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Long-Term Remission of Recurrent Anaplastic Oligodendroglioma With WT-1-Specific CD8+ T-Cell Therapy: A Case Report

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We report a case of complete remission in anaplastic oligodendroglioma following adoptive cell therapy (ACT) with autologous Wilms tumor 1 (WT-1)-specific CD8+ T cells. A 40-year-old woman referred to our hospital for adjuvant chemotherapy after recurrent anaplastic oligodendroglioma initially presented with a left frontal tumor, diagnosed through seizure onset, and subtotal resection confirmed oligodendroglioma (WHO grade 2). Radiation therapy treated the residual tumor, achieving partial remission until recurrence 2.5 years later when malignant transformation to anaplastic oligodendroglioma (WHO grade 3) occurred following a second craniotomy. After three cycles of procarbazine, lomustine, and vincristine chemotherapy, the residual tumor stabilized for 3 years. However, follow-up MRI identified a new enhancing lesion, prompting a third craniotomy. Recurrent anaplastic oligodendroglioma was confirmed, and adjuvant proton beam therapy and temozolomide chemotherapy were initiated. Two years later, another enhancing lesion appeared on the adjacent medial frontal lobe. Following multidisciplinary review, we introduced WT-1-specific ACT. Although transient swelling was observed 1 month post-therapy, the tumor demonstrated a response within 3–9 months. Continued regression led to complete remission—confirmed via MRI at the 15-month follow-up and sustained for 4.7 years. The patient's peripheral blood monocyte profiles and immune-associated cytokine analysis indicated T-cell activation following WT-1 sensitization.

Keywords Anaplastic oligodendroglioma; Recurrent; Wilms tumor 1; Cell therapy.

INTRODUCTION

Gliomas are incurable, central nervous system–infiltrating tumors that are resistant to chemotherapy and radiotherapy, with malignant transformation occurring upon recurrence [1]. Among the histological subtypes, oligodendrogliomas (ODG) are known to have a relatively good prognosis and respond well to adjuvant chemo- and radiotherapy [2]. However, despite maximal surgical debulking followed by chemo- or radiotherapy, these treatments remain insufficient to achieve a cure or complete remission, although some long-term survivors have been observed [3,4]. Once transformed into anaplastic ODG, the tumor follows a clinical course similar to that of other malignant gliomas, despite proven benefits from salvage chemotherapy with procarbazine, lomustine, and vincristine (PCV), and temozolomide (TMZ) [5,6].

Immunotherapy for gliomas has recently gained attention for its potential to overcome chemotherapy and radiotherapy resistance by activating the patient's immune system to target the tumor. However, gliomas are often referred to as "cold tumors" owing to their antigenic heterogeneity, low mutation burden, and lack of tumor-infiltrating T cells. Therefore, monoclonal antibodies, immune checkpoint inhibitors, and dendritic

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cell vaccines have shown limited success in glioblastoma treatment [7]. Among the various immunotherapy strategies, adoptive cell therapy (ACT) is designed to activate the patient's T cells by sensitizing tumor-specific CD8+ T cells with tumor-specific antigens *ex vivo*, followed by their infusion into the patient. Infused CD8+ T cells are expected to activate a pro-inflammatory, anti-tumor microenvironment and promote "epitope spreading," a process that induces secondary anti-tumor responses against other released tumor antigens [8,9]. This "cancer-immunity cycle" is critical for inducing durable, complete regression of the tumor [10].

We present a case of a patient with recurrent anaplastic ODG over 11 years, who had exhausted all resources for adjuvant or salvage therapy. After the third recurrence, we administered ACT targeting the Wilms tumor 1 (WT-1) antigen. The patient achieved a slow but complete remission over 1 year, which was maintained for 4.7 years after the administration. At the 1-year follow-up after complete remission, we summarize the patient's peripheral blood monocyte cell (PBMC) subset profiles and cytokine kinetics along with clinical courses and follow-up MRI, which align with the patient's response to WT-1 ACT.

CASE REPORT

A 40-year-old woman diagnosed with anaplastic ODG was referred to the neuro-oncology clinic at our institute for adjuvant chemotherapy, following a referral from the department of neurosurgery at a nearby general hospital (KHY) in January 2012. The transfer note indicated that she had been diagnosed with a primary brain tumor, initially presenting with a seizure. Her brain MRI showed a predominantly non-enhancing T1-low and T2-high infiltrating mass in the left frontal lobe, involving the insular cortex (Fig. 1A). The first surgery was performed in June 2009, where gross total removal was attempted, but language disturbance during awake surgery led to a subtotal resection. Pathological examination confirmed ODG (World Health Organization [WHO] grade 2). Adjuvant radiation therapy was administered to the tumor bed and residual tumor (5,940 cGy/33 fractions) (Supplementary Fig. 1 in the online-only Data Supplement).

