OXFORD

Oxford Medical Case Reports, 2023, **11**, 403–406
https://doi.org/10.1093/omcr/omad118
Case Report

Follicular lymphoma with secondary central nervous system relapse: a case report and literature review

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Abstract

Secondary central nervous system (CNS) relapse by aggressive non-Hodgkin's lymphoma is a well-known complication portending a very poor prognosis. Conversely, patients with indolent lymphoma-like follicular lymphoma (FL) rarely present with CNS involvement and, thus, limited information is currently available. We herein describe a patient with FL who developed CNS involvement during chemotherapy. Treatment including high-dose methotrexate and radiation therapy was ineffective and the patient died 5 months after CNS relapse. In a literature review, there were 8 case reports of the secondary CNS relapse of FL. The findings obtained suggest that bone marrow infiltration is a risk factor for CNS relapse. Moreover, 5 out of 9 patients died within 2.5 years, indicating a poorer prognosis than that of FL. Therefore, it is important to promptly perform detailed examinations as soon as neurological findings appear.

INTRODUCTION

Follicular lymphoma (FL) is the second most common type of non-Hodgkin's lymphoma after diffuse large B-cell lymphoma (DLBCL). FL is characterized by diffuse lymphadenopathy, bone marrow involvement, and splenomegaly. Extranodal involvement including the central nervous system (CNS) is uncommon. FL generally has an indolent course and good prognosis with a 10-year overall survival rate of 80% [1].

Secondary CNS involvement often occurs in patients with aggressive non-Hodgkin lymphoma. The frequency of CNS relapse in DLBCL ranged between 5% and 25% [2]. Extranodal lesions susceptible to DLBCL CNS relapse include testicular, breast, renal/adrenal, and bone marrow, for which prophylaxis with high-dose methotrexate (HD-MTX) or an intrathecal injection of methotrexate (IT-MTX) is considered [3]. CNS involvement in low-grade lymphomas, such as FL, is as rare as 3% [4]; therefore, treatment responses and prognosis remain unclear. We herein report a case of FL with CNS invasion secondary to chemotherapy.

CASE REPORT

A 62-year-old woman presented to a previous hospital with lower back pain. Computed tomography (CT) showed osteolytic lesions in L4 level vertebra, S1 level right sacral wing, right situs, right iliac bone, and left acetabulum, enlarged thoracoabdominal lymph nodes, and multiple mass lesions in bilateral kidneys which enlarged 86 mm on both sides, pancreas enlarged as 131 mm, and two nodules in right lung. Due to the patient's poor general condition, positron emission tomography CT was not performed. Intraperitoneal lymph node excisional biopsy was performed. A pathological examination showed the proliferation of follicular structures, mainly composed of large to medium cells. Immunohistochemical staining revealed that abnormal lymphocytes were $CD3^-$, $CD5^-$, $CD10^+$, $CD20^+$, $CD79a^+$, $BCL2^+$, $BCL6^+$, Ki67 index 20%. A chromosomal analysis showed t (14; 18). The patient was diagnosed with grade 2 stage IV FL.

She received 1 course of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone followed by 3 courses of rituximab and bendamustine. During treatment, she developed weakness in both lower limbs, which slowly worsened, and had difficulty walking after 1 month. The day before admission, she developed generalized tonic clonic seizure and transferred to our hospital for detailed examinations. On admission, she had left hemispatial neglect, left upper limb loss of organization, and left incomplete paralysis. The meningeal sign was negative. Blood tests showed a white blood cell count of 2000/μl, soluble interleukin-2 receptor 573 U/ml, and lactate dehydrogenase 275 U/l. A cerebrospinal fluid examination revealed an initial pressure of 235 mmH_2O and elevated protein level of 80 mg/dl, while flow cytometry (FCM) and cytology were negative. Contrast-enhanced CT of the trunk showed that the bone lesions were sclerosed, the kidneys shrunk to 58 mm on the right and 41 mm on the left, the pancreatic lesions reduced to 62 mm, and nodular lesions in the lung disappeared. Brain magnetic resonance imaging (MRI) displayed masses with largest diameter of 31 mm and mass effect in the convexity of the frontal and parietal lobes. Also, there were several 15–20 mm masses in the temporal lobe and cerebellar hemispheres (Fig. 1); therefore, cranial biopsy was performed. Histopathology of the brain tissue showed a cluster of medium-sized lymphocyte-like cells throughout the specimen (Fig. 2(i)). These cells were $CD3^-$, $CD5^-$, $CD10^+$, $CD20^+$, $BCL2^+$ and

Received: April 6, 2023. **Revised:** August 28, 2023. **Accepted:** September 12, 2023

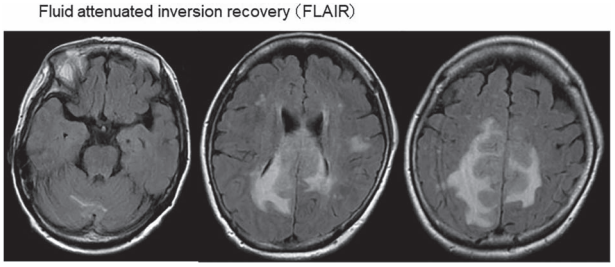

Figure 1. Brain MRI findings. Brain MRI findings of CNS relapse are shown.

