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## High-Grade Transformation in a Splenic Marginal Zone Lymphoma with a Cerebral Manifestation

Authors' Contribution:  
Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
Funds Collection G

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**Patient:** Female, 31  
**Final Diagnosis:** Histological transformation of splenic low-grade lymphoma  
**Symptoms:** Fatigue • night sweats  
**Medication:** —  
**Clinical Procedure:** Intravenous methylprednisolone followed by high-dose methotrexate  
**Specialty:** Hematology

**Objective:** Unusual clinical course

**Background:** Splenic marginal zone lymphomas (SMZLs) are generally uncommon, indolent lymphomas that typically affect older adults, but the development of the transformation to high-grade lymphoma may occur in a small proportion of patients and represents a rare event with blastic cell infiltration in the lymph nodes and bone marrow.

**Case Report:** Here, we present a young adult patient who was diagnosed with a SMZL and developed a high-grade transformation to diffuse large B cell lymphoma (DLBCL) with central nervous system involvement. The patient was a 31-year-old woman whose hematologic medical history began with severe anemia and thrombocytopenia associated with atypical lymphoid infiltrate in the bone marrow and massive splenomegaly. A splenectomy was performed and revealed the SMZL. She was first treated with the CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone) and subsequently with the R-FMD regimen (rituximab, fludarabine, mitoxantrone, and dexamethasone) because the peripheral blood leukocytes were remarkably increased postoperatively. Six months after the splenectomy, she complained of headaches. A magnetic resonance imaging scan of her brain revealed intracerebral tumorous lesions from which a biopsy was taken. On morphological and immunohistochemical examination, the tumor fulfilled the criteria for a DLBCL. Treatment with pulse-dose intravenous methylprednisolone followed by high-dose methotrexate was promptly initiated, but the patient's condition continued to deteriorate and she died of the disease 13 months after the splenectomy.

**Conclusions:** Although there is a general tendency for SMZL to display low aggressiveness, central nervous system involvement associated with a histological transformation to high-grade lymphoma, as presented here, can occur in advanced stage of the disease.

**MeSH Keywords:** Diagnosis • Lymphoma, B-Cell, Marginal Zone • Lymphoma, Large B-Cell, Diffuse

**Full-text PDF:** <http://www.amjcaserep.com/abstract/index/idArt/903679v>



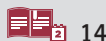
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## Background

Splenic marginal zone lymphoma (SMZL) is a special subtype of mature B cell lymphoma, accounting for fewer than 2% of all non-Hodgkin's lymphoma cases [1]. Median age was 68 years (range, 22–79 years) with female: male ratio of 1.8: 1 [2]. SMZLs generally present with massive splenomegaly with frequent involvement of the small splenic hilar lymph nodes, peripheral blood, and bone marrow [3]. Most patients with SMZLs display indolent courses; however, similar to other indolent lymphomas, a small proportion of patients follow an aggressive course, such as the development of the transformation to a high-grade lymphoma with blastic cell infiltration of the bone marrow, liver, spleen, and lymph nodes [4–7]. The risk of central nervous system (CNS) involvement for indolent lymphomas was reported to be low [8,9]. In a study of 1163 patients with low-grade non-Hodgkin's lymphoma, the proportion with CNS involvement at 5 years was 2.8% [8]. Remarkably, in another study, CNS involvement occurred in 7% of patients with low-grade non-Hodgkin's lymphoma, which was associated with a transformation to high-grade malignancy in all these patients [9]. However, there has been only 1 case report showing a high-grade blastic transformation within the CNS in a patient with SMZL [10], who was found to have isolated cerebral involvement by diffuse large B cell lymphoma (DLBCL) without nodal or other extranodal involvement 3.5 years after the diagnosis of SMZL.

In the present study, we present a 31-year-old patient with clinical, histological, and immunophenotypic findings consistent with SMZL. The secondary CNS involvement of DLBCL due to blastic transformation of SMZL, along with concomitant other extranodal disease, occurred at 8 months after the diagnosis, suggesting CNS involvement may be part of the manifestation of the systemic disease progression. We reviewed the literature on SMZL cases with histologic transformations to high-grade lymphomas, and describe the clinical characteristics of such cases.

