with cancer.

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Radiological Insights Gained from Monitoring IO-OV for Brain Tumors

While MRI is an established procedure for routine follow-up in patients with brain tumors, it is essential to add PET-FET when relapse is suspected, or clinical deterioration occurs. FET-PET-MRI not only helps clarify equivocal diagnoses in brain tumor patients, particularly on detection of progression, but also facilitates clinical management by distinguishing true tumor progression and pseudo-progression as therapy-related alterations [14]. These characteristics make FET-PET-MRI an ideal tool for the assessment of OVT efficacy [11]. As shown in our patient, OV-induced immune-mediated inflammation typically causes a halo of abnormal metabolic uptake around the tumor site. When additional 3D imaging is applied, detailed tumor site assessment enables determination of tumor volume and identification of areas of the best treatment response, thereby guiding to lesions needing further treatment. Combining FET-PET and 3D imaging also enables differentiation between stable disease, partial response, progression or pseudo-progression. Future studies should aim to profile OV- and immune-related radiological features and correlate them with laboratory and clinical findings to improve monitoring of brain tumor therapy.

Ethical Considerations, QoL, and Choice of Treatment

The extensive multifocal relapse resulted in inoperability from the outset in our palliative patient, such that it was of the utmost importance to maintain the best possible QoL and to avoid therapeutic approaches with potentially severe side effects. Thus, we decided to offer individualized experimental treatment by combining two approaches:

- Insertion of an Ommaya reservoir and IO-OV: catheter insertion of the reservoir was performed by a neurosurgeon under CT-guidance, rendering it low-risk and enabling optimal positioning of the injection tip. Low-dose OV administration was associated with almost no side effects, and even when OVs were later injected IV and IA, no QoL-impairing side effects occurred.
- Supplemental EHT: each OV administration was followed by EHT, an adjuvant anticancer modality which has been shown to impart pleiotropic effects on cells and tissues. The resulting rise in tissue temperatures to above optimal physiological levels, directly affect the physical properties of the treated cells as well as their responses. In addition, it can modify the cellular microenvironment, oxygen supply and vascularization, which all bear immediate consequences on tumor survival and spread. These cellular effects have been suggested to lie at the root of its synergistic interaction with radiation therapy and chemotherapy in patients with brain and other types of tumors [15]. Such multimodal treatments may provide the specific advantage of a significant improvement in tumor control and progression-free survival without increasing side effects. However, its impact on OVT outcomes needs to be further investigated. Of note, EHT was tolerated well, with no severe side effects in our patient.

Our treatment regimen was explained in detail to the patient and her family, and potentially lethal complications, e.g., intracranial bleeding or treatment failure, were discussed. Given the poor prognosis due to inoperability, ineligibility for radiotherapy and the limited effectiveness of chemotherapy with temozolomide, OVT offered a promising experimental approach. The patient understood the ethical and medical issues before providing informed consent and was involved in all developments and decisions regarding disease course and treatment decisions.

Conclusion

OVT for an end-stage patient with an incurable astrocytoma proved to be an effective experimental approach that led to significant clinical improvement and radiological NED, with a continuously maintained high QoL. Thus, IO-OV might be a promising and effective alternative to radio- and chemotherapy in inoperable brain tumors and should be evaluated as an adjunct to first-line therapy for this cancer entity.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent for publication of this case report and any accompanying images was obtained from the patient's next of kin. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material at https://doi.org/10.1159/000545004.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization, investigation, and supervision: A.S. and H.Sa.; methodology and data curation: C.W. and H.Sc.; formal analysis: B.G. and J.S.R.; and writing, B.G., C.Y.B., R.E., and Y.P. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from B.G. upon reasonable request.

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