

Unusual Uterine Recurrence of Primary Central Nervous System Lymphoma

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A 37-year-old woman with a longstanding history of migraine headaches and repeatedly negative magnetic resonance imaging (MRI) presented with a change in her usual headache pattern. An MRI showed a right frontal mass. Stereotactic brain biopsy revealed diffuse large B-cell lymphoma (DLBCL). The staging work-up, including computed tomography (CT) scans of the chest, abdomen, and pelvis; MRIs of the spine; single photon emission CT (SPECT) scan; and a bone marrow biopsy, was negative. She received seven cycles of intravenous methotrexate (8 g/m²), with regression of disease shown on serial MRIs until an MRI at 6 months showed growth of the right frontal lesion. She underwent whole-brain irradiation and achieved a complete remission. MRIs every 4–6 months demonstrated no evidence of disease recurrence.

Two years after completing radiotherapy, the patient presented with dysfunctional uterine bleeding. A transvaginal ultrasound revealed a uterine mass. Biopsy confirmed DLBCL of the uterus. MRI of the brain showed no evidence of recurrent disease. CT scans showed only inguinal lymphadenopathy. An MRI of the pelvis showed diffuse adenomyosis and a solid right ovarian mass, considered to be a complex myoma with degenerative changes. A positron emission tomography (PET) scan showed evidence of pelvic bony involvement and hypermetabolic activity in the retroperitoneum and portal hepatitis. A bone marrow biopsy was unremarkable. Laboratory evaluation noted hypercalcemia, which was treated with zoledronic acid (Zometa, Novartis). Chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone and rituximab (Rituxan, Genentech/Biogen Idec) was administered. After four of

the planned eight cycles of treatment, CT showed regression of the lymphadenopathy and the PET scan had normalized. Over the next several months the patient began to experience right-side paralysis and left-side weakness. Brain MRI revealed evidence of recurrent central nervous system (CNS) disease. Steroids, high-dose cytarabine, and etoposide were administered in anticipation of stem cell transplantation. The tumor size regressed by 30% and some neurologic recovery occurred after one cycle. After two cycles of treatment she had progression of disease with cranial nerve impingement and hydrocephalus. The patient died 42 months after diagnosis.

Discussion

Primary central nervous system lymphoma (PCNSL) is a non-Hodgkin B-cell malignancy confined to the CNS.¹ A rare malignancy, accounting for only 2% of all non-Hodgkin lymphoma (NHL) cases and 5% of all primary brain tumors, its incidence has been increasing over the past two decades among older, immunocompetent individuals.^{2,3} Patients do poorly without therapy, with a mean survival of 1–3 months.¹ Approximately 20–30% of cases may be cured with current treatment regimens.⁴ The great majority of patients relapse within the CNS and succumb to complications of the disease.

The optimal therapy for PCNSL remains unclear, but current data support the use of a methotrexate-based chemotherapy regimen alone with deferred radiotherapy for persistent or progressive disease.^{4,5} Though radiotherapy alone followed by radiotherapy combined with chemotherapy had been the standard of care for this disease, recent phase II trials assessing chemotherapy alone have shown similar response rates and median survivals when compared with chemotherapy followed by radiotherapy (71% vs 81% and 50 vs 46 months, respectively), with a significantly decreased incidence of delayed neurotoxicity, especially among the elderly.^{6–8}

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Despite advances in therapy and prolonged disease-free survival, relapse occurs in most cases and is typically confined to the CNS (90–93%, including the original brain site, distant brain sites, leptomeninges, and/or the eye), whereas only 7–10% of relapses occur systemically.⁹ The majority of extracerebral metastases occur in the kidneys, lymph nodes, testicles, and gastrointestinal tract, and, more rarely, in the lungs, adrenals, retroperitoneum, heart, mediastinum, breast, nasal cavity, skull, bone, thyroid, nerve, and bone marrow.⁹ With extension of remission and survival now seen with current treatment regimens, the natural history of this disease may be changing. We present a patient with an unusual uterine recurrence of PCNSL after successful initial therapy.

Marjanovic and colleagues¹⁰ reported a pediatric case of PCNSL found, 2 months after diagnosis, to have a uterine lymphoma. The investigators suggested that this was either a case of primary uterine lymphoma having spread along the peripheral nerves, thereby seeding the CNS, or a PCNSL having seeded the peritoneum by way of a lumboperitoneal shunt. Although this case differs from our case both temporally and by the implantation of a mechanism for potential metastases, it is the only other case in the literature suggesting that PCNSL may travel to the uterus.