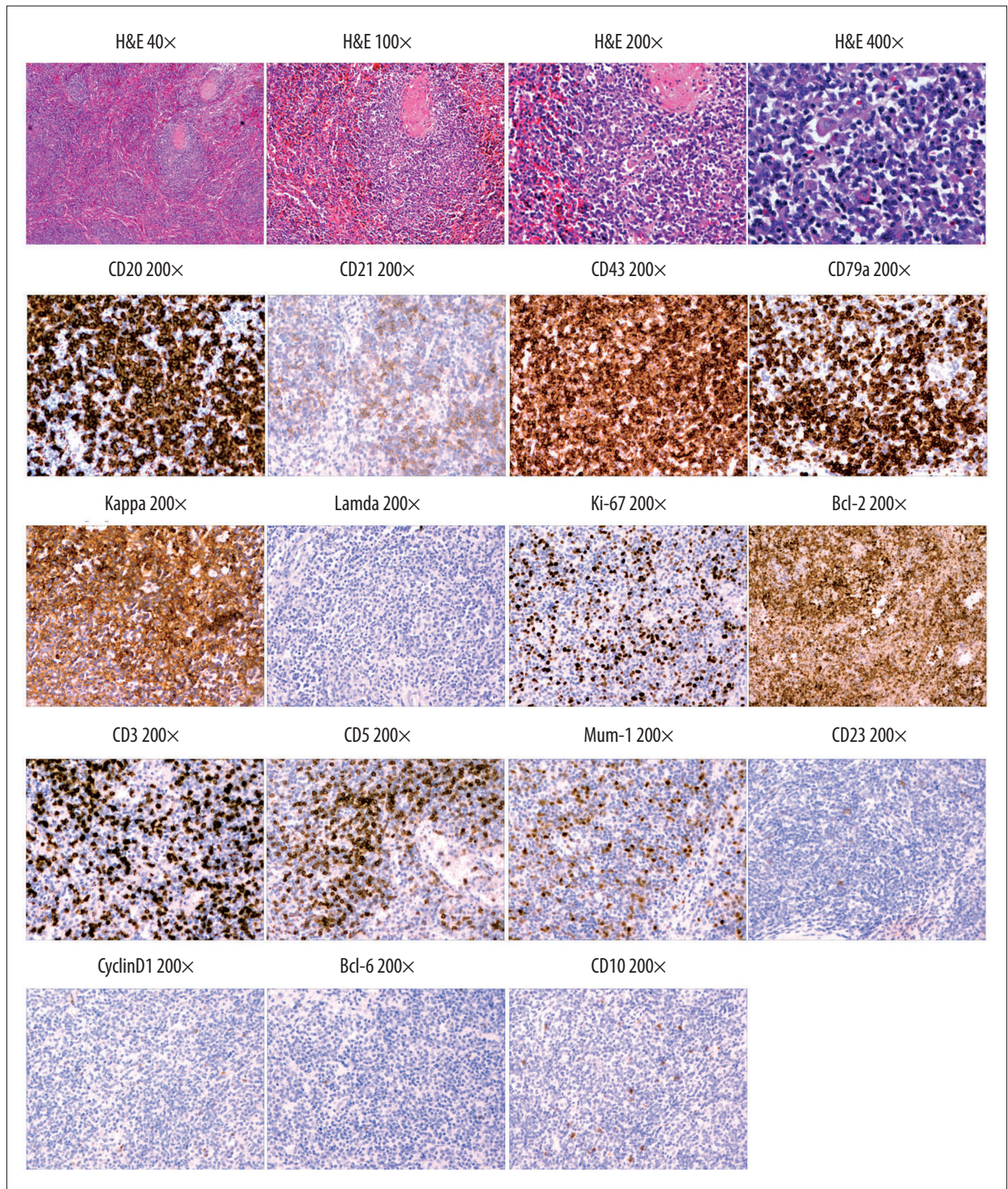
## Case Report

A 31-year-old woman presented in April 2014 with a 1-month history of progressive abdominal fullness, fatigue, and night sweats. She denied fever or weight loss. A physical examination was notable for a palpable spleen 8 cm below the navel. A complete blood count revealed severe anemia (hemoglobin level, 58 g/L), thrombocytopenia (platelet count,  $32 \times 10^9/L$ ), and a normal white blood cell count of  $4.31 \times 10^9/L$  with 18% neutrophils, 66% lymphocytes, 5% monocytes, and 10% atypical lymphocytes. The levels of  $\beta$ -2-microglobulin (0.937 mg/dL, normal range, 0.07–0.18 mg/dL) and lactic dehydrogenase (443.6 U/L, normal range, 40–250 U/L) were significantly

