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Treatment of refractory recurrent malignant glioma with adoptive cellular immunotherapy: a case report

Yiwu Huang [a], Roberta L. Hayes [b,c,*], Shelley Wertheim [d], Ehud Arbit [e], Ronald Scheff [f]

[a] *The Department of Medicine, Sanford R. Nalitt Institute for Cancer and Blood-Related Diseases, Staten Island University Hospital, 256 Mason Avenue, Staten Island, NY 10305, USA*

[b] *Immunotherapy Program, Sanford R. Nalitt Institute for Cancer and Blood-Related Diseases, Staten Island University Hospital, 256 Mason Avenue, Staten Island, NY 10305, USA*

[c] *Department of Laboratory Medicine, Sanford R. Nalitt Institute for Cancer and Blood-Related Diseases, Staten Island University Hospital, 256 Mason Avenue, Staten Island, NY 10305, USA*

[d] *Department of Radiology Sanford R. Nalitt Institute for Cancer and Blood-Related Diseases, Staten Island, University Hospital, 256 Mason Avenue, Staten Island, NY 10305, USA*

[e] *Department of Neurosurgery, Sanford R. Nalitt Institute for Cancer and Blood-Related Diseases, Staten Island University Hospital, 256 Mason Avenue, Staten Island, NY 10305, USA*

[f] *Medical Oncology, Sanford R. Nalitt Institute for Cancer and Blood-Related Diseases, Staten Island University Hospital, 256 Mason Avenue, Staten Island, NY 10305, USA*

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Abstract

We report the successful treatment of a patient with recurrent malignant glioma with adoptive cellular immunotherapy. The patient is a young adult with recurrent progressive disease refractory to aggressive multi-modality therapy including repetitive surgical resection, radiation, radiosurgery and chemotherapy. He received multiple courses of local administration of autologous lymphokine-activated killer (LAK) cells in combination with a low dose of interleukin-2 (IL-2) through an Ommaya reservoir-catheter system. The side-effects of this treatment were limited and manageable. The patient achieved a complete remission, as demonstrated by MRI and confirmed by glucose-positron emission tomography (PET) imaging 11 months after initiation of immune therapy. Twenty-six months later, the patient is still in remission with improving performance status. Adoptive cellular immunotherapy utilizing autologous LAK cells with low dose IL-2 appears to be a safe and effective therapy for a subset of patients with primary, recurrent or progressive malignant glioma following conventional therapy. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Glioblastoma; IL-2; Immunotherapy; Interleukin-2; LAK; Lymphokine-activated killer cells; Malignant glioma; Survival

* Corresponding author. Fax: +1-718-2266467.
E-mail address: roberta_hayes@siuh.edu (R.L. Hayes).

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1. Introduction

In the United States, primary central nervous system malignancies are the second and fourth most common causes of cancer death in children and young people aged 15–34 respectively [1,2], and are the fourth fastest growing type of cancer in the elderly [3]. Over 17 000 new cases and more than 13 000 deaths were projected to occur in 1998 [2], with the majority of mortality resulting from high-grade astrocytic neoplasms [4]. Current standard therapeutic approaches including neurosurgery, radiation therapy and chemotherapy have only slightly improved the prognosis of these tumors. None of these approaches are generally associated with long-term durable responses. Patients who fail to respond or relapse after conventional combination therapy have an extremely poor prognosis, with a median survival of 9 months following recurrence for glioblastoma multiforme [4,5]. Hence, more effective treatments for these fatal diseases are needed. Adoptive cellular immunotherapy is a relatively new therapeutic approach that transfers cells with antitumor activity to the tumor-bearing host. These cells are generated by ex-vivo stimulation of autologous peripheral blood lymphocytes with various lymphocyte-activating agents such as interleukin-2 (IL-2), T cell mitogens or anti-CD3 antibodies. The activated mononuclear cells develop the ability to kill tumor cells, sparing normal host cells [6–8]. Although early clinical trials using adoptive immunotherapy with high-dose IL-2 in brain tumor patients had limited success [9–12], the results of several recent studies have been encouraging [3,9,12,13]. Here, we present a patient with refractory recurrent malignant glioma who was treated with adoptive cellular immunotherapy.