Two and a half years later, a follow-up MRI revealed an increasing T2-high signal with a thick, ellipsoidal superficial enhancement at the tumor bed (Fig. 1B). A second salvage surgery confirmed malignant transformation to anaplastic ODG (WHO grade 3). The patient was treated with the PCV regimen, but after three cycles, it was discontinued owing to grade 3 thrombocytopenia, which did not resolve despite a month-long delay. A brain MRI with perfusion showed minimal residual infiltrative lesions on T2-weighted images, with reactive thin linear enhancement at the surgical margin, interpreted as postoperative change (Fig. 1C and Supplementary Fig. 2 in the online-only Data Supplement).

She was followed up clinically and radiologically as stable, with regular MRI check-ups every 6 months. The reactive enhancement disappeared 1.5 years after the second craniotomy (Supplementary Fig. 3A in the online-only Data Supplement). In September 2016 (4.5 years after the second craniotomy) her

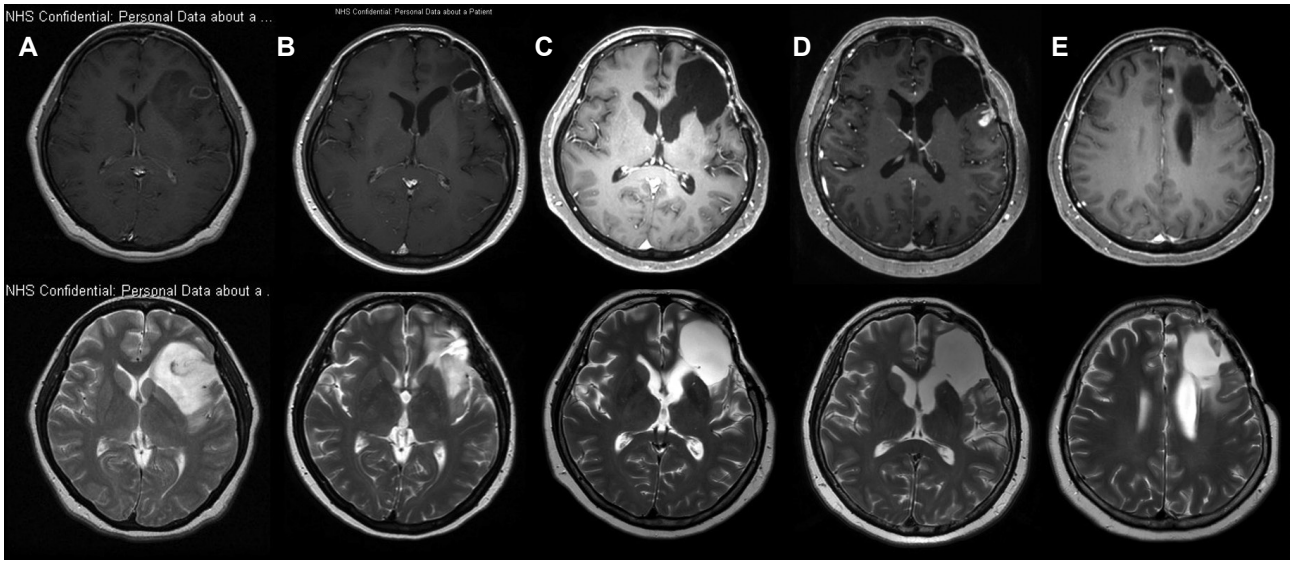

Fig. 1. MRI findings of recurrent oligodendroglioma (upper row: T1-weighted gadolinium-enhanced images, lower row: T2-weighted images). These images demonstrate the progression of the tumor through multiple recurrences and malignant transformation into anaplastic oligodendroglioma after the second recurrence. A: Initial diagnosis. B: Recurrence 2.5 years after the initial surgery and adjuvant radiotherapy. C: Post-surgical remission status after the second surgery, followed by chemotherapy, with minimal residual disease. D: The second recurrence, showing leptomeningeal spread confirmed on cerebrospinal fluid cytology and treated with surgery followed by temozolomide. E: Third recurrence observed in the adjacent medial frontal lobe, treated before initiating Wilms tumor 1 immune therapy.