Ki67 index 50–80% (Fig. 2(ii)), suggesting the CNS involvement of FL. The patient received a course of chemotherapy including HD-MTX 1000 mg/m^2, day1, 10, 20; rituximab 375 mg/m^2, day 3, 12 and 22; ranimustine 40 mg/m^2, day 1; methylprednisolone 60 mg/m^2, day 1–20, and 4 times of IT-MTX 15 mg/time. In the repeated MRI, the largest 31 mm mass was shrunk to 12 mm. However, within 2 months, the tumor regrowth to 16 mm and brain edema worsened. Whole-brain irradiation with 37.5 Gy was performed, but due to progressive disease the patient died 5 months after CNS relapse.

DISCUSSION

We encountered a patient with FL who developed CNS involvement during chemotherapy. The CNS relapse of FL is rare, and only 9 cases have been reported to date (Table 1) [5–9]. No sex differences were observed. Age ranged between 43 and 78 years old. Histopathology at initial diagnosis was Grade 1–2, indicating CNS relapse occur regardless of the histological malignancy. While 7 out of 9 cases had bone marrow involvement at initial diagnosis and it might be related to CNS relapse. The time to CNS relapse varied from a few months to 10 years. The diagnosis was triggered by neurological symptoms, such as paralysis and diplopia. Lesions varied from the cerebral parenchyma, cerebellum, and periventricular area to the meninges. The histology of most of the cases were transformed to DLBCL, while 3 cases, including our case, remained as FL. Although treatment after relapse mainly consisted of HD-MTX, IT-MTX, and radiotherapy, 5 out of 9 patients died within 2.5 years, indicating a poorer prognosis. Among them, cases 1, 4, 6, and 9 had a particularly poor prognosis. The reasons for this include the appearance of CNS lesions during chemotherapy (cases 1, 6, and 9), the presence of sepsis (case 6), and the refusal of effective chemotherapy (case 4). In the present case, the CNS lesion appeared during chemotherapy, and one month elapsed between the appearance of abnormal neurological findings and detailed examinations, which may have affected the prognosis.

In the post-rituximab era, the isolated CNS invasion of lymphoma has become a common pattern of relapse [2]. Recently, MARIETTA trial (MATRix and R-ICE chemotherapy and thiotepa-conditioned autologous stem cell transplant) reported preferable outcome: 1 year progression free survival of 58% for DLBCL with secondary CNS involvement [10]. Although treatment strategy for FL with CNS relapse is not established, accumulation of cases should help to identify them in FL as well.

Based on the findings obtained from the case reports, the presence of bone marrow infiltration appears to be a risk factor for CNS relapse. In addition, CNS relapse during chemotherapy is associated with a worse prognosis. Moreover, if neurological

Table 1. Previous reports of follicular lymphoma with CNS involvement

Case	Age/Sex	Histology at first	Extranodal lesions	Duration (year)	Neurological symptoms	Locatin	Histology at relapse	Treatment for CNS	Prognosis (year)
1	43/F	FL(G2)	BM	7	diplopia	Parenchymal, leptomeningeal	–	HD-MTX MTX-IT, RT	0.9
2	60/F	FL(G1)	BM	0.5	consciousness disorder	Parenchymal	DLBCL	HD-MTX MTX-IT	2.5
3	73/F	FL(G1)	BM	4	acalculia, agraphia, hemiplegia	Parenchymal	DLBCL	HD-MTX MTX-IT	>2
4	78/F	FL(G2)	–	4	hemiplegia, dysarthria	leptomeningeal	DLBCL	Dex	0.25
5	53/M	FL(G1)	Vertebral body	8	spinal cord compression	Parietal-occipital lobe	DLBCL	Surgery RT	–
6	67/M	FL(G1)	BM	0.4	meningeal irritation symptoms	Periventricular	–	HD-MTX RT	0.08
7	57/M	FL(G2)	BM	1	vertigo, ataxia	cerebellum	FL	R, Flu, CPA, RT	> 1
8	52/M	FL(G2)	–	10	diplopia, ptosis	leptomeningeal	FL	–	–
9 (our case)	63/F	FL(G2)	Kidney, lung, pancreas, BM	0.35	hemiplegia, convulsion	parietal lobe	FL	HD-MTX MTX-IT, R, MCNU, mPSL, RT	0.4

Abbreviations: FL, follicular lymphoma. G, grade. BM, bone marrow. DLBCL, diffuse large B-cell lymphoma. –, not documented. HD-MTX, high-dose methotrexate. MTX-IT, intrathecal injection of methotrexate. RT, radiation therapy. Dex, dexamethasone. R, rituximab. Flu, fludarabine. CPA, cyclophosphamide. MCNU, ranimustine. mPSL, methylprednisolone.