2. Case report

PD is a 35 year old white male who initially presented with a seizure in October 1989 and was diagnosed with a right fronto-parietal grade II/IV astrocytoma. He underwent a craniotomy with a subtotal removal of the tumor on October 23, 1989 and then underwent wide-field radiation therapy to a dose of 54 Gy to the tumor area. The residual non-enhancing lesion remained essentially stable during follow-ups throughout 1990–1992; however, a follow-up MRI performed on October 25, 1993 indicated progression of the tumor. A second surgery was performed on November 11, 1993. Pathologic examination of the tissue indicated an anaplastic mixed oligoastrocytoma, grade III/IV. From December 1993 to March 1994, the patient received three cycles of PCV [procarbazine, lomustine (CCNU) and vincristine] chemotherapy at Massachusetts General Hospital. The chemotherapy was stopped prematurely because of peripheral neuropathy. The tumor again remained stable until the end of 1996 when a tumor recurrence was noted radiographically.

The patient presented to Staten Island University Hospital in April 1997 and intravenous paclitaxel (Taxol) chemotherapy (80 mg/m^2) plus fractionated stereotactic radiosurgery was initiated to a tumor volume of 60.2 cm^3, weekly times 4. The radiosurgery dose was 6 Gy at the 90% isodose line times 4. In July 1997, tumor progression was noted, and on August 6, 1997 a gross total resection was performed to remove a 5–6 cm right frontal parasagittal mass extending to the ventricle. During surgery, an Ommaya reservoir/catheter system was placed for subsequent regional immune therapy. Pathologic examination of the newly resected tumor was consistent with high-grade glioblastoma multiforme with areas of necrosis and treatment-related effects. Following surgery, the patient underwent a second course of paclitaxel chemotherapy plus fractionated stereotactic radiosurgery to the residual tumor bed area in October 1997 (80 mg/m^2 taxol plus 6 Gy times 4).

Upon a follow-up visit in December 1997, a contrast enhanced MRI showed further enhancement within the surgical bed with extension beyond the solid component, most consistent with progression of neoplasm or less likely radiation necrosis, due to extension. (Fig. 1A, B). The patient was referred for initiation of adoptive immunotherapy. Autologous peripheral blood mononuclear cells were harvested by leukapheresis [3]. Following a 5–7 day ex-vivo incubation with high dose IL-2, activated killer cells (5×10^8 to 8×10^8 cells per cycle) were infused into the post-operative tumor cavity through the Ommaya reservoir with additional low-dose IL-2. LAK cells were infused on the first day of each cycle, followed by repetitive intracavitary boluses of IL-2 alone given five times during each 2 week period, generally on a Monday, Wednesday, Friday schedule. After a 2 week break, LAK cells and IL-2 were again administered into the Ommaya reservoir over 2 weeks to complete one 6 week course of therapy. The patient received four courses of treatment at 3 month intervals and then maintenance treatment every 6 months. His last treatment was in December 1999.

The patient tolerated the treatments moderately well, although, individual IL-2 doses were held during later cycles of treatment for symptom management. During the first cycle of treatment, the patient exhibited signs of increased intracranial pressure. Reversible diffuse parenchymal edema surrounding the tumor was observed on non-contrast CT scan,

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and the initial starting dose of IL-2 (0.9 Million IU) was de-escalated in subsequent doses of therapy to 0.6 MIU. Additional dose reductions were made for headache and increased extremity weakness, to 0.3 MIU and finally 0.2 MIU per dose during the maintenance phase of treatment. Results of routine chemistry and hematological studies were stable throughout the entire course of therapy. The main side-effects of this treatment were manifested as fever, headache with nausea and transient worsening of focal neurological symptoms (i.e. decreased movement of the affected extremities) that responded to conventional management with acetaminophen, prochlorperazine, ondansetron and oral corticosteroids. In order to avoid immunosuppression, corticosteroid use was carefully monitored, and additional doses were used