MRI revealed a new T2-high signal/T1 gadolinium-enhancing linear lesion, located distant from the previous surgical margin (Supplementary Fig. 3B in the online-only Data Supplement). Perfusion MRI suggested that this lesion was a reactive enhancement, as it was difficult to distinguish from normal cortical perfusion (Supplementary Fig. 3C in the online-only Data Supplement). A follow-up MRI 3 months later showed the lesion becoming ellipsoidal and spreading over the pial surface (Fig. 1D). Based on these findings, we performed cerebrospinal fluid (CSF) cytology, but the results were negative, showing only atypical cells, ruling out leptomeningeal metastasis. The multidisciplinary tumor board recommended excisional biopsy to confirm the tumor, and the patient agreed to an exploratory craniotomy. The third craniotomy revealed a mass with pial involvement, and pathology confirmed anaplastic ODG with isocitrate dehydrogenase-1 (IDH-1) mutation and 1p19q co-deletion (Fig. 2). Postoperative proton beam therapy was administered a month later at 4,000 cGy/16 fractions (Supplementary Fig. 4 in the online-only Data Supplement).

Following the completion of palliative radiation, we repeated CSF cytology based on operative findings, which were now suggestive of tumor involvement (anaplastic ODG from the previous operation). The patient agreed to salvage chemotherapy, and adjuvant TMZ (200 mg/m^2, 5 days per 28 days) was initiated. After one cycle of TMZ chemotherapy, CSF cytology results turned negative and remained negative through two additional cytology examinations 3 months apart. The patient had good compliance with treatment and did not experience any severe adverse events. TMZ was continued for 24 cycles over almost 2 years without any radiological evidence of progression.

On "chemo-off" follow-up MRIs every 6 months and 2.5 years after the third craniotomy, a new oval-shaped enhancing lesion appeared on the adjacent medial frontal lobe (Fig. 1E). Following a multidisciplinary discussion, excisional biopsy was recommended, but the patient refused further surgical intervention. Instead, she agreed to participate in a phase I clinical trial of ACT using WT-1-specific CD8+ T (WTiNT) cells, which was available for glioma patients at our institution (NCCCTS-12-629) (Fig. 3). WTiNT cells were prepared by isolating and expanding WT-1-specific CD8+ T cells from PBMCs over 31 days, as previously reported [11]. The patient received 4×10^8 CD8+ T cells per square meter of body sur-

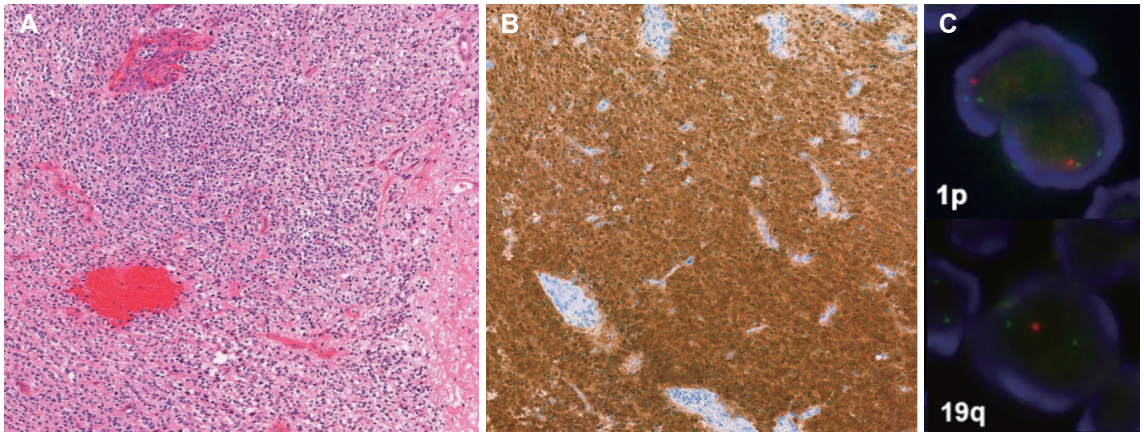

Fig. 2. Histological findings of anaplastic oligodendroglioma obtained during the third craniotomy. A: Tumor cells exhibit characteristic features such as round nuclei, well-defined cell membranes, and clear cytoplasm (fried egg appearance). Histological features indicative of aggressive behavior include high cellularity, nuclear hyperchromasia, and prominent endothelial vascular proliferation (hematoxylin and eosin stain, ×100 magnification). B: Immunohistochemistry reveals mutated isocitrate dehydrogenase-1 protein expression in the tumor (×100 magnification). C: Fluorescence *in situ* hybridization analysis confirms 1p19q co-deletion.

