CASE REPORT

Isolated secondary CNS relapse in a case of stage I diffuse large B-cell lymphoma

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SUMMARY

A 55-year-old woman was admitted to our hospital with a 10-day history of right arm weakness and numbness. The patient's medical history was notable for lobular carcinoma in situ of the right breast in 2008 and stage I diffuse large B-cell lymphoma of the left axilla. The patient had completed treatment with chemotherapy and radiation 2 months prior to presentation. Blood counts, metabolic panel and lumbar puncture were unremarkable. MRI of the brain revealed multiple enhancing masses. The patient was started on dexamethasone, with rapid symptom improvement. A stereotactic brain biopsy revealed CD20 diffuse large B-cell lymphoma. The patient was started on high-dose intravenous methotrexate. She has received 11 cycles and has regained near normal function of the right arm. The patient's most recent brain MRI showed near complete resolution of all previously seen abnormal foci of enhancement.

BACKGROUND

Diffuse large B-cell lymphoma (DLBCL) accounts for approximately 25% of all cases of non-Hodgkin lymphomas (NHL).¹ Approximately 60% of patients have advanced disease at presentation (stage III or IV), and extranodal, extramedullary disease occurs in up to 40% of cases.² While the central nervous system (CNS) is a sanctuary for lymphoma cells, NHL relapse can occur in the brain parenchyma, leptomeninges, eyes or spinal cord, and occurs in approximately 5% of patients.³ Isolated CNS relapse with no evidence of lymphoma outside the CNS at the time of relapse occurs in about 1% of patients with NHL.³ Involvement of the CNS not evident at the time of initiation of treatment for systemic lymphoma is termed secondary CNS lymphoma (SCNSL), first described in 1870.^{4 5} The average incidence of secondary CNS involvement in systemic NHL correlates with the aggressiveness of the disease, varying from 3% to 27% for indolent and highly aggressive NHLs, respectively.⁶

CASE PRESENTATION

A 55-year-old woman was transferred to our hospital with a 10-day history of right arm numbness, weakness and increasing difficulty with writing and hand grip. Her medical history was notable for a history of lobular carcinoma in situ of the right breast diagnosed in 2008 for which she had undergone lumpectomy, followed by maintenance tamoxifen. Five months prior to her current presentation, she developed left axillary lymphadenopathy and an

excisional biopsy had revealed DLBCL. As the patient did not have evidence of bone marrow or other organ involvement, her disease was staged as I a. Her lactate dehydrogenase (LDH) at the time of diagnosis was 291 U/L, and the revised international prognostic index (R-IPI) identified the patient to be in the good prognostic group (4-year progression free survival (PFS) 80%, overall survival (OS) 79%).⁷ She received three cycles of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone followed by local radiation to the axilla. Her chemotherapy had concluded 2 months prior to current presentation, and a whole body surveillance fludeoxyglucose positron emission tomography scan, including the brain, had been negative 2 weeks prior.

INVESTIGATIONS

MRI of the brain revealed multiple enhancing masses with diffuse borders, the largest of which was located in the left centrum semiovale and left parietal subcortical white matter, measuring 2.7 cm in the greatest axial diameter. Several other smaller enhancing lesions were scattered throughout the brain parenchyma bilaterally (figure 1). Complete blood count, metabolic panel and inflammatory

Figure 1 MRI of the brain: an axial flair section showing the largest lesion in the left centrum semiovale and left parietal subcortical matter, with several smaller satellite lesions bilaterally.

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markers (erythrocyte sedimentation rate and C reactive protein) were unremarkable. Her LDH at the time of presentation was 192 U/L.

The patient was started on 8 mg dexamethasone twice daily with significant improvement in her neurological symptoms. HIV testing was negative. A lumbar puncture revealed protein of 26 mg/dL and white cell count 2/ μ L with 18% lymphocytes. CSF cytology was negative and flow cytometry did not identify a discrete lymphoid population. The patient underwent a stereotactic brain biopsy that revealed CD20 DLBCL. She subsequently underwent an ophthalmic evaluation that revealed the absence of any intraocular involvement.

DIFFERENTIAL DIAGNOSIS

Broadly, our differential diagnosis included malignant versus infectious aetiology. Malignant considerations included recurrent breast adenocarcinoma, relapsed CNS lymphoma, or metastatic disease from a different primary oncological process. It was felt that a primary CNS malignancy was less likely due to the presence of multiple lesions. Infectious aetiologies included brain abscesses, toxoplasmosis, cryptococcosis and tuberculosis, especially in light of the fact that the patient had previously been treated with chemotherapy. Progressive multifocal leucoencephalopathy, which has been described in a few cases as a complication of rituximab therapy, was also contemplated. Other possibilities considered were neurosarcoidosis, a demyelinating process, and cerebral infarctions. To note, our colleagues in neurosurgery were concerned about lymphoma because of the radiological appearance of the patient's brain lesions on MRI, specifically the presence of enhancing masses with diffuse borders.

