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Case Study

Orbital MALT Lymphoma after Autologous Stem Cell Transplantation for Follicular Lymphoma as Relapse of Diffuse Large B-Cell Lymphoma

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We report a patient who developed orbital MALT lymphoma after autologous peripheral blood stem cell transplantation for follicular lymphoma as relapse of diffuse large B-cell lymphoma. A 54-year-old woman with systemic lymphadenopathy was diagnosed with diffuse large B-cell lymphoma by left supraclavicular lymph node biopsy, and underwent 6 courses of R-CHOP chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone, leading to complete response. Five years later in the follow-up, an abdominal mass with abnormal uptake was found by whole-body 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography, and computed tomography-guided biopsy demonstrated follicular lymphoma. She underwent 4 courses of R-IDEA chemotherapy with rituximab, ifosfamide, dexamethasone, etoposide, and cytarabine, resulting in partial response, and then, underwent autologous peripheral blood stem cell transplantation with myeloablative conditioning with R-MCEC chemotherapy (rituximab, ranimustine, cyclophosphamide, etoposide, and carboplatin). She was well for the following 3 years with no treatment until the development of a right orbital mass. The excisional biopsy this time revealed MALT lymphoma. She underwent 3 courses with rituximab monotherapy and local orbital radiation at the total dose of 30 Gy. She had no relapse for the following three years. Relapse as MALT lymphoma after hematopoietic stem cell transplantation for relapsed and refractory lymphoma may not be a poor prognostic sign.〔*J Clin Exp Hematop 56(3):170-175, 2017*〕

Keywords: diffuse large B-cell lymphoma, autologous peripheral blood stem cell transplantation, relapse, extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT), follicular lymphoma

INTRODUCTION

Hematopoietic stem cell transplantation is the standard treatment for relapsed or refractory aggressive non-Hodgkin lymphoma such as diffuse large B-cell lymphoma[1-6] or follicular lymphoma.[6,7] Further relapse after hematopoietic stem cell transplantation has been understood as a poor prognostic sign in lymphoma treatment.[8,9] Recently, high-dose chemotherapy and autologous stem cell transplantation have been evaluated as a first-line therapy for aggressive non-Hodgkin lymphoma with poor prognostic indicators.[10-12] In this study, we report a patient who developed orbital MALT lymphoma after autologous peripheral blood stem cell transplantation for follicular lymphoma as the relapse of diffuse large B-cell lymphoma.

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CASE REPORT

A 54-year-old woman noticed cervical swelling on the left side in June 2003, with its gradual increase in the following two months. On the referral to an oncologist in September 2003, she had bilateral cervical and supraclavicular lymph node enlargement, and CT scan disclosed paraaortic, bilateral iliac, mesenteric, and bilateral inguinal lymphadenopathy. Excisional biopsy of the supraclavicular lymph node on the left side revealed diffuse large B-cell lymphoma (Fig. 1). Large cells with irregularly-shaped large nuclei in diffuse distribution (Fig. 1A) were positive for CD20 (Fig. 1D), CD79a (Fig. 1E), and Ki67 (Fig. 1F), but negative for CD3 (Fig. 1B), CD21, CD30 (BerH2), and CD15 (LeuM1).

These large cells were accompanied by a small population of monotonous cells, positive for CD45RO (UCHL1), a marker for activated T cells (Fig. 1C). She underwent 6 courses of R-CHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) from October 2003 to February 2004, leading to complete response.

She was well until August 2008 when whole-body 2-[^{18}F] fluoro-2-deoxy-D-glucose positron emission tomography fused with computed tomography (FDG-PET/CT) demonstrated a large abdominal mass in size of approximately 6 cm with abnormal uptake. CT-guided biopsy of the abdominal mass revealed the relapse to be follicular lymphoma (Fig. 2). Monotonous cells (Fig. 2A) were positive for CD10 (Fig. 2B) and CD20 (Fig. 2C), but negative for CD3 (Fig. 2E) and CD5 (Fig. 2D), indicative of follicular center cells. Ki67-positive cells were observed (Fig. 2F, 10% at Ki67 index). She had no B symptoms, and her general health performance status was 2 by the WHO scale. She underwent 4 courses of R-IDEA chemotherapy (rituximab, ifosfamide, dexamethasone, etoposide, and cytarabine)[13] from October 2008 to January 2009, resulting in partial response. At the end of the third course, bone marrow tap detected no apparent involvement of lymphoma cells, and peripheral blood stem cells were harvested. In February 2009, she had no B symptoms and underwent autologous peripheral blood stem cell transplantation with myeloablative conditioning with R-MCEC chemotherapy (rituximab, ranimustine, cyclophosphamide, etoposide, and carboplatin). She demonstrated complete response.