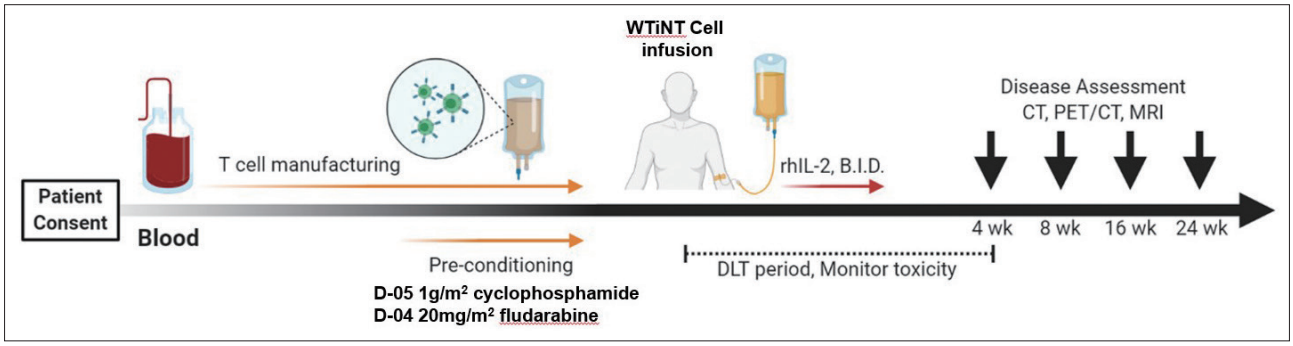

Fig. 3. Schematic diagram of Wilms tumor 1 adoptive immune cell therapy.

face area, following lymphodepletion with 1 g/m^2 cyclophosphamide on day -5 and 20 mg/m^2 fludarabine on day -4, along with recombinant human interleukin (IL)-2 (Proleukin, 250,000 IU/m^2 per injection for 7 days, BID). During the first week of observation post-WTiNT cell infusion, she experienced no adverse event and was discharged to outpatient clinic follow-up.

According to the trial protocol, she returned to the outpatient clinic on days 14 and 28 for follow-up assessments. MRI was conducted at baseline (-1), 4, 16, and 24 weeks pre- and post-infusion of WTiNT cells, with regular follow-up every 6 months thereafter (Fig. 4). Serial analysis of the T1-weighted gadolinium-enhanced lesions showed that the enhancing lesion increased progressively from 2 months before ACT to 4 weeks after treatment. The largest diameter of the lesion increased from 4.0 mm (D-57) to 5.0 mm (D-7) and then to 5.8 mm (D28). However, the lesion size gradually decreased over the next year, ultimately disappearing by day 420, with complete remission maintained for up to 4.7 years of follow-up MRI. This temporal increase in lesion size at 4 weeks is consistent with "pseudo-progression" [12], likely resulting from inflammation, with the slow but sustained response to WT-1 ACT leading to complete remission.

PBMC subset profiles and cytokine change after WT-1 ACT

Heparinized blood samples were collected from the patient at designated intervals according to the protocol and analyzed for immune cell subsets and cytokine profiles. The total PBMC count sharply decreased following lymphodepletion with cyclophosphamide and fludarabine but gradually recovered over the next 2−3 weeks (Fig. 5A). Consistent with PBMC kinetics, the percentages of CD4+ T cells, CD8+ T cells, and CD14+ monocytes were temporarily reduced owing to the prior lymphodepletion but showed recovery within the subsequent 2 weeks (Fig. 5B). Notably, among various immune cell subsets, CD3+ T cells—particularly CD8+ T cells—continued to increase among PBMCs day 14 onwards (Fig. 5B and C), eventually surpassing the initial levels of CD8+ T cells by day 116 (Fig. 5D). The percentage of CD28+ young cells among the CD8+ T cells peaked at day 14 and then gradually decreased (Fig. 5E), while CD57+ senescent cells among the CD8+ T cells gradually increased starting from day 14 (Fig. 5F). Given that most CD8+ T cells were likely endogenous rather than infused, these data suggest that the patient's endogenous CD8+ T cells, including tumor-reactive CD8+ T cells, were persistently activated and expanded after WTiNT cell infusion, possibly contributing to the observed pseudo-progression in the lesion.