TREATMENT

The patient was started on intravenous high-dose methotrexate (8000 mg/m² every 3 weeks, planned for a total of 12 cycles).

OUTCOME AND FOLLOW-UP

At the time of submission of this report, our patient had completed 11 of 12 planned cycles of high-dose methotrexate. Cycle 2 was delayed for a few days because the patient had thrombocytopenia, which has since resolved. Throughout her treatment course, she has had fatigue, mild diarrhoea and occasional nausea. Her right hand is no longer numb. The patient feels her hand function is near normal, but she continues to have some trouble taking a tight lid off a jar.

The patient's most recent CT of the brain showed near complete resolution of all previously seen abnormal foci of enhancement, with only trace residual enhancement seen in the patient's previous largest lesion in the posterior left frontal lobe, which is consistent with post-therapy response. On follow-up MRI, there was barely perceptible trace enhancement noted in the previously seen largest left posterior frontal/parietal lesion, with no evidence of enhancement within the enhancing lesions seen on prior MRI (figure 2).

DISCUSSION

Isolated CNS relapse with no evidence of disease outside the CNS occurs in approximately only 1% of patients with NHL.³ Isolated CNS relapse in early stage DLBCL is even less common. The presence of more than one site of extranodal disease, elevated LDH and high-risk IPI³⁻⁵ at the time of initial diagnosis have been associated with a higher risk of CNS relapse. Age adjusted IPI of 0 or 1 has been associated with a lower risk of CNS relapse/progression in younger patients with aggressive

Figure 2 Repeat MRI post nine cycles of high-dose methotrexate showing trace enhancement in the previously seen largest left posterior frontal/parietal lesion, with no evidence of enhancement within previously visualised lesions.

B-cell lymphomas.⁸ Survival appears to be worse in patients with NHL with isolated secondary CNS relapse as compared with patients with CNS involvement at the time of presentation,⁹ and patients with primary CNS lymphoma.¹⁰ The median survival in these patients varies from 4 to 7 months.¹⁰⁻¹²

The International Primary CNS Lymphoma Collaborative Group (IPCG) reported contrasting data from their retrospective analysis of 113 patients with isolated relapse with brain parenchymal involvement, 83% of whom had DLBCL.³ Twenty-five patients in this study had stage I disease. Median time to brain relapse was 1.8 years, median overall survival from date of brain

Learning points

- ▶ Non-Hodgkin's lymphoma (NHL) relapse can occur in the brain parenchyma, leptomeninges, eyes or spinal cord, and occurs in about 5% of patients. Isolated central nervous system (CNS) relapse, with no other evidence of disease, occurs in only approximately 1% of patients with NHL.
- ▶ Secondary CNS lymphoma (SCNSL) refers to CNS involvement that was not evident at the time of initiation of treatment for systemic lymphoma, and incidence correlates with the aggressiveness of the primary disease.
- ▶ Factors associated with higher risk of CNS relapse include more than one site of extranodal disease, elevated lactate dehydrogenase and high-risk international prognostic index³⁻⁵ at initial diagnosis.
- ▶ Survival appears to be worse in patients with NHL with isolated secondary CNS relapse than in patients with CNS involvement at the time of presentation or patients with primary CNS lymphoma, with median survival ranging from 4 to 7 months.
- ▶ While most patients with SCNSL initially present with stage III/IV disease, clinicians should have a low index of suspicion for this entity even in patients treated for early stage who develop acute neurological symptoms.

relapse was 1.6 years and age less than 60 years was associated with longer survival. In total, 68% of patients who received treatment of brain relapse developed CNS disease progression. Only 50% of patients presented with two or more parenchymal lesions, and the majority occurred in the cerebral hemispheres. CSF cytology was positive in only 10% of cases.

Our patient is unusual in that despite her young age and limited stage disease, she presented with relapse within 2 months of attaining complete remission with definitive therapy, a setting in which the cure rate is expected to be 76%.¹³ Furthermore, the patient had isolated brain parenchymal relapse, which occurs in only about 1% of patients.³ While published studies have reported isolated SCNSL relapses in patients with stage I disease, most patients with SCNSL initially present with stage III/IV disease. Clinicians should have a low index of suspicion even in early stage, treated patients with NHL, who develop acute neurological symptoms.

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Competing interests None.

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