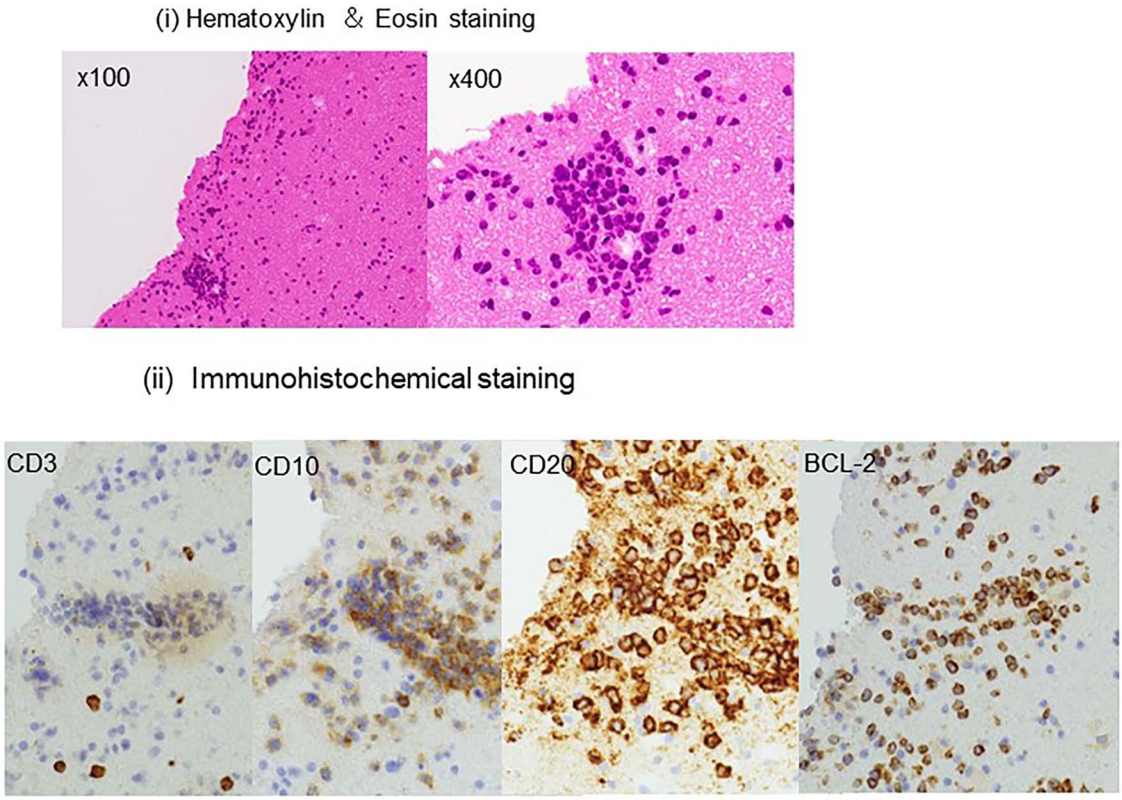

Figure 2. Pathological examination of brain tissue at relapse. (i) Hematoxylin & Eosin staining; magnifications, ×100 (left) and ×400 (right) (ii) Immunohistochemical staining for each antibody is shown: CD3, CD10, CD20, and BCL2.

findings occur, it is important to promptly perform detailed examinations, such as MRI and spinal fluid examinations. Further studies will enable us to classify risks and formulate effective treatment strategies for CNS relapse in FL.

ACKNOWLEDGEMENTS

We would like to thank Editage (www.editage.com) for English language editing.

CONFLICT OF INTEREST STATEMENT

Y.T., M.S., A.K., T.S., M.S., and A.S. declare no conflicts of interest.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

DATA AVAILABILITY

Data and materials are available upon reasonable request.

ETHICAL APPROVAL

The present study was approved by the Institutional Review Board at Hitachi General Hospital.

INFORMED CONSENT

Written informed consent was obtained from the patient.

GUARANTOR

Yuri Tsuboi.

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