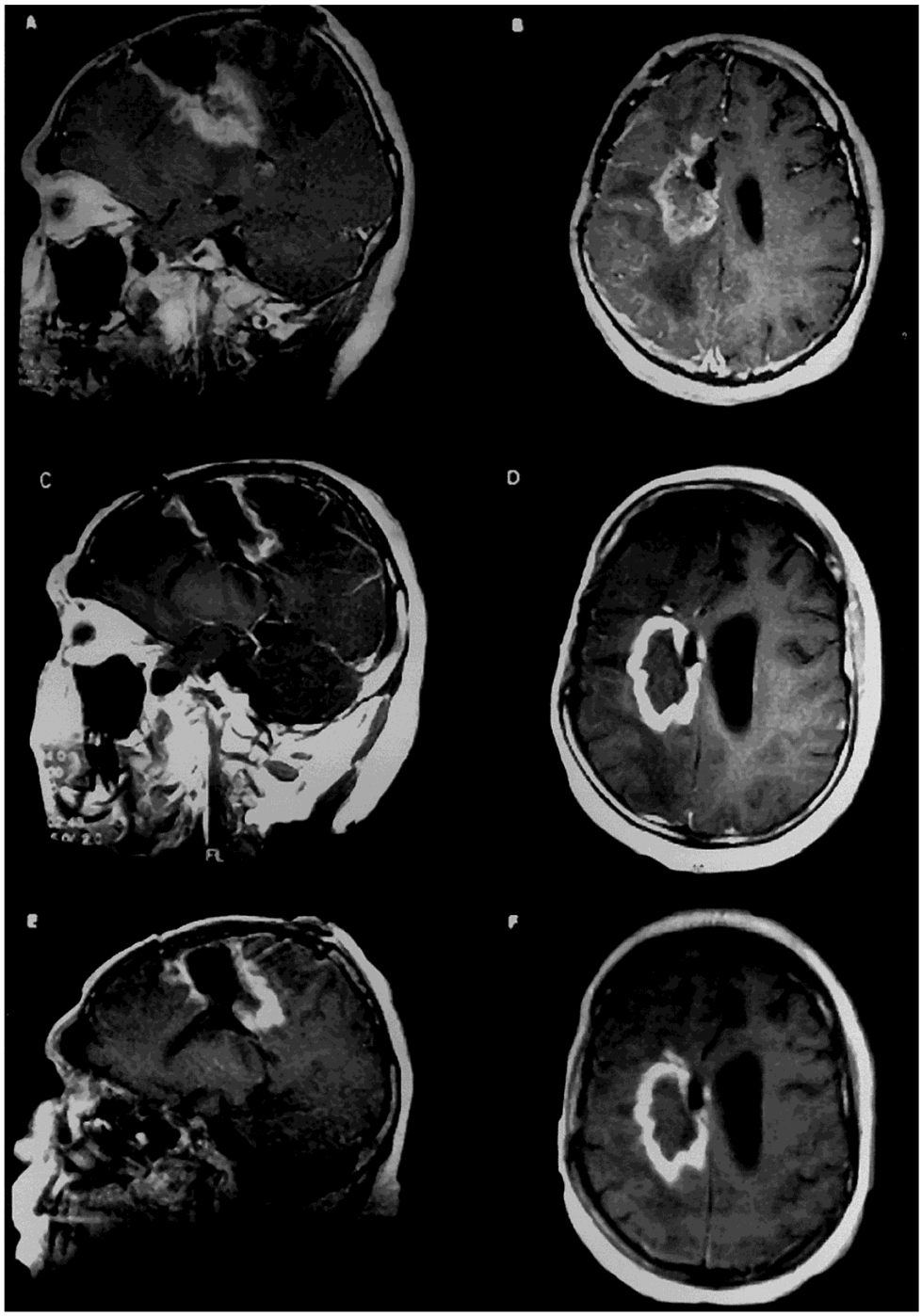

Fig. 1. Contrast-enhanced MRI of the brain: prior to initiation of immunotherapy (A, B); 11 months after initiation of immunotherapy (C, D); and 13 months after initiation of immunotherapy (E, F).

