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Hyperosmolar and methotrexate therapy avoiding surgery in the acute presentation of primary central nervous system lymphoma

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Abstract

Background: Primary central nervous system lymphoma (PCNSL) is an aggressive type of extra-nodal non-Hodgkin lymphoma. Without treatment, PCNSL is associated with significant morbidity and mortality, including rapid neurological deterioration. In contrast to other high-grade intracranial neoplasms, PCNSL is considered to have a high response rate to conventional medical therapy, especially in younger patients, and therefore warrants particular attention in terms of nonsurgical treatment.

Case Description: We report a case of the medical management of acute deterioration due to rapidly growing PCNSL with mass effect to highlight the efficacy of temporization with hyperosmolar therapy while awaiting the known rapid effects of dexamethasone and methotrexate (MTX) treatment. Surgical intervention was avoided, and tumor response was rapid. The patient had corresponding clinical resolution of symptoms of elevated intracranial pressure with return to neurologic baseline.

Conclusions: Despite the evidence that PCNSL responds well to steroids and MTX, the rapidity of onset with which this occurs can vary. In patients presenting with mass effect and rapid neurologic decline, there is little evidence to support medical over surgical intervention. Herein we present an illustrative case of a large PCNSL lesion presenting with rapid decline. With clinical improvement in one day and a 50% reduction in tumor volume over less than seven days, the authors present the specific time frame with which PCNSL responds to medical therapy and a safe strategy for medical temporization.

Key Words: Dexamethasone, hyperosmolar therapy, high-dose steroid, methotrexate, primary central nervous system lymphoma

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BACKGROUND AND IMPORTANCE

Primary central nervous system lymphoma (PCNSL) is an aggressive type of extra-nodal non-Hodgkin lymphoma, the most common subtype being diffuse large B-cell lymphoma. PCNSL accounts for approximately 4% of all intracranial neoplasms and by definition is located exclusively in the central nervous system (CNS). Systemic involvement changes the diagnosis from primary to secondary CNS lymphoma. The incidence

of PCNSL in the United States is approximately 4.6 per million, with a median age at onset between 60 and 65 years in non-immunocompromised patients.[21] Without treatment, PCNSL is associated with significant morbidity and mortality, including rapid neurological deterioration conveying a median overall survival (OS) of approximately 11.8 months.[14] In contrast to other malignant primary intracranial neoplasms, PCNSL has a high response rate to conventional therapy, especially in younger patients, and therefore warrants particular attention in terms of treatment.[20] Common management options of PCNSL consist of high-dose steroids, whole brain radiotherapy (WBRT), systemic chemotherapy, intrathecal chemotherapy, and systemic chemotherapy. With these therapies, complete radiographic remission is possible.[1] Radiographic response to steroids may be a positive prognostic indicator, with OS increasing to 117 months compared with 5.5 months in non-responders.[14] However, the efficacy of steroids is short-lived.[14] Despite the evidence that PCNSL may respond well to medical therapies, the rapidity of onset with which this occurs is not well-documented and is an important factor in determining management strategies in the patient presenting with neurologic decline related to tumor mass effect.

Radiation therapy is often used in the treatment of PCNSL.[20] While weighing toxicities, radiotherapy may be combined with chemotherapy, increasing remission rates and potentially prolonging OS.[5] Among many chemotherapeutic agents, methotrexate (MTX) is the only agent established as a standard of care in PCNSL.[20] MTX is often given in high doses of 8 g/m^2 in two-week intervals.[2] Numerous reports of MTX as monotherapy document favorable OS and progression-free survival rate (PFS).[4,9,18] MTX induction (8 g/m^2) demonstrated an overall response rate of 85% in a large single institution cohort study involving 117 evaluable patients.[4] Complete response (CR) was achieved in 58% of patients after a median of six cycles of therapy over a period of three months. OS was seven years, and PFS was 3.1 years. PFS was higher (3.5 years) in patients who continued to receive MTX every three months, as opposed to those who discontinued MTX after one year (2.9 years).[4] A multi-center, phase II study of single MTX use (8 g/m^2) in 23 PCNSL patients demonstrated CR of 52%, partial response (PR) of 22%, and PFS of 13 months during the median follow-up period of 25 months.[2] Radiographic response was the end point of that trial, and CR was determined after a maximum of eight cycles (14 days each cycle). These response rates are appropriately focused on long-term outcome and are often determined after multiple cycles, with median published follow-up ranging from 1 to 37 months.[2]