She was well until April 2012 when she noticed upper eyelid swelling on the right side with gradual exacerbation. Magnetic resonance imaging at the referral visit to an ophthalmologist in October disclosed an orbital mass, involving the lacrimal gland, on the right side (Fig. 3A). In November, the excisional biopsy revealed extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) (Fig. 4). Monotonous small cells, infiltrating around and inside the deformed follicles (Fig. 4A, 4B) were positive for CD20 (Fig. 4C), Ki67 (Fig. 4F), and bcl2 (Fig. 4H), but negative for CD10 (Fig. 4I) and cyclin D1

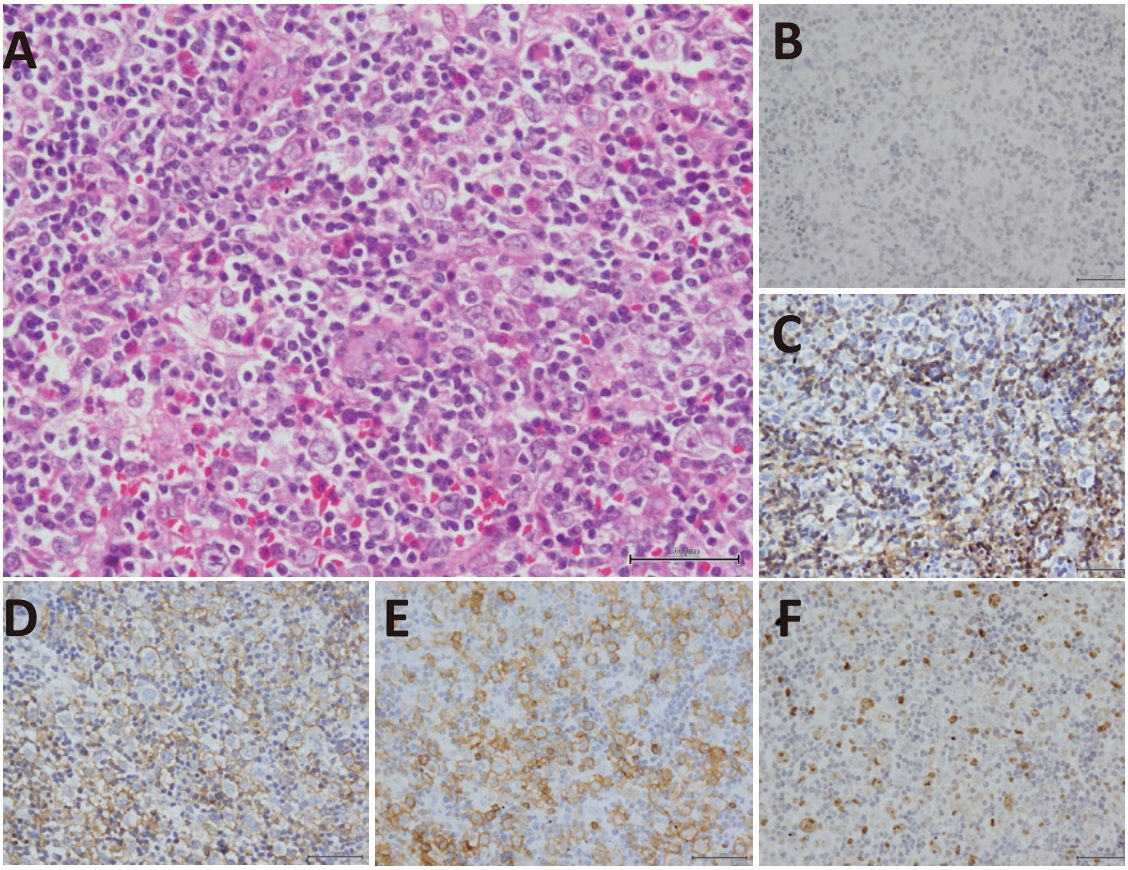

Fig. 1. Immunohistopathology of supraclavicular lymph node biopsy in 2003. Diffuse large B-cell lymphoma was diagnosed by large cells with irregularly-shaped nuclei in a diffuse distribution (***A***, hematoxylin-eosin staining), positive for CD20 (***D***), CD79a (***E***), and Ki67 (***F***, 25% at Ki67 index), but negative for CD3 (***B***). These large cells are accompanied by a small population of monotonous cells, positive for CD45RO (UCHL1), a marker for activated T cells (***C***). Bar = 50 μm.