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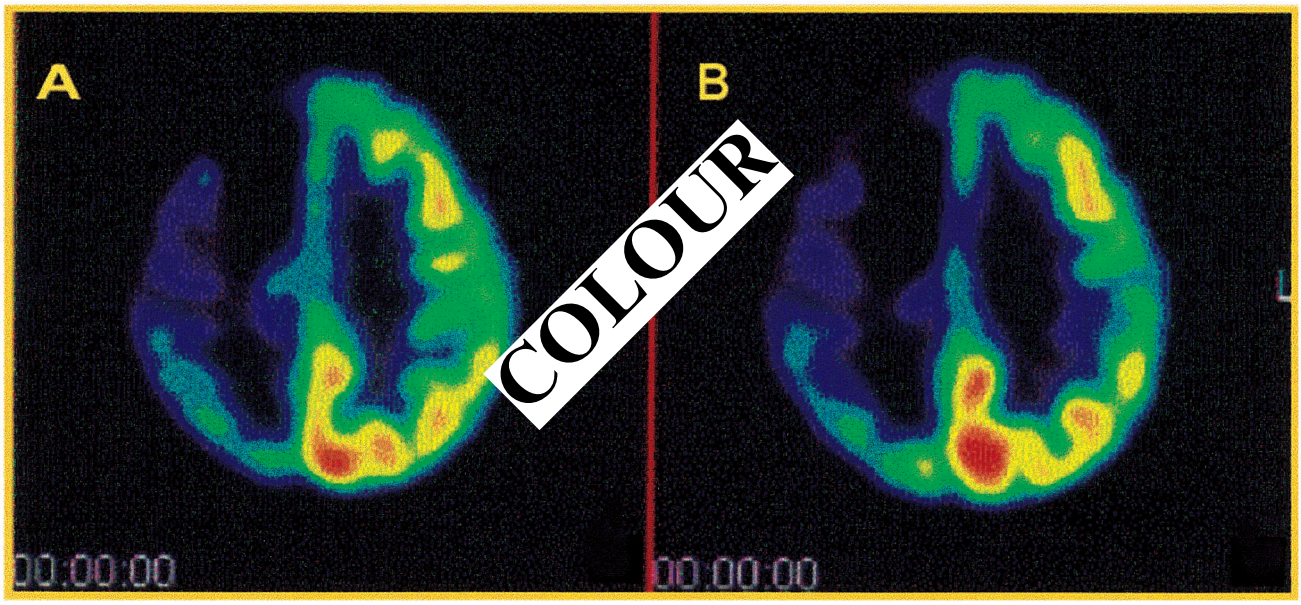

Fig. 2. ^{18}Fluoro-deoxy glucose (FDG)-PET scan showing no evidence of increased metabolic activity in the region corresponding to the contrast-enhanced rim observed on corresponding MRI (A, B)

only as needed to moderate side-effects. This patient presented with more acute signs and symptoms of intracranial pressure than the other patients previously treated with immune therapy, and we interpret this finding to the communication of the tumor cavity with the right lateral ventricle, and the likelihood that some of the patient's migraine-like headaches were due to meningeal irritation.

In March 1998, following the first course of immunotherapy, a contrast-enhanced MRI demonstrated diminished central enhancement. Serial contrast-enhanced MRIs (Fig. 1C, D, E, F) showed a continued lack of central enhancement within a thin enhanced rim with no change in mass effect. In order to help discriminate whether the rim of tumor enhancement noted on MRI was due to residual disease or a gliotic or fibrotic scar, an ^{18}F-2-fluorodeoxyglucose positron emission tomographic (PET) scan was requested. An ^{18}FDG PET scan performed on November 3, 1998 (Fig. 2) showed no evidence of increased metabolic activity in the region corresponding to the contrast-enhanced rim seen on MRI. Twenty-six months after initiation of the immunotherapy, the patient is still in remission with excellent performance status and improving neurologic function.