Response criteria for PCNSL typically incorporate clinical evaluation including Eastern Cooperative Oncology Group (ECOG) performance score and Karnofsky performance scale (KPS), laboratory evaluations, including CSF cytology and serum lactate dehydrogenase level, and radiographic evaluation using gadolinium-enhanced magnetic resonance imaging (MRI).[1] Criteria for CR include complete disappearance of all enhancing lesions on gadolinium-enhanced MRI, no evidence of active ocular lymphoma, negative CSF cytology, and discontinuation of all steroids for at least two weeks at the time of CR determination.[1] In contrast, response to therapy is made on a primarily radiographic basis using the McDonald Criteria after multiple chemotherapy cycles, which generally spans a period of two months.[16] It is therefore recommended that gadolinium-enhanced MRI be performed approximately every two months during active therapy and no longer than two months after completion of all planned therapy for the assessment of overall treatment response.[1] At this time point, approximately 58% of patients achieve CR.[4] PR is defined as lesion reduction of less than 50% of enhancing tumor volume,[1] and is seen in approximately 27% of patients.[2] Radiographic response appears to predict OS in PCNSL patients treated with chemotherapy.[18]

With such robust responses to medical therapy and with the CNS-wide involvement of disease, surgical interventions in the treatment of PCNSL are usually limited to biopsy for tissue diagnosis and Ommaya reservoir placement for intrathecal chemotherapy.[6,7] More aggressive tumor debulking and resection may be reserved for acute decompensation secondary to lesional mass effect.[6] Although the initial response rate to medical therapy is high,[11,12] and many reports exist of vanishing lesions following steroid therapy,[17] the time frame in which lesion reduction is achieved is poorly defined. The goal of this report is to better elucidate the specific time-to-response when utilizing medical therapy and to assist in decisions regarding the safety of temporizing medical management in the acute presentation of PCNSL.

CLINICAL PRESENTATION

A 45-year-old previously healthy male presented to the emergency department with two days of right-sided tooth pain, jaw swelling, and one week of fever. Patient also had mild headaches prompting a computed tomography (CT) scan of the brain, which revealed a large right-sided insular lesion measuring 6 cm in maximal diameter with surrounding edema leading to effacement of right lateral ventricle with a mild right-to-left midline shift. On admission, the patient's neurologic exam was notable for slightly delayed response, mild left lower facial droop, and mild downward pronator drift of the left upper extremity. The patient underwent a right frontal stereotactic biopsy and was placed on a steroid taper postoperatively. Patient

was discharged to an acute rehabilitation facility in a stable condition on postoperative day two and arranged for follow-up for initiation of chemotherapy, pending biopsy results. Final pathology revealed PCNSL. Following discharge, the patient developed a rapid functional decline while at a rehabilitation facility. Repeat CT brain scan performed eight days after discharge demonstrated marked tumor progression and mass effect causing 1.5 cm right-to-left midline shift with early left ventricular trapping. Total tumor volume of the largest lesion seen on CT was estimated at 76 cm^3 [Figure 1]. The patient was admitted to the Neurological Intensive Care Unit for further management. On examination, patient was noted to be lethargic and dysarthric, with dense left hemiplegia. Patient was started on a high-dose steroid treatment of dexamethasone 10 mg intravenous (IV) every six hours. Hypertonic therapy with 3% NaCl was initiated for the acute treatment of cerebral edema, with goal serum sodium level between 145 and 150 mEq/L. The patient was also placed on sodium bicarbonate to achieve urine pH >7 to initiate MTX treatment, making the maintenance of a hyperosmolar state more difficult. With this aggressive medical treatment, patient's exam improved significantly but would fluctuate with changes in serum sodium concentrations. A total of 23% NaCl was used to achieve rapid increase in sodium levels during acute symptomatic declines and was required multiple times over the course of his admission. Surgical intervention was planned in the event the patient stopped responding well to the medical interventions.