(Fig. 4G). The lesion was also infiltrated with monotonous cells positive for CD3 (Fig. 4D) and CD5 (Fig. 4E). Clonal analysis of the orbital lesion by polymerase chain reaction amplification of the immunoglobulin heavy chain gene[14,15] suggested the monoclonal origin of lymphoma cells. In a parallel study, paraffin sections and blocks for the initial lymph node lesion in 2003 and the abdominal lesion in relapse in 2008 did not lead to the amplification of DNA fragments.

FDG-PET/CT demonstrated abnormal uptake in the cervical lymph node (maximum standardized uptake value: SUVmax=4.31, Fig. 3D), supraclavicular lymph node (SUVmax=3.05), and parasternal lymph node (SUVmax=4.24, Fig. 3C) on the right side, in addition to the right orbit (SUVmax=13.10, Fig. 3B). In December 2012, she underwent a course of rituximab monotherapy with partial response. In May 2013, she exhibited regrowth of the right orbital lesion (FDG-PET/CT SUVmax=12.39) and underwent external radiation at the total dose of 30 Gy in June. She underwent three additional courses of rituximab monotherapy in the interval of half a year, resulting in complete response. She had no relapse without treatment in the follow-up until August 2016.

DISCUSSION

The present patient sequentially demonstrated three different pathological types of malignant lymphoma: diffuse large B-cell lymphoma at the initial presentation, follicular lymphoma as relapse after R-CHOP chemotherapy, and MALT lymphoma as relapse after IDEA chemotherapy with autologous peripheral blood stem cell transplantation. These three pathological types of lymphoma were all of B-cell lineage. Changes in pathological types in relapse of lymphoma have been documented in patients with long-term survival after chemotherapy.[16-19] The clonality of lymphoma cells was the same or different between the initial lesion with one pathological type and the relapsed lesion with another pathological type.[16-19] We did not have evidence to determine same or different clonality among the initial lymph node lesion, the abdominal lesion in relapse, and the final orbital lesion of the present patient.

