Central Nervous System Lymphoma Newly Developed 12 Years after Remission of an Ocular Adnexal Lymphoma

Keiko Morikawa^a Takahiro Tsuji^a Hiroshi Yamasaki^a Yasuo Toyozumi^b
Nobuyuki Arima^b Koichi Ohshima^c Hiroyuki Tsuda^a

Departments of ^aHematology and Oncology, and ^bPathology, Kumamoto City Hospital, Kumamoto, and
^cDepartment of Pathology, Kurume University School of Medicine, Fukuoka, Japan

Key Words

Central nervous system lymphoma · Molecular genetic analysis · Non-Hodgkin's lymphoma · Second neoplasm

Abstract

Recurrence of non-Hodgkin's lymphoma more than 5 years after the initial diagnosis is rare. When late relapse occurs, it is difficult to determine whether it is a true recurrence or a new lesion. We experienced a case of an 81-year-old woman who developed central nervous system (CNS) lymphoma 12 years after remission of ocular adnexal lymphoma. Both showed the histology of diffuse large B-cell lymphoma. To elucidate whether the CNS lymphoma was clonally related to the first lymphoma, rearrangement of the immunoglobulin heavy chain genes of each lymphoma was studied using a polymerase chain reaction-based method. The results revealed that the sizes of the amplified products of the rearranged regions from the two lymphomas were different. This suggested different clonal origins of the lymphomas. It is clinically important to determine the origin of a second neoplasm because patients with a clonally related second lymphoma are usually treated with more intensive regimens, while those with a clonally unrelated lymphoma receive standard first-line therapy. The present case shows that, in

the case of recurrent non-Hodgkin's lymphoma, not only histological confirmation but also genetic assessment is important to clarify the origin of the second lymphoma.

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Introduction

Recent advances in therapy have significantly improved the outcome of malignant lymphomas, a heterogeneous group of neoplasms. However, a substantial number of patients experience early relapse. For example, a population-based study in British Columbia showed that progression-free survival of all patients with diffuse large B-cell lymphoma (DLBCL) treated with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) plus rituximab is about 70%, indicating a relapse rate of about 30% [1]. Generally, these cases of relapse have been thought to originate from residual clones of the original lymphomas.

When a second lymphoma presents long after the complete remission of the first lymphoma, it is difficult to determine simply on the basis of clinical and pathological findings whether it is a true recurrence or a new lesion. Lately, molecular techniques have become available to

Fig. 1. Histology of the first (ocular adnexal) and second (CNS) lymphomas. Both lymphomas showed DLBCL histology: ocular adnexal lymphoma (upper left, HE staining; lower left, immunohistochemical staining of CD20) and CNS lymphoma (upper right, HE; lower right, CD20).

help elucidate the genetic background and diversity of second lymphomas [2].

We report the case of a new central nervous system (CNS) lymphoma which developed 12 years after remission of ocular adnexal lymphoma, both of which had DLBCL histology. In order to assess the origin of the CNS lymphoma, we studied the diversity of the rearrangement of immunoglobulin heavy chain (IgH) genes of both lymphomas using a polymerase chain reaction (PCR)-based method.

Case Report

An 81-year-old woman developed ocular adnexal lymphoma in 2000. The affected lesion was in the right orbit and cervical lymph nodes. The pathological diagnosis was DLBCL (fig. 1), and the clinical stage was IIEA. Ocular adnexal marginal zone B-cell lymphoma has been reported to be associated with *Chlamydia psittaci*. Although we have not confirmed her chlamydial infection, she never had a history of professional or domestic exposure to animals [3]. She was treated with three cycles of chemotherapy (CHOP) followed by radiotherapy (50 Gy), and complete remission was achieved. Remission lasted 12 years without any additional treatment.

In May 2012, she was admitted to our hospital due to hyposthenia of the left arm and leg. CT of the brain revealed a mass ~2 cm in diameter in the frontal parietal lobe. An extensive low-density area was observed in the subcortical area of the right temporal lobe, approximately reflecting edema surrounding the tumor.

MRI disclosed multifocal tumors in the left cerebellopontine angle and bilateral parietal lobes, as well as in the right frontal parietal lobe. Except for a slight elevation in lactate dehydrogenase, complete laboratory profiles of the serum, including tumor markers such as carcinoembryonic antigen, carbohydrate antigen 19-9, cancer antigen 125, squamous cell carcinoma antigen, and soluble interleukin-2 receptor, were almost normal. Brain biopsy was performed, and DLBCL was diagnosed (fig. 1). No lymphoma lesion was identified in the other parts of the body in a whole-body CT. Therefore, the clinical stage was IEA. Considering her age and performance status (grade 4 according to the ECOG scale), we selected radiotherapy. She was treated with whole-brain radiotherapy (40 Gy) followed by additional radiation focused on the mass in the right frontal parietal lobe (16 Gy). After treatment, the mass in the right frontal parietal lobe had almost disappeared, but the other tumors were still present on MRI (fig. 2). Hyposthenia of the left arm and leg gradually improved and she became able to walk with a walking aid. She was transferred to another hospital for further rehabilitation.