Additionally, the cytokine profile of T cells was assessed by stimulating PBMCs with phorbol myristate acetate and ionomycin for pan-T cell activation or with WT-1 peptides used to amplify WTiNT cells for 48 hours. Stimulation with WT-1 peptides did not induce significant cytokine expression, except for IL-6, which peaked at day 4 (Fig. 6). Pan-T cell stimulation minimally induced pro-tumoral cytokines such as IL-4

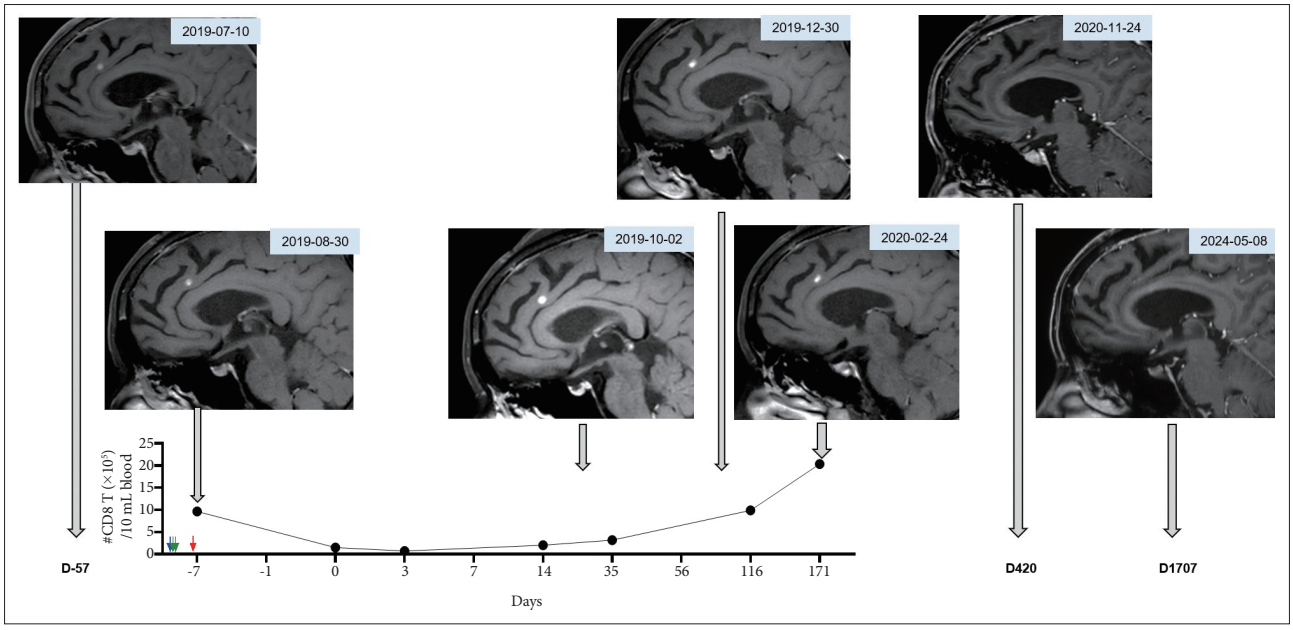

Fig. 4. Tumor response and CD8+ T-cell kinetics following Wilms tumor 1 adoptive immune cell therapy. Chronological changes in the medial frontal tumor mass size and peripheral CD8+ T-cell concentration. The transient increase in tumor size at day 28, likely due to "pseudo-progression," eventually decreased, leading to complete remission at day 420. Complete remission was maintained for up to 4.7 years post-treatment.