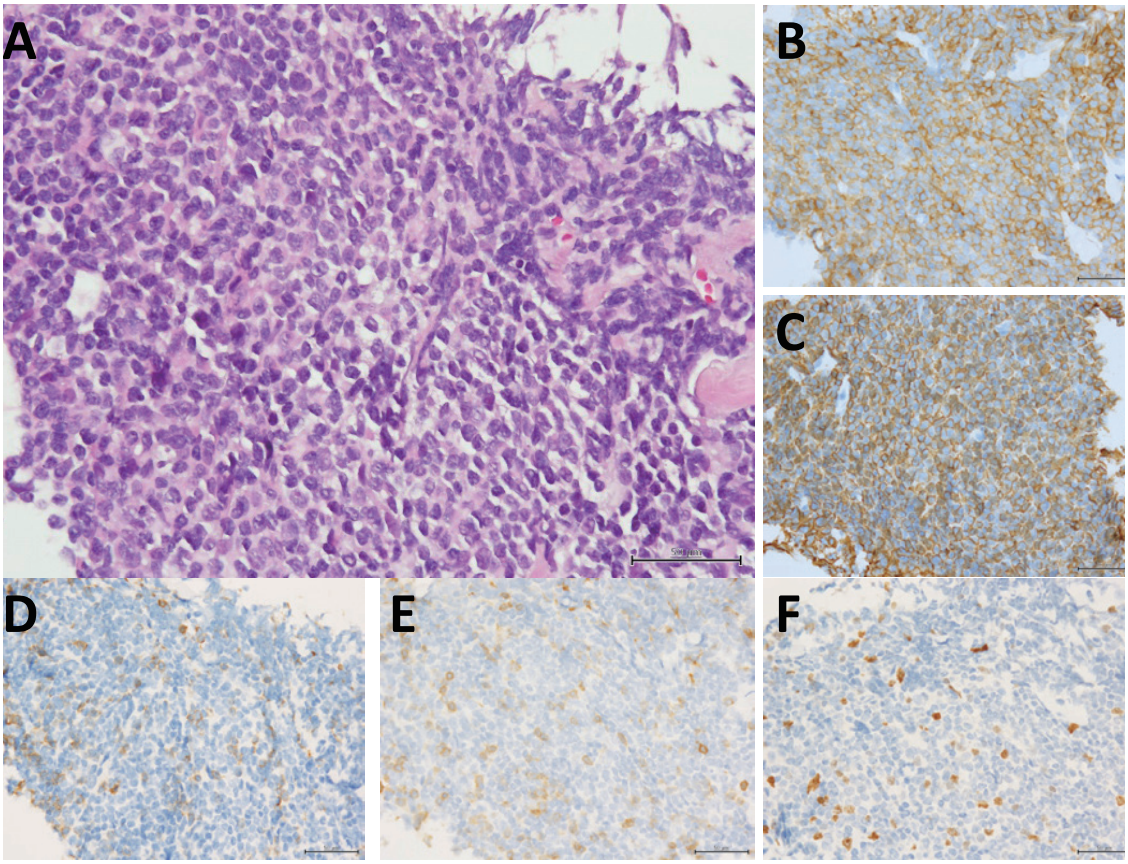

Fig. 2. Immunohistopathology of computed tomography-guided needle biopsy of abdominal lymph node in 2008. Follicular lymphoma was diagnosed by monotonous cells (***A***, hematoxylin-eosin staining), positive for CD10 (***B***) and CD20 (***C***), but negative for CD5 (***D***) and CD3 (***E***). Note that Ki67-positive cells are not rare (***F***, 10% at Ki67 index). Bar = 50 μm.

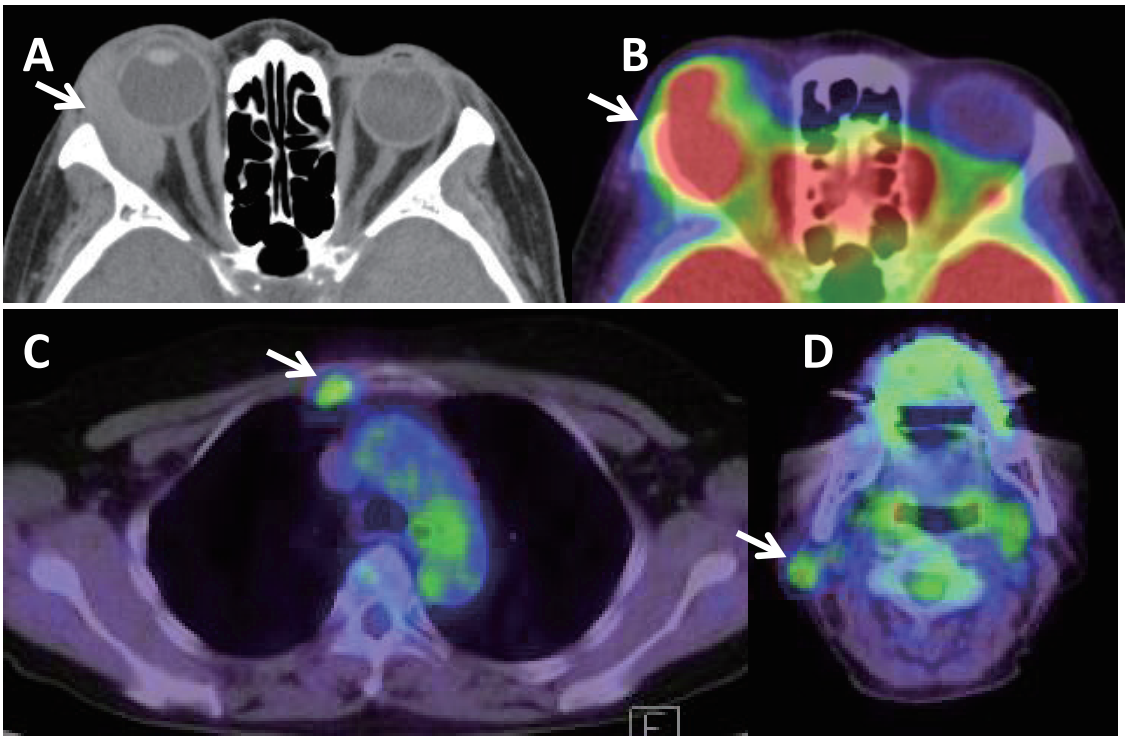

Fig. 3. Magnetic resonance imaging (***A***) and 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography fused with computed tomography (FDG-PET/CT) (***B***) of the orbital lesion (maximum standardized uptake value: SUVmax = 13.10) on the right side in 2012. Note also abnormal uptake sites in parasternal lymph node (SUVmax = 4.24, ***C***) and cervical lymph node (SUVmax = 4.31, ***D***) on the right side, revealed by FDG-PET/CT.