In order to elucidate whether this CNS lymphoma was a true relapse of the previous disease or a newly developed primary lymphoma, we performed molecular analysis of the IgH gene rearrangement. During early stages of B-cell maturation, variable (V), diversity (D), and joining (J) gene segments of the IgH gene are linked together to encode a functional antigen receptor. The IgH gene remains mostly unmodified during clonal expansion of neoplastic cells, regardless of the maturation state. Since B cells from a clonal population have identical IgH genes, monoclonal VDJ rearrangement can be easily distinguished from polyclonal VDJ rearrangement by amplification of the joined VDJ segment of B-cell IgH genes by PCR [4]. DNA extracts from both lymphomas were studied by a seminested PCR method using as primers oligonucle-

Fig. 2. MRI images of the brain before (a–c) and after (d–f) treatment. The mass in the right frontal parietal lobe almost disappeared (a, d) but the other tumors were still present (b, c, e, f) after radiotherapy.

otides homologous to the conserved sequences in the framework II region (FR2B) and joining (JH) region (CFW1 and SJHb). The amplified products from the lymphoma samples were electrophoresed in parallel. A single distinct band found in each lane indicated their clonal nature (fig. 3). However, the molecular sizes of the bands were slightly but distinctly different (fig. 3). This suggested that the first ocular adnexal lymphoma and the second CNS lymphoma originated from different clones.

Discussion

Patients with DLBCL usually relapse within the first 2–3 years after diagnosis. Late relapses after more than 5 years are rare [5, 6]. Traditionally, even if a late relapse occurs, a relapsing lymphoid neoplasm may represent a recurrence of the original clone. However, this concept has recently been questioned [7, 8]. This is in part due to the treatment progress over recent decades. More patients can survive their first lymphoma and have an opportunity to develop a new second lymphoma. Additionally, the progress of molecular techniques has helped to gain a deeper insight into the genetic background [9].

Analysis of VDJ rearrangement of the IgH gene is a powerful tool for the identification of relapse in lymphoma because it occurs at the earliest stages of tumorigenesis and is not altered during progression [10]. In our case, PCR-based molecular analysis of the VDJ region clearly showed that the first and second lymphomas had different origins.

Fig. 3. IgH VDJ amplified PCR products. M = 50-bp DNA ladder marker; 1 = ocular adnexal lymphoma; 2 = CNS lymphoma; 3/4 = β -actin.

It is not clear how two clonally unrelated lymphomas appeared in the same individual. This patient might have some underlying genetic defects that confer susceptibility to the development of lymphomas. Alternatively, environmental factors can contribute to lymphomagenesis. In the present case, the patient's brother died of a lymphoma, although the detailed pathology is not known. However, neither of the above possibilities can be eliminated at this time.

Recently, accumulating evidence has shown that somatic alterations in uncommitted hematopoietic progenitors contribute to lymphomagenesis in some mature lymphoid malignancies [11]. It is plausible that at the stage before genetic rearrangement of antigen receptor loci those progenitors serve as reservoirs for further clonal evolution and contribute to the development of a second lymphoma. Sanchez et al. [12] reported that several percent of B-cell malignancies, including large cell lymphomas, consist of more than one B-cell clone. Therefore, another possibility is that the very minor clone in the initial tumor developed to the second lymphoma during the long incubation period after the dominant clone was eliminated by treatment. In this case, the former seems more plausible since only one clone was detectable in the first lymphoma sample, at least by PCR. However, further study is needed to clarify these possibilities.

Some patients do not undergo an additional biopsy at relapse, but we should make a histopathological diagnosis

of the recurrent lesions [4]. Histological transformation is not a rare phenomenon [13]. However, a histological match does not necessarily mean that there is a match in the clone. Similarly, a histological discrepancy does not necessarily mean that there is a discrepancy in the clone. Thus, nowadays, it is acknowledged that non-Hodgkin's lymphoma recurrence, even within a shorter period of time, with or without a different histology might represent a clonally unrelated secondary neoplasm. Therefore, clonal analysis by molecular methods is quite important.

Usually, more intensive therapy protocols are applied for recurrent lymphomas since future treatment resistance is anticipated. However, it has been suggested that patients with clonally unrelated second lymphoma should not receive aggressive treatment but be treated by standard first-line therapy [14]. Therefore, when we encounter recurrence of lymphoma, we should perform tissue diagnosis and, if possible, molecular genetic analysis to clarify the origins of both the first and the second lymphoma.

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