The patient was then started on MTX therapy (8 g/m^2) with leukovorin. His level of consciousness immediately improved following the initiation of this multimodal medical therapy. On treatment day one, the patient was drowsy with stable left hemiparesis, but followed commands throughout. His level of alertness continued to fluctuate over the first two days of treatment and additional doses of 23% NaCl were administered while targeting a sodium goal of 150-160. CT scan performed on day one of therapy revealed persistent mass effect with midline shift [Figure 2]. By post-treatment day two, the patient began to demonstrate increased verbal responses and brisk responses to commands. By treatment day four, his clinical improvements were more consistent, without fluctuation, and by treatment day seven, he had returned to his neurologic baseline. Repeat MRI on this day revealed a significant interval decrease in size of the right insular mass (50% volume reduction, to approximately 38 from 76 cm^3) [Figures 1 and 3] with decreasing edema, mass effect, and midline shift. On treatment day 14, the patient received another cycle of MTX therapy (8 g/m^2). Hypertonic saline and high-dose steroid therapy with dexamethasone 10 mg IV every six hours was continued throughout the hospital course. Dexamethasone was decreased to 8 mg IV every six hours over 2 weeks' time. Patient was discharged to skilled nursing facility on dexamethasone 8 mg twice a day on hospital day 19 in a stable condition.

Despite rapid response, the patient proved refractory to primary medical therapy and started WBRT one month following presentation with excellent results. He was most recently seen on follow up 16 months after the initial diagnosis with MRI revealing tumor mass resolution with no enhancement and only treatment-related changes [Figure 4]. He has experienced marked functional improvement, allowing him to live at home and be independent in activities of daily living.

DISCUSSION

This report illustrates three main points in the management of PCNSL. First, this case highlights the rapidity of onset at which acute mass effect of PCNSL responds to medical management. While robust response to therapy has been previously established, the expected time to response to medical therapy is not well-defined