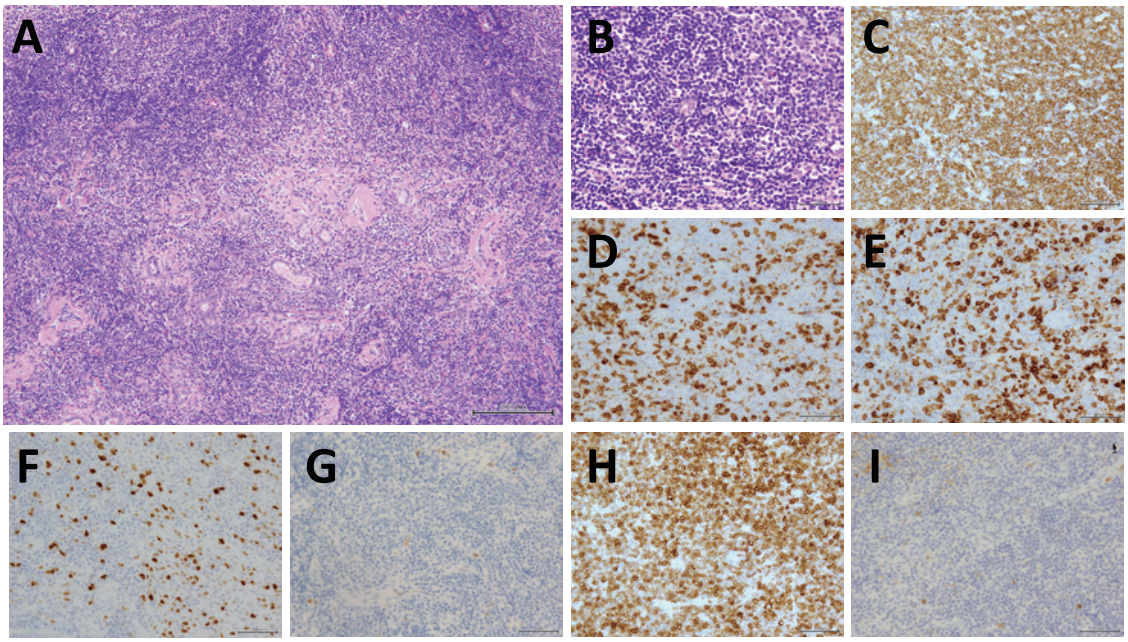

Fig. 4. Immunohistochemistry of excisional biopsy of the right orbital lesion in 2012. MALT lymphoma was diagnosed by monotonous small cells, infiltrating around and inside deformed follicles (***A***, ***B***, hematoxylin-eosin staining), which are positive for CD20 (***C***), Ki67 (***F***, 40% at Ki67 index), and bcl2 (***H***), but negative for CD10 (***I***) and cyclin D1 (***G***). Note also another population of small cells, positive for CD3 (***D***) and CD5 (***E***). Bar = 50 μm on all panels, except for bar = 200 μm on the top left panel (***A***).

The orbit, especially the lacrimal gland, is one of the common sites involved in lymphoproliferative disorders that include both lymphoma and inflammation.[18-21] Pathological diagnosis by excisional biopsy of the orbital lesions is mandatory because lymphoma may change its pathological type in relapse. In the present patient, we assumed that relapse of aggressive lymphoma after autologous peripheral blood stem cell transplantation may lead to a poor prognostic course.[8,9] Contrary to our expectations, the orbital relapse was proven as MALT lymphoma. PET/CT demonstrated abnormal uptake sites in lymph nodes, in addition to the orbital lesion, indicating systemic involvement with lymphoma. We, therefore, chose rituximab monotherapy, and then added local irradiation to the remaining orbital lesion. The two additional courses of rituximab monotherapy for consolidation successfully led to complete response, with no treatment at all during the follow-up in the present patient.

In conclusion, orbital MALT lymphoma, manifesting as the relapse of aggressive lymphoma after hematopoietic stem cell transplantation, may not be a poor prognostic sign in the long-term course of lymphoma. The pathological diagnosis of lymphoma type changes is crucial for an accurate estimate of prognosis in the era of high-dose chemotherapy with autologous hematopoietic stem cell transplantation as a first-line or second-line treatment for aggressive lymphoma.

CONFLICT OF INTEREST

The authors declare no conflict of interest in this study.

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