elevated, but the serum albumin was normal. Whole-body positron emission tomography/computed tomography (PET/CT) revealed massive splenomegaly with heterogeneously increased 18F-fluorodeoxyglucose (FDG) uptake (maximum standard uptake value [SUVmax] 5.7), hepatic hilum and retroperitoneal adenopathies with increased FDG uptakes (SUVmax 5.0), mediastinal, cardiophrenic angle, bilateral axillary and internal mammary adenopathies with low-grade FDG uptakes (SUV range, 1.6–3.2), bilateral pelvic side wall and inguinal adenopathies with low-grade FDG uptakes (SUV range, 2.1), and diffusely increased FDG uptake (SUVmax 2.4) in the long bones and the pelvic bone. A bone marrow biopsy revealed intrasinusoidal or interstitial infiltration of small-sized lymphocytes with slightly coarse clumping of the chromatin. Bone marrow immunophenotyping by flow cytometry revealed a clonal population of mature B cells with a kappa light chain restriction. The clonal B cells were positive for CD19 and CD20; partially positive for CD5, CD23, CD43, CD38, and CD11c; and negative for CD10, CD25, CD103, and CD22. A diagnosis of SMZL stage IV B (Ann Arbor classification) was made.

Due to the advanced stage of the disease, the combination chemotherapy regimen composed of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) was administered to the patient. The patient refused to use rituximab for economic reasons. A splenectomy was performed in June 2014 because after the initial course of chemotherapy, the patient's spleen exhibited mild shrinkage but then progressively re-enlarged. Hematoxylin and eosin (H&E) staining of the spleen revealed the lymphoid cells with marked monocytoid or plasmacytoid differentiation were infiltrated in the splenic white pulp, the red pulp, and partial splenic sinus with a nodular pattern (Figure 1). Immunohistochemical staining demonstrated the neoplastic cells were positive for CD43, Kappa, Ki-67 (30%), CD79a, MUM-1, CD21 (FDC), and CD20 (B cells) but negative for Cyclin D1, Bcl-6, CD10, Lambda, and CD23, which was consistent with the initial diagnosis of SMZL (Figure 1).

Postoperatively, her disease progressed with a rapid increase in peripheral blood leukocytes ( $27.49 \times 10^9/L$ ) with 40% atypical lymphocytes, and the hemoglobin and platelet count returned to normal. A repeat PET/CT scan revealed that compared with the previous PET/CT scan, the patient had greater increases in FDG uptake (SUVmax 7.93 vs. 5.0) in the hepatic hilum and retroperitoneal lymph nodes and greater increases in the volumes and FDG uptakes (SUVmax 6.88 vs. 1.6–3.2) of the bilateral pelvic side wall and the inguinal lymph nodes. She was then given 3 additional courses of CHOP chemotherapy every 3 weeks. However, her white blood cell count continued to increase and reached  $50.57 \times 10^9/L$  with 34% atypical lymphocytes in October 2014, 4 months after the splenectomy. Flow cytometric immunophenotyping of the peripheral blood confirmed the clonal B cell nature with kappa light chain restriction



**Figure 1.** Histological examination of the splenectomy specimen. Lymphoid hyperplasia in the splenic white pulp with a nodular pattern of infiltration accompanied by the involvement of the red pulp and partial splenic sinus is shown. The tumor cells exhibited a monocytoid morphology with partial plasmacytic differentiation. The immunohistochemistry detection revealed that the cells were positive for CD43, Kappa, Ki-67 (30%), CD79a, MUM-1, CD21 (FDC), and CD20 (B cells) but were negative for Cyclin D1, Bcl-6, CD10, Lambda, and CD23, which agrees with the diagnosis of SMZL. The residual T cells were positive for CD3, CD5, and Bcl-2.

expression. Due to the progression of the disease, 2 cycles of chemoimmunotherapy regimen composed of rituximab, fludarabine, mitoxantrone, and dexamethasone (R-FMD) were administered every 4 weeks. After the treatment, the white blood cell count dropped to a normal level.