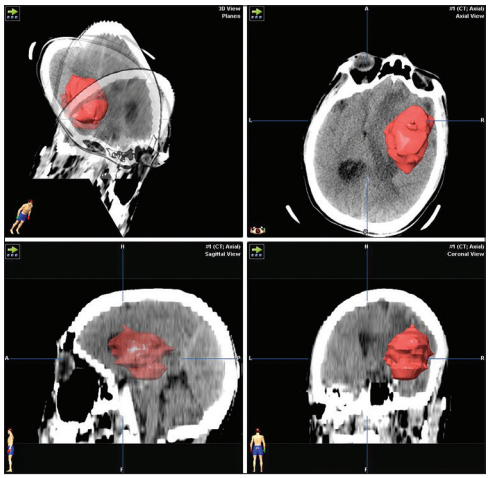

Figure 1: Volumetric CT reconstruction pretreatment day one

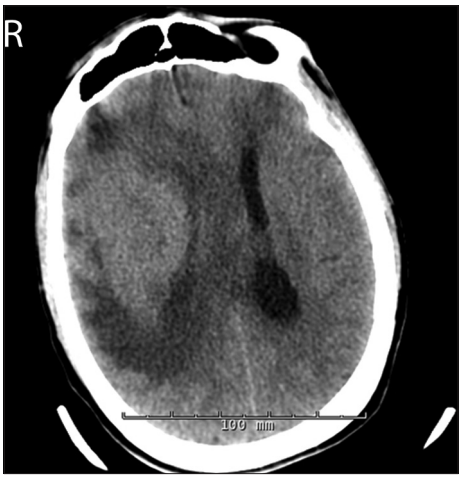

Figure 2: Interval CT on treatment day one

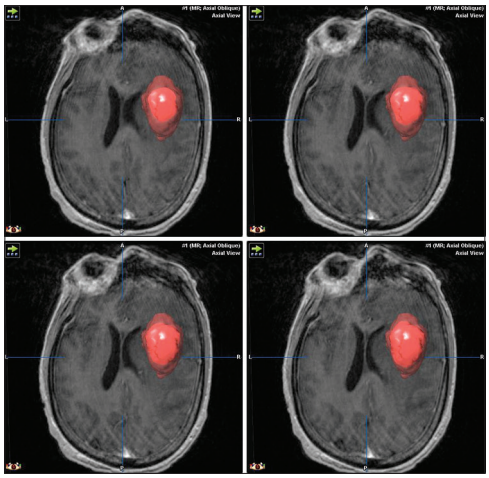

Figure 3: Volumetric MRI reconstruction posttreatment day seven

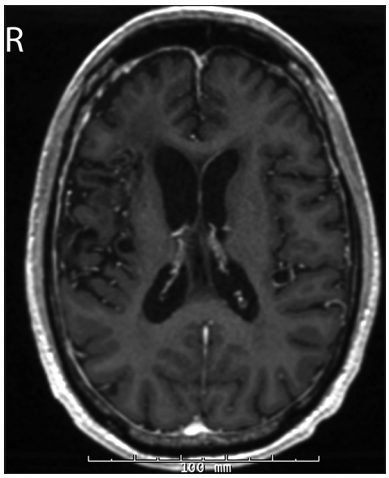

Figure 4: Most recent MRI brain with contrast

in the current literature. Second, in cases of significant mass effect, the authors propose that it is reasonable to temporize intracranial pressure with the knowledge that medical therapy may achieve clinically significant cytoreduction within days. Finally, hyperosmolar therapy is a potentially safe and efficacious short-term treatment of cerebral edema secondary to tumor mass effect.

Significant response of PCNSL to high-dose steroid use has been well-documented in literature, with clinical improvement shown in at least 90% of patients.[15] Time to response, however, has not been well-defined, particularly prior to two months. In this report, clinical response was seen after only one day with 50% reduction in tumor volume and resolution of acute symptoms by seven days. In murine models, lymphoid tumor cells, which were shown to contain specific cortisol receptors involved in the initial events of hormone action, were killed by adrenal steroids.[3] However, in the steroid-resistant lymphoma cell populations, in which specific binding was less than that of the parent lines, cell-killing activity was much less effective, and cortisol concentration required to kill the lymphoma cells in the two different populations was significantly different.[3] High-dose steroids have also been demonstrated to be effective in non-lymphoma brain tumors. There have been case reports describing the medical therapy composed only of high-dose steroids to induce reduction of tumor volume and edema size, along with resolution of symptoms as rapid as within seven days.[11] Complete regression of the tumor in three weeks has been reported as well.[23] Alternatively, much of the initial improvement following steroid therapy may be related to edema-reduction rather than cytotoxicity. This concept is supported by several case reports of rebound increase in tumor enhancement following discontinuation of steroids, suggesting that the effect is predominantly not cytotoxic in nature.[17] Overall, most case reports describe such regression of tumor ranging from seven days to three weeks.[11-13,23]

We report the rapid response to high-dose steroids in less than seven days and also illustrate the feasibility of utilizing hyperosmolar therapy in conjunction with MTX to temporize the clinical mass effect under medical treatments. In our case, the patient's response to hyperosmolar therapy was immediate and well-tolerated, and tumor volume was reduced by 50% in less than seven days after the initiation of dexamethasone and MTX.

