



Highly Active Antiretroviral Therapy and Gamma Knife Radiosurgery for the Treatment of AIDS-Related Primary Central Nervous System Lymphoma

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Key words

- AIDS
- CD4
- Lymphoma
- Oncology
- Primary central nervous system lymphoma
- Radiosurgery
- Retrovirals

Abbreviations and Acronyms

AIDS: Acquired immunodeficiency syndrome

GKRS: Gamma knife radiosurgery

HAART: Highly active antiretroviral therapy

HIV: Human immunodeficiency virus

MATRIX: Methotrexate, cytarabine, thiotepe, and rituximab

PCNSL: Primary central nervous system lymphoma

WBRT: Whole brain radiation

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Citation: *World Neurosurg.* (2019) 124:310-312.

<https://doi.org/10.1016/j.wneu.2018.12.182>

Journal homepage: www.journals.elsevier.com/world-neurosurgery

Available online: www.sciencedirect.com

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INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is a rare disease with a yearly incidence of 0.5 cases per 100,000 people,¹ accounting for <4% of brain tumors. The tumor is exclusively located in the central nervous system, usually progressing to compromise the brain parenchyma, spinal cord, meninges, and portions of the intracranial nerves and eyes.² Most PCNSLs are histologically characterized as diffuse, large B cell lymphomas that express multiple glycoprotein markers. A subset of this unusual cerebral

■ **BACKGROUND:** The criterion standard for the treatment of newly diagnosed primary central nervous system lymphoma (PCNSL) remains high-dose chemotherapy in conjunction with palliative whole-brain radiotherapy; however, there may be a role for novel combined approaches in immunocompromised patients.

■ **CASE DESCRIPTION:** A 66-year-old man presented with acute cephalalgia, disorientation, and lethargy. His condition was evaluated in the emergency department, and he was admitted with probable hydrocephalus. Magnetic resonance imaging (MRI) of the brain revealed multiple nonspecific brain lesions, predominantly involving the right temporal lobe, which on biopsy led to a diagnosis of PCNSL. Subsequent laboratory studies demonstrated active human immunodeficiency virus (HIV) infection, with a CD4 count of 21 cells/ μ L and an HIV viral load (VL) of >400,000 copies/mL. The patient was eventually given highly active antiretroviral therapy (HAART). He declined palliative whole-brain radiotherapy but was amenable to gamma knife radiosurgery (GKRS) for treatment of the right temporal brain lesions. Three months later, the patient's neurologic symptoms had improved; similarly, his CD4 count increased to 176 cells/mL, and his HIV viral load was <90 copies/mL. By the 12-month follow-up visit, the patient was asymptomatic, and at 36 months, MRI of the brain demonstrated total remission without new brain lesions.

■ **CONCLUSIONS:** The criterion standard for treatment of newly diagnosed PCNSL remains high-dose chemotherapy in conjunction with palliative whole-brain radiotherapy; however, there may be a role for novel combined approaches using chemotherapy, HAART, and GKRS to have a positive impact on survival rates of PCNSL related to AIDS.

malignancy (~15%) is associated with infection with human immunodeficiency virus (HIV) and characteristically demonstrates co-infection with Epstein-Barr virus. The median age at diagnosis of HIV-associated PCNSL is over 60 years, with a median survival of 10 to 20 months and a 5-year survival of 20% to 30%.³ Patients with acquired immunodeficiency syndrome (AIDS) typically have a poorer prognosis, with a median survival of 13.5 months, even when treated with multimodal therapy.

CASE REPORT

A 66-year-old Cuban-American man presented to the emergency department with

cephalgia, disorientation, and lethargy. His laboratory study results were notable for a CD4 count of 21 cells/mL and an HIV viral load of 400,000 copies/mL. Magnetic resonance imaging (MRI) of the brain showed multiple nonspecific brain lesions predominantly involving the right temporal lobe, diffuse white matter signal abnormality throughout the cerebral hemispheres, mild enlargement of the lateral ventricles, and a 1-centimeter left temperoparietal mass. The differential diagnosis included neurocysticercosis; however, the patient's neurologic status declined to frank stupor, despite a 7-day course of appropriate antibiotic therapy. In light of his global cognitive defects in the absence of focal motor neurologic