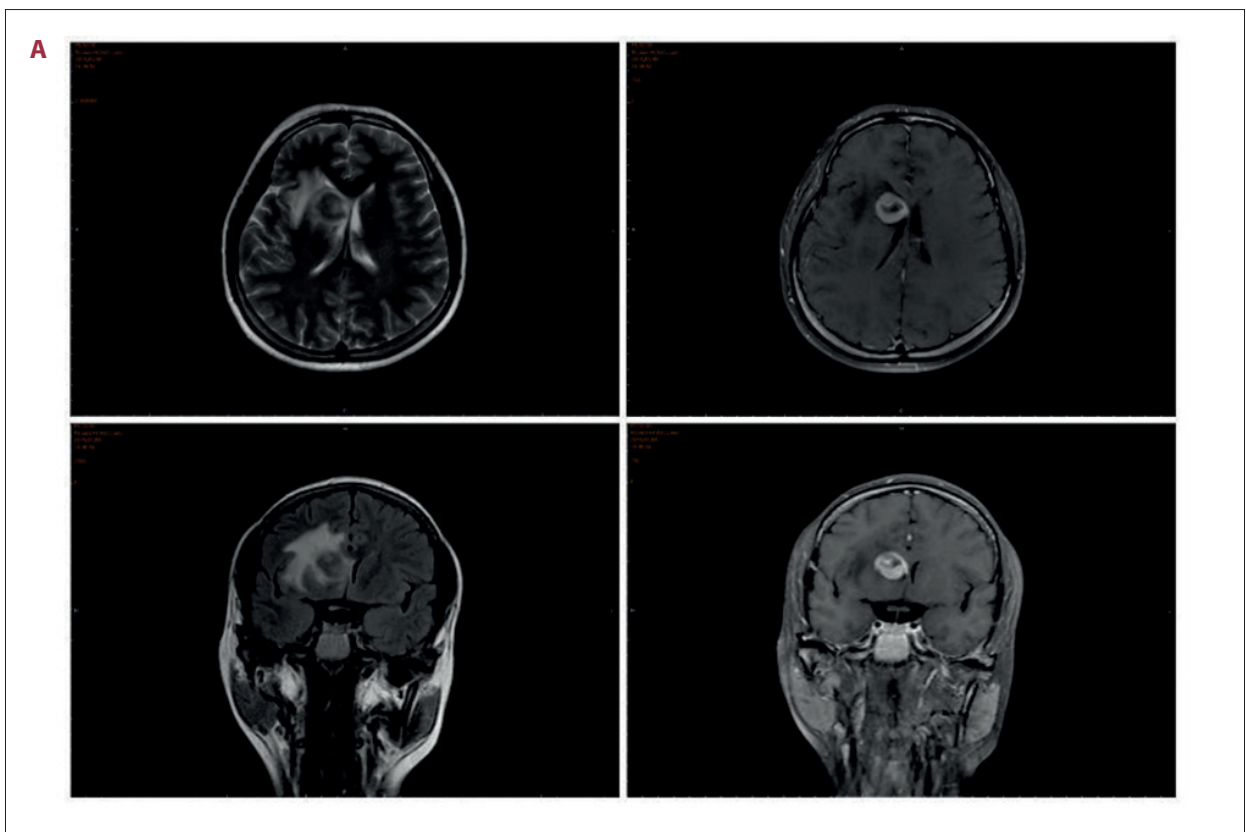
In December 2014, the patient complained of a headache. Cerebral magnetic resonance imaging (MRI) revealed a brain mass within the right basal ganglia, measuring 2.2×2.1 cm (Figure 2A). Pathological examination of the lesion with a MRI-guided stereotactic brain biopsy revealed infiltration of brain tissue by medium-to-large-sized atypical lymphocytes, which were positive for CD20, Bcl-6, MUM-1, and Ki-67 (75%) and negative for CD3, CD10, CD30, Cyclin D1, CK, ALK, Kappa, and Lambda by immunohistochemistry detection, in keeping with a transformation to a DLBCL with a non-germinal center B cell type (Figure 2B). Bone marrow aspiration and flow cytometric immunophenotyping revealed no signs of neoplastic involvement. A PET/CT scan revealed an increased FDG uptake in the left pelvic side wall and right anterior abdominal wall compared with the previous PET/CT scan beside the mass within the right basal ganglia, suggesting the cerebral tumor was part of the manifestation of progression of the systemic disease. The patient was treated with pulse-dose intravenous methylprednisolone followed by high-dose methotrexate at 3 g/m<sup>2</sup> for 2 cycles (each cycle administered every 2 weeks). After the