3. Discussion

In this case report and in previous studies [3], we have demonstrated that regional adoptive cellular immunotherapy can exert a significant anti-glioma effect, alter the course of progressive malignant glioma and induce durable response in some patients with recurrent refractory malignant glioma. The initial course of the disease in this case was consistent with low-grade astrocytoma that remained stable after surgical resection and radiation therapy. Three years later, the tumor recurred and was treated with a second subtotal tumor resection and PCV chemotherapy. Pathological diagnosis at this time was high-grade mixed oligoastrocytoma. The tumor then remained stable for another 3 years. Prior to initiation of immunotherapy, acceleration of disease progression was observed by increasing tumor size, edema and mass effect on MRI as well as a worsening of neurological symptoms despite repeated tumor resection, chemotherapy and stereotactic radiosurgery. The clinical behavior and pathologic features of the last resected tumor were consistent with glioblastoma multiforme. After four courses of immunotherapy, the improvement in neurological signs and symptoms as well as MRI and FDG-PET studies are consistent with complete remission.

Many studies have shown that patients with malignant glioma have deficiencies in immune responses including impairment of B- and T cell functions and antibody-mediated cytotoxicity [16]. During the last decade, IL-2 has been widely used to boost the immune system to fight tumor cells, and incubation of peripheral blood mononuclear cells with high-dose of IL-2 ex vivo can result in the appearance of a heterogeneous group of non-restricted killer cells (LAK cells) that are distinct from classic natural killer (NK) cells or cytotoxic T lymphocytes (CTL). These cells

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are capable of killing a variety of tumor cell targets including malignant glioma cells but not normal host cells such as normal brain cells [7,17–19]. Studies have shown that direct contact between LAK cells and tumor cells is necessary for initiating tumor cell lysis [3,7]. Because the majority of intravenously administered LAK cells will migrate to liver, spleen and lung, with only a very small portion of cells entering the brain tumor site [20], several brain tumor immunotherapy trials have focused on the local regional delivery of therapy directly into the brain tumor lesions or resection cavities through a reservoir/catheter system in order to reduce systemic toxicities and concentrate the local immunotherapeutic effects where most needed [3,9,11]. Several immunotherapy trials have yielded various clinical response rates ranging from 10 to 40% with very few complete responses [3,9,11,14–16,21–34]. Our approach was one of the first to report clinical benefit as well as to demonstrate increased survival [3]. It is extremely difficult to evaluate the overall clinical efficacy of these clinical trials because of the small patient numbers, the variability of the clinical protocols used, and patients' conditions.

We used a regimen consisting of multiple administrations of autologous LAK cells followed by small doses of IL-2, in order to sustain the viability and cytotoxicity of the infused LAK cells in vivo and to recruit a host antitumor response [3,7]. Regional low doses of IL-2 have been shown to increase the tolerance and decrease the life-threatening toxicities of IL-2, and may prolong the antitumor activity of LAK cells. However, high doses of IL-2 can induce severe cerebral edema in patients with brain tumors and the apoptosis of LAK cells [11]. In addition, it is very important to limit the use of corticosteroids during immune therapy because high doses of steroids may decrease the effectiveness and cytolytic activity of LAK cells [18,35] and the recruitment of host CTL [9].

Uptake and metabolism of glucose, as measured by FDG-PET scan, has been successfully used to predict the grade of malignancy, localize biopsy sites, identify tumor recurrence, and distinguish tumor recurrence from radiation necrosis, as well as discriminate residual tumor from post-operative enhancement seen in CT and MRI [36]. In addition, unlike MRI or CT enhancement, FDG metabolism is not affected by the administration of corticosteroids [36]. In order to determine whether the post-treatment enhanced lesion seen in this patient's MRI represents a reactive gliosis (reactive astrocytes) or residual tumor cells, FDG-PET imaging was performed to rule out the presence of high metabolic tumor cells.

This case demonstrated that intracavitary infusion of autologous LAK cells and IL-2 in patients with recurrent malignant glioma refractory to other modalities could result in complete remission. However, it is still unknown which patients will benefit from this type of treatment. Previous observations [3] that the increased eosinophils in the intracavitary fluid obtained via the Ommaya reservoir during early immunotherapy may predict the clinical response were also noted in this case, suggesting that these cells may play an integral role in the anti-tumor response, although the exact mechanism of action is unknown [37,38].