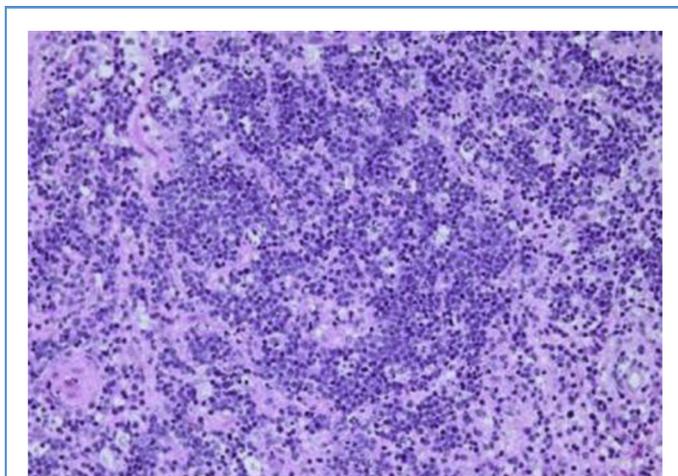


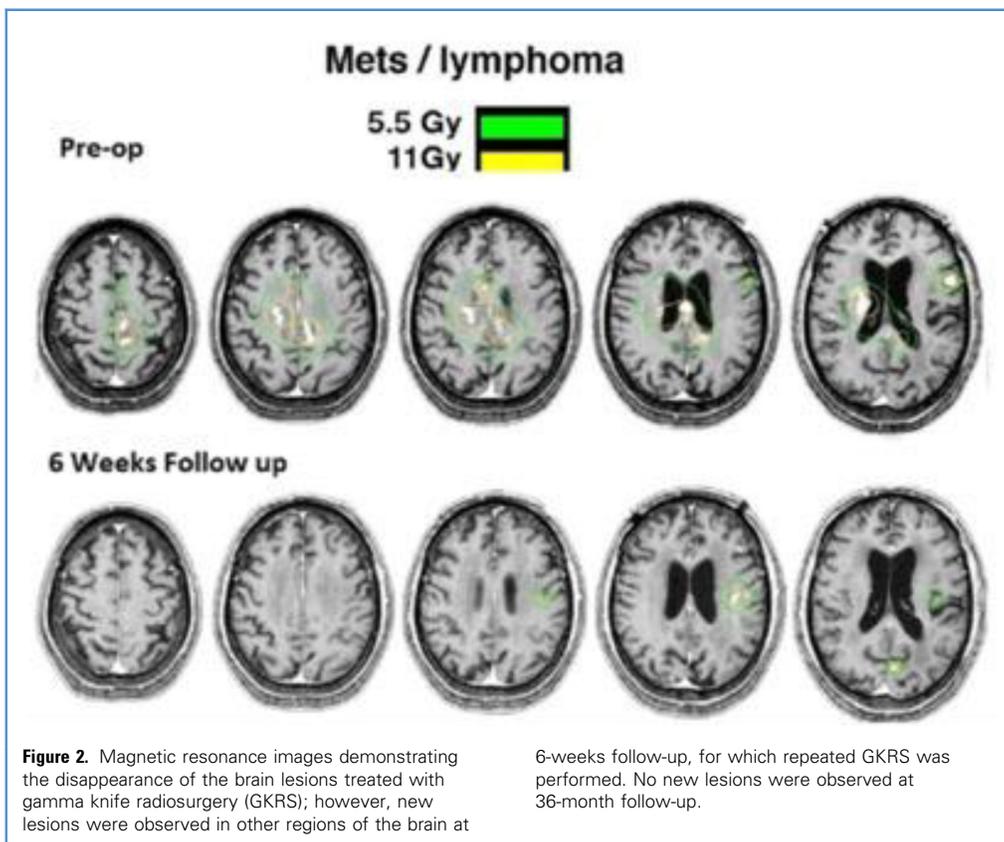
Figure 1. Histologic sample of stereotactic-guided brain biopsy specimens showing diffuse infiltrate of lymphocytes encircling central nervous system, identified as diffuse large B-cell lymphomas.