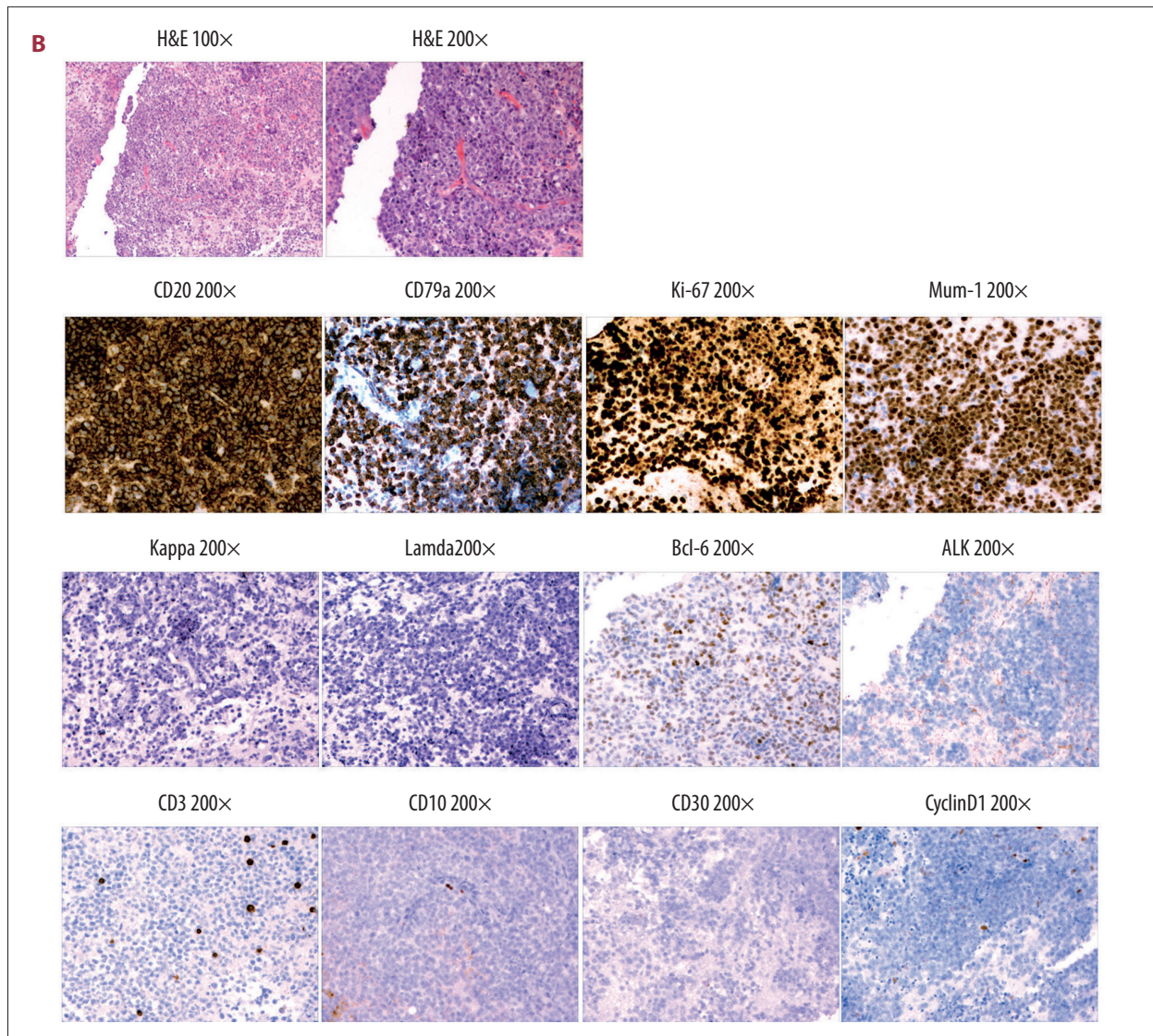
first cycle of treatment, she complained of severe headache with vomiting. A physical examination revealed that 1 pupil was dilated and failed to constrict in response to light. After the second cycle of treatment, her symptoms of headache and vomiting were relieved, and an MRI scan of the brain revealed that the tumor had shrunk and the mass effect from edema was reduced. However, the chemotherapy treatment was self-discontinued by the patient and, although it was re-initiated 2 months later, her condition continued to deteriorate. She died to her illness in July 2015.

