White-matter abnormalities in unirradiated patients cured of primary central nervous system lymphoma

Abstract On MRI, primary brain tumors are commonly seen as contrast-enhancing masses surrounded by areas of abnormal signal on T2-weighted images. Following successful treatment tumors may no longer show contrast enhancement. The residual abnormalities are assumed to be represent “edema” and infiltrating tumor cells. We report nine patients with primary lymphoma of the central nervous system who had complete responses to intravenous methotrexate, but did not receive intrathecal chemotherapy or cranial irradiation. After complete resolution of contrast-enhancing lesions, persistent abnormalities on T2-weighted images in the region of prior tumor were initially assumed to reflect residual viable tumor. As they remained unchanged for years, however, this may not hold true in the cases in which primary central nervous system lymphoma responds to chemotherapy alone.

Key words Lymphoma, primary central nervous system · Chemotherapy · Magnetic resonance imaging

Introduction

Primary lymphoma of the central nervous system represents 1.5% of brain tumors. Although seen typically in patients with acquired or drug-induced immunosuppression, this tumor is increasingly diagnosed in immunocompetent patients. T1-weighted MRI shows isointense or low signal, often adjacent to the ventricular system, with isointense or high signal on T2 weighting. The lesions, which may be multiple, usually enhance intensely and homogeneously with contrast medium, the tumor being sharply demarcated from surrounding, nonenhancing edema. Calcification, cysts, and necrotic changes, seen in malignant gliomas, are uncommon.

Radiation therapy has been the mainstay of the treatment for the newly diagnosed primary central nervous system lymphoma (PCNSL). However, despite initial complete resolution of tumor, whole-brain irradiation at 42 Gy rarely yields long-term survival [1]; survival seldom exceeds 2 years. Methotrexate (MTX), alone [2] or in combination with other agents [3, 4], yields complete dissolution of tumor in over 80% of patients with median survivals approaching 4 years in most series [5]. Most recently [2], we have given induc-
tion chemotherapy (MTX 8 g/m²) followed by maintenance chemotherapy (MTX 3.5 g/m²) to achieve complete disappearance of tumor, in the absence of steroid therapy. A complete response (CR), defined as resolution of all contrast-enhancing masses in the absence of corticosteroid treatment, was achieved in 90% of recipients, and maintained for as long as 52 months. However, despite maintained of clinical improvement and disappearance of enhancing masses, MRI revealed persistent of foci with low signal on T1- and high signal on T2-weighted images.

Following chemotherapy and irradiation, successfully treated brain tumors (such as anaplastic oligodendrogliomas or metastases of breast origin), tend no longer to show contrast enhancement. Residual abnormalities on T2-weighted images are assumed to represent “edema” and infiltrating tumor cells. This assumption may not hold true for primary central nervous system lymphomas which are responsive to chemotherapy alone. We have successfully provided MTX chemotherapy, without irradiation, to nine patients with PCNSL. Durable complete responses consisted of resolution of both clinical deficits as well as gadolinium-enhancing lesions. The T2 abnormalities which persisted in the region of prior tumor were initially assumed to reflect residual viable tumor, but as these lesions have remained unchanged for years, this assumption is not supported. We present three of nine primary CNS lymphoma patients who were cured of disease with intravenous MTX alone.

Results

Despite the successful treatment, all nine patients showed persisting abnormal signal on T2-weighted images in close proximity to the original enhancing masses. These changes have not progressed over time. We assumed that there was residual disease existed within these areas. On the T2-weighted images, patient 4 developed a new lesion in proximity to the original one, while patient 8 had two new lesions distant from the original focus.

All patients, except patient 8, who still needs help with financial matters, regained full abilities and returned to unlimited work. No neurologic toxicity of chemotherapy has been seen (previous reports have described myoclonus, dementia, seizures, immunosuppressive disorders, migraine, and hypothalamic dysfunction). Patient 8 remains mildly disoriented following a complete radiologic response. The cognitive sparing of the remainder has been noted in patients receiving chemotherapy with blood-brain barrier modification [6], without whole-brain irradiation. Three illustrative case reports follow.

Case 1 (Fig. 1)

A 48-year-old man had diminishing visual acuity. MRI of the orbit was normal, but vitreous biopsy revealed a T-cell lymphoma which responded to radiation (47 Gy to each eye). He had normal cranial MRI and lumbar spinal fluid 6 and 12 months later, but 14 months after presentation developed progressive fatigue, depression and memory loss. MRI of the brain 19 months later revealed a 5 × 2 × 2 cm mass in the splenium of the corpus callosum isointense or giving high signal on T2 weighting, contrast-enhancing, and with subependymal enhancement. The was a mild degree of surrounding high signal on T2-weighted images. Stereotactic biopsy revealed a large B-cell lymphoma, but there was no recurrence of the ocular lymphoma. The lumbar spinal fluid now revealed “atypical lymphoid cells”, of which 80–90% were T cells by fluorescence-activated cell sorting. The patient received 13 cycles of MTX (8 g/m² for three cycles, then 3.5 g/m²). For the past 9 months, after cycle 9, he has shown no recurrence of enhancing lesions. He has returned to work and is without symptoms.

Case 2 (Fig. 2)

A 57-year-old woman developed intractable vomiting. MRI showed a contrast-enhancing lesion in the left corona radiata, for which she refused biopsy. After 50 months she developed rapidly progressive left-sided weakness, and MRI showed a contrast-enhancing 4 × 2.5 cm right frontoparietal mass, giving isointense or

Materials and methods

MTX-based chemotherapy, without radiation or intrathecal medication, produced disappearance of contrast-enhancing masses on MRI in nine patients aged 45–76 years. At the time of diagnosis, the patients had a total of 19 contrast-enhancing masses within areas appearing abnormal on T2-weighted images.

The patients then received 111 cycles of MTX (median 12 cycles each). Complete response was equated with disappearance of all contrast-enhancing lesions. The median duration of complete response was 19 months. Two patients were successfully retreated with intravenous MTX for radiologic relapses: patient 6 was retreated with intravenous MTX (3.5 g/m² every month for two cycles) for one radiologic recurrence 25 months ago (14 months after diagnosis) and, after a hiatus, resumed maintenance chemotherapy 4 months ago; he has been in CR for 23 months. Patient 7 was successfully retreated with induction and maintenance parenteral MTX for two radiologic relapses 36 and 21 months ago (30 and 45 months after diagnosis); he has been in CR for 20 months.

There are six patients still receiving maintenance MTX (3.5 g/m² every 3 months); three other patients declined further treatment but remain under care.

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