In summary, this report demonstrates that enhancement of host antitumor immunity by repetitive cycles of local LAK cell administrations along with low doses of IL-2 may lead to sustained remission in some patients with recurrent malignant glioma. Because of the poor prognosis of this disease, this novel therapy in combination with conventional therapies may be a reasonable effective alternative for some patients with malignant glioma, particularly for those with a good clinical performance status after subtotal surgical debulking, or in the adjuvant setting, following initial surgery and radiation therapy. More clinical trials are warranted to evaluate the efficacy of immune therapy and to identify those patients who may benefit from this treatment.

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Biographies

Yiwu Huang received his MD in 1984 from the Fujian Medical School in China, followed by a Ph.D. in 1989 from the Peking Union Medical College in Beijing where he studied monoclonal antibodies against hepatomas. From 1990 to 1997, he was a member of the laboratory of Ellen Vitetta at the University of Texas Southwestern Medical School in Dallas where he studied adhesion molecules and antibody activity against multiple myeloma. In 1997, he joined Staten Island University Hospital as a resident physician. He is currently a Clinical Fellow in Hematology an Oncology at the Robert Wood Johnson Medical School in New Brunswick, New Jersey.

Roberta Hayes received her Ph.D. from the University of Colorado Health Sciences Center in Denver in 1982 in Immunology and Microbiology under the mentorship of Henry Claman, M.D. Subsequently, she was a post-doctoral fellow at Rush Medical College in Chicago, Illinois, where she studied cytotoxic T cell differentiation and helper cell growth factors. In 1986, she joined the research faculty at New York University Medical Center in Neurosurgery to develop immune-based approaches for the treatment of primary brain

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tumors. At NYUMC, clinical trials were initiated for patients with high-grade astrocytic tumors with Maxim Koslow, M.D. and Joseph Ransohoff, M.D. In 1996, she became the Director of the Cancer Inununotherapy Program at Staten Island University Hospital's Nalitt Cancer Institute in Staten Island, NY, and currently holds academic appointments in Medicine at the SUNY Health Sciences Center in Brooklyn, and in Microbiology at NYUMC. Her research interests include immune and gene therapy, cancer vaccines, and molecular epidemiology.

Shelley Wertheim received her MD at the State University of New York (SUNY) Downstate Medical Center, College of Medicine, in Brooklyn in 1984. She was an Intern in Medicine at Beth Israel Medical Center in New York, and did her Residency in Diagnostic Radiology followed by a Fellowship in Neuroradiology at the SUNY Downstate-Kings County Hospital Center in Brooklyn, NY. In 1989, she joined Staten Island University Hospital and currently serves as Chief of Neuroradiology in the Department of Radiology. Her areas of research interest are the MR and SPECT appearances of brain lesions.

Ehud Arbit received his medical degree from Tel Aviv University Medical School in 1973. He went on to complete his Neurosurgery residency at New York Hospital-Cornell Medical Center in 1981. He has worked as an attending neurosurgeon at the Jewish General Hospital in Montreal and has been Chief of Neurosurgery at both Memorial Sloan Kettering Cancer Center and Staten Island University Hospital. He has had numerous teaching appointments throughout his career, including Professor of Neurosurgery at Cornell University Medical College. He is presently the Executive Medical and Scientific Advisor for a biotechnology company in the New York metropolitan area. He has published over 100 papers and chapters covering neurosurgery and neuro-oncology.

Ronald Scheff received his MD from Columbia University College of Physicians and Surgeons in New York in 1988. He completed his Internship and Residency in Internal Medicine a the Deaconess Hospital in Boston, MA, before returning to New York to pursue a Hematology and Medical Oncology Fellowship at the Memorial Sloan Kettering Cancer Center, Cornell University Medical Center. In 1995, he joined the Nalitt Institute for Cancer and Blood-related Diseases at Staten Island University Hospital, where he also serves as the Director of Cancer Genetics and Risk Assessment.

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