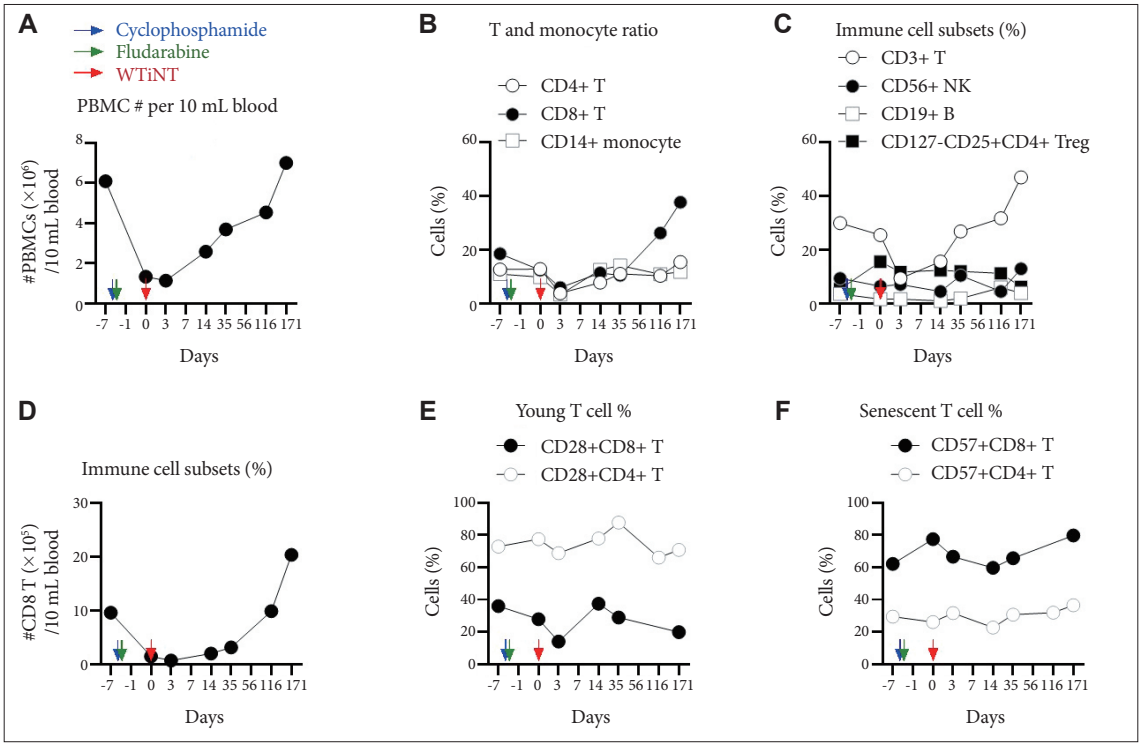

Fig. 5. Immune cell subset kinetics in peripheral blood. Heparinized blood samples were collected at the indicated time points. Peripheral blood monocyte cells (PBMCs) were isolated via Ficoll-gradient centrifugation, stained with specific monoclonal antibodies, and analyzed using flow cytometry (FACSCalibur, BD Biosciences). A: Absolute PBMC counts over time. B: Percentages of CD4+ T cells, CD8+ T cells, and CD14+ monocytes in PBMCs. C: Percentages of CD3+ T cells, CD56+ NK cells, CD19+ B cells, and CD127-CD25+CD4+ naïve regulatory T cells (Treg). D: Absolute numbers of CD8+ T cells over time. E: Percentages of CD28+ cells within the CD4+ and CD8+ T-cell populations. F: Percentages of CD57+ senescent cells within the CD4+ and CD8+ T-cell populations.

and IL-10, except for IL-6, but strongly induced anti-tumoral cytokines like IL-2, tumor necrosis factor, and interferon-gamma (Fig. 6). The sustained expression of IL-2, a key anti-tumor cytokine and essential growth factor for activated T cells, up to 6 months post-infusion suggests that the infusion of WTiNT cells not only directly suppressed tumor growth but also played a role in continuously activating endogenous anti-tumor T cells.

DISCUSSION

Multiple recurrence events of anaplastic ODG including leptomeningeal metastasis

Anaplastic ODG is a relatively rare tumor, accounting for 5%–25% of malignant gliomas, and is characterized by a variable clinical course [2,13]. For primary anaplastic ODG, clinical trials such as RTOG 9402 and EORTC 26951 have demonstrated the long-term benefit of PCV adjuvant chemotherapy [3,4]. However, for recurrent anaplastic ODG, there is no standardized salvage treatment, although PCV and TMZ have shown some benefit in case reports and retrospective studies [5,14,15]. In the present case, the initial presentation was typical of a young patient with a low-grade glioma, and adjuvant radiation was administered following subtotal resection. Upon the first recurrence after 2.5 years, histological examination revealed malignant transformation to anaplastic ODG. Given the high risk of radiation injury, re-irradiation was deemed inappropriate, and PCV chemotherapy was administered as an adjuvant treatment, resulting in stable disease for 5 years.