findings, the patient was referred to hospice care. Subsequent MRI of the brain showed progression of the aforementioned multiple nonspecific brain lesions, for which evaluation from the neurosurgery service was requested. The patient

underwent stereotactic guided brain biopsy, which established a diagnosis of PCNSL (Figure 1). The risks and benefits of standard therapy, consisting of chemotherapy and palliative whole-brain radiotherapy (WBRT), were discussed

with both the patient and his family, who subsequently refused standard treatment. Thus, a second option using highly active antiretroviral therapy (HAART) in conjunction with gamma knife radiosurgery (GKRS) was proposed as a rescue therapy, for which the patient and his family were amenable.

The infectious disease consultant promptly initiated HAART, and GKRS was begun 4 weeks thereafter (Figure 2). At the 6-week follow-up visit, our patient began to recover his memory, and by 12 weeks he was successfully ambulating. Similarly, his CD4 count improved to 176 cells/mL, and his HIV viral load decreased to <90 copies/mL. At the 12 months follow-up visit, our patient was relatively asymptomatic. MRI of the brain at the 36 month follow-up visit demonstrated total remission without new brain lesions (Figure 2), at which point the patient described regaining weight and experiencing mild psychomotor symptoms. At the most recent follow-up visit, our patient's CD4 count was 390 cells/mL, and his HIV viral load was



nondetectable. His cognitive function and quality of life significantly improved, and he reported successful ambulation without assistance, ability to manage his own medications, and ability to independently carry out all of his activities of daily living. His most recent brain MRI continues to show no evidence of recurrent PCNSL. At the time of this publication, he was entertaining thoughts of returning to work and driving his vehicle again.

DISCUSSION

The understanding of PCNSL in AIDS has lagged behind that of the much more common systemic nodal lymphomas. The reasons for this include the rarity of PCNSL and the fact that lesions demonstrated by imaging can be related to the sequelae of HIV infection.² The dilemma faced in the treatment of PCNSL is the determination of a less invasive approach that will simultaneously offer higher success rates while limiting the adverse effects, such as neurocognitive weakness, neurotoxicity, and brain atrophy. Although the current standard of treatment for patients with newly diagnosed PCNSL remains high-dose methotrexate and WBRT, the use of such doses of methotrexate in elderly and/or immunodeficient patients may be associated with a higher risk of systemic toxicity because of the increased prevalence of comorbidities.⁴ Combination chemotherapy regimens, such as methotrexate, cytarabine, thiopeta, and rituximab (MATRix), are associated with a greater amount of hematologic

complications, including anemia, neutropenia, and thrombocytopenia.³

Historically, there has been a high incidence of severe neurotoxicity in patients receiving, WBRT predominantly those older than 60 years of age.^{1,2} For patients who present with PCNSL as their initial AIDS-defining event, effective HAART has been reported as an optional initial treatment, WBRT and corticosteroids being reserved for those who show signs of impending neurologic demise. Chemotherapy and other novel approaches could also be considered for selected patients with lesser degrees of immune suppression and high baseline functional status.

GKRS, in comparison with WBRT, provides targeted radiation to a multilesion presentation (as identified by imaging), perhaps attributed to a lower incidence of neurotoxicity and long-term cognitive effects. Of note, the aforementioned patient did not experience any permanent mental or memory impairment after 36 months of therapy, which is in partial agreement with an earlier report: Kenai et al.⁵ described a mean recurrence-free period of 24.4 months for their patients. Additionally, there seemed to be a predisposition to progression to new tumor growth in individuals who underwent standard-of-care therapy.

CONCLUSION

Overall, GKRS in combination with HAART appears to be a valuable method for the management of primary CNSL related to AIDS because it enables local control in a short-term period without

severe complications. Chemotherapy and other novel approaches could also be considered for certain individuals with lesser degrees of immune suppression and high baseline neurologic and systemic status.

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Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received 23 October 2018; accepted 24 December 2018

Citation: *World Neurosurg.* (2019) 124:310-312.

<https://doi.org/10.1016/j.wneu.2018.12.182>

Journal homepage: www.journals.elsevier.com/world-neurosurgery

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