Three scenarios may explain the findings in the present case: (1) the extranodal uterine lymphoma may have been missed in the initial staging work-up; (2) the CNS and uterus may represent two different primaries separated in time and space; or (3) this is a rare case of PCNSL recurring in the uterus. Studies examining SPECT versus PET scanning in both initial staging and restaging of NHL have shown PET to be significantly superior when used alone for both initial staging and monitoring of disease treatment and progression. In combination with conventional staging, however, the difference between SPECT and PET becomes nonsignificant.^{11–13} It is therefore unlikely that a significant abdominal lymphoma was missed on initial staging. Our patient showed no signs or symptoms of uterine pathology for 24 months after the initial brain lesion was discovered, supporting the notion of this being a case of PCNSL recurring in the uterus or a case of two primary NHLs separated by time and space. B-cell receptor gene rearrangement analysis was performed on both the uterine and original brain mass specimens.

Unfortunately, only a polyclonal result was obtained on the uterine tissue, therefore the possibility of two different primaries could not be confirmed. We believe this case is in fact delayed uterine relapse of PCNSL. It is important that this patient had regular follow-up with serial MRIs showing no evidence of recurrence. Her presentation with dysfunctional uterine bleeding was considered unlikely to be connected to her prior diagnosis. We hypothesize that with more successful treatment of PCNSL, the natural history of this disease may change, and more unusual sites of systemic relapse in PCNSL may be observed. As patients with PCNSL are surviving longer, the appropriate follow-up for patients with this disease may need to include systemic evaluation with body CT and/or PET scanning in order to anticipate recurrence outside the CNS.

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Review

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Nichols and colleagues¹ present an interesting PCNSL patient with first recurrence in the uterus. This case raises a number of points regarding the biology and pathogenesis of PCNSL as well as the optimal management and follow-up for PCNSL patients.

PCNSL is an extranodal NHL usually of B-cell origin that is defined as being confined to the brain, eyes, cerebrospinal fluid, and spinal cord. The origin and pathogenesis of the malignant lymphocytes resulting in PCNSL are unclear, and at least three hypotheses have been proposed. It is possible that PCNSL arises initially as a systemic lymphoma and that all sites, with the exception of the CNS, are eradicated by immune surveillance. Alternatively, it is possible that a monoclonal malignant B-cell population results following an inflammatory process in the CNS. Another possibility would be a “homing” process, whereby malignant B cells are preferentially attracted to and proliferate within the CNS. Though each of these hypotheses has limitations, there are some preliminary data to support the first and third hypotheses. A recent report by Jahnke and coauthors² suggests that some PCNSL patients have subclinical levels of circulating lymphocytes with identical clonal IgH gene rearrangements as seen in their primary tumor. This finding supports at least the possibility of concomitant, albeit subclinical, lymphoma in some PCNSL patients. Smith and coworkers³ recently reported on the presence of a B-cell-attracting chemokine in PCNSL and other extranodal lymphomas, which may support the homing hypothesis. Further studies to elucidate the pathogenesis and biologic spectrum of PCNSL will be critical to improving our understanding of this disease and its clinical potential for systemic involvement.

From a practical point of view, this case raises important questions regarding the need for systemic staging and follow-up. The incidence of occult systemic lymphoma coincident with the diagnosis of CNS lymphoma ranges from less than 3% to as high as 8%.^{4,5} As a result, there has been controversy regarding the need for and extent of

systemic staging. A recent international workshop report to standardize evaluation and response criteria recommended that all PCNSL patients have a baseline bone marrow biopsy and CT scan of the chest, abdomen, and pelvis at diagnosis; testicular examination and ultrasound is appropriate for older men.⁶ Furthermore, approximately 10% of PCNSL patients who relapse will fail systemically, which underscores the need for careful follow-up of systemic symptoms. A significant proportion of these systemic failures occur in extranodal sites that may not be detected by the use of routine body CT scans (eg, breast, testes, muscle) and therefore require clinical follow-up, examination, and vigilance on the part of the physician. There has been a long debate as to whether systemic failure represents true CNS metastases to systemic metastases or is, in fact, a new primary lymphoma. Although careful comparison of gene rearrangements in the two tumors would be ideal, such comparison has been largely unsuccessful to date. The report from Jahnke and coauthors² supports the concept of systemic failure representing true metastatic disease; however, none of the patients in this series went on to develop clinical systemic disease.

Finally, a word of caution regarding the treatment of newly diagnosed PCNSL. Although the optimal treatment of PCNSL has not been clearly delineated, the best results to date have been achieved with high-dose methotrexate-based chemotherapy regimens in combination with whole brain radiotherapy.^{7,8} Even though older patients may experience a significant risk of treatment-related neurotoxicity with this approach, it seems clear that young patients enjoy prolonged disease-free survival with this combined modality management. Deferring whole-brain radiotherapy or even decreasing the dose may significantly curtail disease control, particularly in young patients.⁸ Similar to systemic NHL trials, the critical endpoint for PCNSL regimens at diagnosis should be event-free or progression-free survival.^{5,8} This endpoint is critical for appropriate comparison and interpretation of initial treatment regimens, as many effective salvage regimens exist and likely contribute to overall survival. However, the chance of curing a patient at relapse is substantially less than at initial diagnosis.

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