The second recurrence manifested as leptomeningeal metastasis, with the lesion developing in the sulci and spreading over the pial surface, as observed on MRI. Intraoperative findings confirmed pial surface involvement. Despite being postoperative, repeated CSF cytology at 2 months was suggestive of anaplastic ODG, a considerable duration for simple spillage. Leptomeningeal metastasis in ODG, whether primary or recurrent, has been reported sporadically [16-19]. Based on our experience with successful and long-term responses to salvage TMZ chemotherapy for anaplastic ODG, alongside other case reports [19,20], TMZ was prescribed as adjuvant therapy after the third craniotomy and as salvage chemotherapy for leptomeningeal involvement. This resulted in a negative cytology conversion and no progression for 2 years. However, the case eventually showed recurrence 6 months after discontinuing TMZ, despite receiving 24 cycles of salvage TMZ chemotherapy.

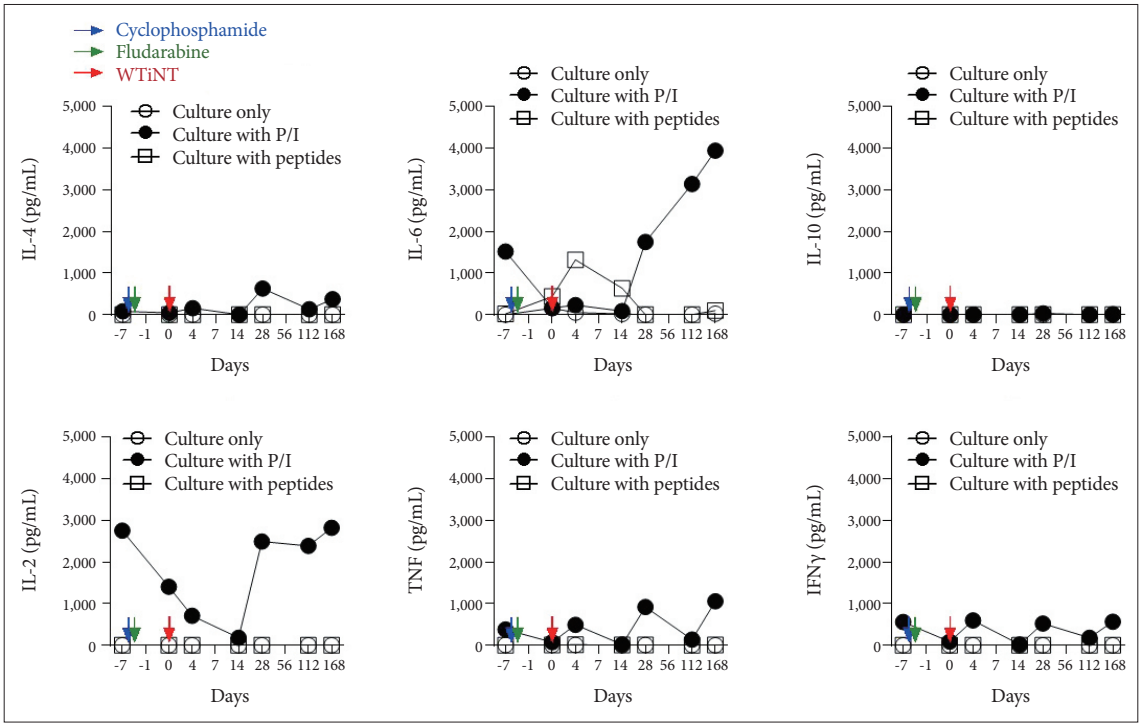

Fig. 6. Cytokine profile of peripheral blood monocyte cells (PBMCs). PBMCs isolated via Ficoll-gradient centrifugation from heparinized blood specimens of the patient at various time points were stimulated for 48 hours with phorbol myristate acetate and ionomycin (P/I) for pan-T cell activation, or with Wilms tumor 1 peptides used to expand Wilms tumor 1–specific CD8+ T cells. Cytokine levels in the culture supernatants were measured using a Th1/2/17 cytokine bead array (BD Biosciences). IL, interleukin; TNF, tumor necrosis factor; IFNγ, interferon-gamma.