## Discussion

Here, we present an unusual case of a secondary CNS lymphoma with a typical DLBCL immunophenotype that arose from a SMZL. This case is unusual in 3 respects. First, SMZLs typically affect older patients, and their occurrence in patients younger than age 35 years is rare. Second, histologic transformation to high-grade B cell lymphomas of SMZLs, as low-grade B cell lymphomas, is rare. Third, CNS involvement as the site of the histologic progression of an SMZL is extremely rare.

Secondary cerebral involvement is an uncommon event during the clinical course of an indolent lymphoma, which is often associated with a transformation to a high-grade aggressive





**Figure 2.** MRI measurement with histological examination of the brain. (A) MRI of the brain showing a solitary ring enhancing lesion with a maximum diameter of 2.2 cm and surrounding edema involving the right basal ganglia. (B) Histological examination of the biopsied intracerebral tumorous lesion revealed that the highly cellular clumps consisted of medium-to-large-sized atypical lymphocytes. The immunohistochemistry detection revealed that the lymphocytes were positive for CD20, Bcl-6, MUM-1, and Ki-67 (75%) and negative for CD3, CD10, CD30, Cyclin D1, CK, ALK, Kappa, and Lambda, in agreement with the diagnosis of a DLBCL with a non-germinal center B cell phenotype.

lymphoma [11]. For SMZLs, the frequency of the histologic transformation varies from 5% to 19% [4–7,12,13]. A recent retrospective study reported an incidence rate of 5% for histological transformation in a large series of 85 SMZL patients, whose median follow-up time was 4.8 years [6]. Other previously published series that focused on SMZLs have reported the rate of transformation to large B cell lymphomas ranges from 10% to 19% [4,5,7,12]. Transformation can occur at any time, from when a low-grade lymphoma is first diagnosed onward. Camacho et al. reported that in a series of 12 SMZL patients, the large B cell lymphoma transformations occurred

from 12 to 85 months after splenectomy (mean 36.5 months) in 10 cases and were present at the diagnosis of the SMZL in 2 cases [4]. Parry-Jones et al. reported that transformations occurred within a median interval of 26 months (range 7–117 months) in another series of 12 SMZL cases [7]. The presence of B-symptoms or elevated serum lactate dehydrogenase should lead to the investigation of possible transformation to a more aggressive lymphoma [11]. The transformation clinically presents as the development of bulky nodes, the appearance of blasts in the peripheral blood, or lymphoma involvement in extranodal sites [7]. The most frequent locations of transformed

lymphomas are in the lymph node and bone marrow [4,5,7], but CNS involvement is extremely rare [8,9]. Thoennissen et al. reported a 51-year-old patient with secondary CNS involvement of DLBCL due to the high-grade blastic transformation of SMZL [10]. The transformation to a high-grade lymphoma is typically either a DLBCL or a B cell lymphoma, unclassified, with features intermediate between DLBCL and Burkitt lymphoma [11], which is consistent with the immunophenotype of the CNS disease in our case. To exclude the possibility of secondary lymphoma, the immunoglobulin heavy chain gene rearrangement should be detected [4], but because of the limited amount of brain biopsy tissue from our case, we could not confirm their clonal relationship between the primary SMZL and the transformed DLBCL. The response to treatment and survival of SMZL patients after transformation are usually poor. In a study of 197 patients with MZL, the transformation into aggressive lymphoma was an independent risk factor for shortened overall survival [14]. In another study of 12 patients with

SMZL, patients with histological progression to large B cell lymphomas showed an overall 5-year survival rate of 55% in contrast with the better survival of SMZL patients overall [4]. Although treatment was promptly initiated, our patient's disease was so refractory that she died of the disease 6 months after diagnosis of the secondary CNS lymphoma, suggesting that the CNS involvement represents an advanced stage and a lethal event during the clinical course of SMZL.

## Conclusions

Although the clinical course of SMZL is generally indolent, CNS involvement associated with histological transformation to high-grade lymphoma can occur in advanced-stage disease. Exploring the biomarkers for risk assessment of higher grade transformation of SMZL would facilitate the treatment and thus improve the prognosis of these patients.

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