Given the previously discussed efficacy of chemotherapy, the rapidity of onset of medical therapy becomes critical to surgical decision-making process in the setting of acute decompensation and in patients not amenable to surgery or radiotherapy.[8] Despite the wealth of data on medical management, more recent studies have suggested that the subtotal or gross total resection of these tumors may offer superior PFS and OS.[25] However, this evidence is retrospective, with possible bias toward multiple lesions and poorer initial prognosis in patients treated with biopsy alone. There remains no compelling level-one evidence supporting surgical resection. Furthermore, the surgical risks that would be incurred in urgent cases, especially with eloquent tumor location, are likely higher than in the previously studied elective population. The temporizing measures undertaken in this case report may offer benefit to patients with acute mass effect from tumors in unfavorable locations or with mass effect that would require extensive or urgent decompressive surgery. It can be argued that this response was far more efficacious and likely less morbid than the reduction in mass effect that may have been achieved safely with surgical resection or urgent decompressive procedures.

Hyperosmolar therapy is an established treatment for elevated intracranial pressure and reduction of cerebral edema.[24] Its use in the setting of known intracranial pressure (ICP) elevation or in patients with clinical signs of herniation is well-documented. The improved

microcirculatory perfusion coupled with the dehydrating effects of hypertonic saline or mannitol can be used in the setting of traumatic brain injury (TBI), intracranial hemorrhage, stroke, subarachnoid hemorrhage, or tumor. A number of studies suggest administration of hypertonic saline over days-to-weeks is safe and may improve outcomes in the pediatric TBI population.[19,22] Despite its efficacy, concerns regarding renal function, hypotension, diuresis, and rebound ICP do exist with the use of hyperosmolar therapy. Mannitol infusion over this period of time may reach cumulative doses, which have been found to precipitate renal insufficiency.[10] In our patient, we utilized 3% hypertonic saline as a continuous infusion targeting a serum sodium between 145 and 160 mmol/L and serum osmolarity of less than 350 mOsm/kg. Serum sodium ranged from 132 to 162 mmol/L during his hospital course. Serum osmolarity measured on hospital day two was 318 mOsm/kg. We observed a dramatic improvement in the patient's clinical examination with this hyperosmolar regimen (in addition to high-dose dexamethasone) without appreciable deleterious effects. The patient continued to fluctuate, however, and periods of lethargy were still observed when serum sodium was 145-150. Bolus doses of 23% NaCl were utilized to treat symptoms of elevated intracranial pressure with immediate clinical response. The patient required a total of 540 cc of 23% NaCl (30 cc ×18), and a peak serum sodium of 162 mmol/L was reached. During this treatment, serum creatinine and urinary output remained stable, experiencing no clinical or subclinical changes. The patient's blood pressure and hemodynamics were undisturbed. Hypokalemia was treated with IV supplementation and over five days, patient required 160 mEq (40 mEq × 4) of potassium. Whether the patient's fluctuating mental status and periodic requirement of 23% NaCl were manifestations of rebound edema is unclear, but a possibility. This clinical picture was overcome with increasing serum sodium goals and close monitoring of renal function.

The medical therapy of acute PCNSL, although documented previously, has not been well-documented in terms of the rapidity of onset. We observed immediate clinical improvement with the implementation of hyperosmolar therapy. These improvements were transient without appreciable change on imaging and requiring additional bolus doses of 23% for transient declines. A durable clinical response was noted on treatment day four, likely due to reduction in tumor volume. On posttreatment day seven, this was confirmed with a reduction in tumor volume of 50%.

CONCLUSION

In this case report, the need for surgical decompression was avoided, and tumor response was shown to be rapid. With a durable clinical response observed within four days of treatment initiation, the authors emphasize that it is a reasonable option to employ medical therapy as a temporizing measure treating acute decompensation in the setting of PCNSL mass effect. Hyperosmolar therapy with dexamethasone and MTX do not constitute first-line therapy, but rather depict the rapidity at which PCNSL can respond to medical therapy, and offer a potential alternative to surgical intervention in the acute presentation of PCNSL associated with symptomatic mass effect.

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