Evidence of tumor remission in response to WT-1 ACT

WT-1 is a non-mutated tumor-associated antigen that is overexpressed in various cancers, particularly brain cancer [11,21]. Owing to the basal expression of WT-1 in normal tissues [21], CD8+ T cells with high affinity for WT-1 are typically eliminated in the thymus during positive and negative selection [22], meaning that WT-1-specific CD8+ T cells are rarely present in the periphery of healthy individuals. However, their frequencies are unexpectedly increased in a significant proportion of cancer patients, providing a reliable platform for producing WT-1-specific CD8+ T cells from cancer patients [23].

Self-antigen-specific CD8+ T cells usually fail to proliferate in response to their respective antigens owing to immune tolerance mechanisms [9,24]. Nonetheless, these tolerant T cells can be rescued and induced to proliferate under lymphopenic conditions when exposed to self-antigens [25]. Because cancer patients often experience transient lymphopenia due to chemotherapy or radiotherapy, it is plausible that tolerant CD8+ T cells reactive to self-tumor antigens, including WT-1, would proliferate during treatment, particularly when tumor cells abundantly express WT-1. Thus, the response rate of CD8+ T cells against WT-1 seems to correlate with the level of WT-1 expression in tumor cells and, consequently, the efficacy of the treatment.

One approach to overcome the unresponsiveness of self-antigen-specific CD8+ T cells is to isolate and expand these antigen-specific T cells *ex vivo* and re-infuse them into the lymphodepleted patient. This case study demonstrates that this therapeutic strategy was effective and possibly resulted in the complete regression of anaplastic ODG through "cancer-immunity cycle" [11]. Additionally, given that cancer patients often undergo transient lymphopenia after chemotherapy or radiotherapy, it is reasonable to expect that tolerant CD8+ T cells reactive to self-tumor antigens, such as WT-1, would proliferate, particularly when dying tumor cells release WT-1 proteins. Therefore, the increased frequencies of WT-1-specific CD8+ T cells appear to reflect higher WT-1 expression in tumor cells, thereby positively correlating with the efficacy of WTiNT cell therapy.

Slow but sustained response of anaplastic ODG to ACT

The clonal heterogeneity of cancer cells in advanced cancer patients presents a significant challenge, with most current cancer treatments offering a very low chance of curing patients. However, cancer immunotherapy, including immune-

oncology drugs and immune cell therapies, has shown the ability to induce complete and durable regression, even in metastatic and recurrent cancers—results that are rarely seen with conventional cytotoxic or targeted anti-cancer therapies [11,12]. The immune system develops anti-cancer immunity through a series of molecular and cellular processes, which can be effectively explained by the cancer-immunity cycle [10]. The ultimate goal of cancer immunotherapy is to sustain this immunity cycle in patients, continually activating and proliferating CD8+ T cells against tumor-associated antigens, including neoantigens. Therefore, modern cancer immunotherapy can be characterized as a driving force that accelerates the cancer-immunity cycle.

In this case, it was observed that the CD8+ T-cell population steadily increased following the infusion of WTiNT cells (Fig. 5D). Initially, the infused WTiNT cells likely targeted and eliminated WT-1+ tumor cells, which could have promoted the induction of secondary anti-tumor responses against other released tumor antigens. The broadening of epitope recognition by the patient's T cells, known as "epitope spreading," is considered essential for achieving durable complete tumor regression [26,27].

Cancer cells also hijack inflammatory processes to support their growth [28,29], ultimately creating an immune-suppressive environment [30-32]. Therefore, the clinical outcome of immunotherapy will depend on its ability to continuously overcome this cancer-mediated immune suppression and accelerate the cancer-immunity cycle. Since many factors influence the balance between enhancing the cancer-immunity cycle and mitigating immune suppression, it is not always predictable when this balance will shift. This may explain why immunotherapy sometimes leads to slow or delayed responses in cancer patients.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14791/btrt.2025.0010.

Ethics Statement

This report was conducted according to the guidelines of the Declaration of Helsinki for biomedical research, and the Institutional Review Board of National Cancer Center exempted the requirement for written informed consent to publish the retrospective case report with a minimal risk for the patient.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Author Contributions

Conceptualization: Ho-Shin Gwak. Data curation: all authors. Investigation: all authors. Methodology: all authors. Project administration: all authors. Resources: Ho-Shin Gwak. Supervision: Ho-Shin Gwak. Validation: Ho-Shin Gwak. Visualization: all authors. Writing—original draft: all authors. Writing—review & editing: all authors.

Conflicts of Interest

Ho-Shin Gwak, the Editor-in-Chief of *Brain Tumor Research and Treatment*, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

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