Clinical Case Report

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Sequential development of multifocal recurrent non-Hodgkin's lymphoma of mucosa-associated lymphoid tissue and diffuse large B-Cell lymphoma in a single patient

A case report

Xubo Yang, MD[a,b], Xiaoxue Min, MMed[a], Weimin He, MD[a,*]

Abstract

Rationale: Diffuse large B-cell lymphoma (DLBCL) and extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) belong to Non-Hodgkin's lymphoma (NHL). DLBCL rarely involves the orbit. MALT lymphomas, which account for 8.0% of NHLs, rarely involve parotid gland, trachea and bronchus.

Patient concerns: We present a rare case of a long-surviving patient (≥10 years) with sequential development of multifocal recurrent non-Hodgkin's lymphoma of mucosa-associated lymphoid tissue (MALT) and diffuse large B-Cell lymphoma (DLBCL). In August 2007, a 41-year-old man developed MALT lymphoma in the parotid gland and local irradiation was administered. In July 2008, he exhibited systemic multifocal lymphadenopathy and was diagnosed with DLBCL. He received standard combination chemotherapy and autologous hematopoietic stem cell transplantation. He was well until February 2013 when he developed MALT lymphoma of the bronchus. Subsequently, he received standard combination chemotherapy. In November 2013, the patient had a relapse of the MALT lymphoma by tracheal biopsy and received local radiation. He was well until March 2015 when he developed a MALT lymphoma of the left thigh. He underwent surgery, local irradiation and rituximab monotherapy. In September 2015, surgical resection of the left orbital masses was performed, and the biopsy revealed the presence of DLBCL. One month later, lymphadenopathy was palpated in the neck, the lower left region of the umbilicus, and the left calf. Then he received chemotherapy with rituximab and lenalidomide. In March 2016, the patient underwent surgical resection for a right popliteal mass, and the resection biopsy revealed DLBCL. To date, the patient is still alive.

Diagnoses: The patient was diagnosed as multifocal recurrent MALT and DLBCL.

Interventions: Repeated positron emission tomography-computed tomography (CT) and biopsy were performed.

Outcomes: CT and biopsy revealed sequential development of multifocal recurrent NHLs of MALT lymphoma and DLBCL. The correlation between MALT and DLBCL may represent a Richter transformation. Standard treatments, such as combination chemotherapy, autologous hematopoietic stem cell transplantation, and irradiation, may be driving factors for phenotypic changes in neoplastic cells.

Lessons: Physicians should pay particular attention to the long-term development of other types of NHL after achieving complete remission of one type of NHL.

Abbreviations: Bcl = B-cell lymphoma, CD = cluster of differentiation, CT = positron emission tomography-computed tomography, DLBCL = diffuse large B-cell lymphoma, *IGH* = immunoglobulin heavy chain, *IGK* = immunoglobulin kappa light chain, MALT = extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue, NHL = Non-Hodgkin's lymphoma.

Keywords: diffuse large B-Cell lymphoma, lymphoma of mucosa-associated lymphoid tissue, multifocal, non-Hodgkin's lymphoma

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The authors declare that they have no conflict of interest.

[a] Department of Ophthalmology, [b] Department of Optometry and Visual Science, West China Hospital of Sichuan University, Chengdu, Sichuan, P.R. China.

[*] Correspondence: Weimin He, Department of Ophthalmology, West China Hospital of Sichuan University, 37 Guoxue Xiang, Chengdu, Sichuan, 610041, P. R. China (e-mail: hewm888@hotmail.com).

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1. Introduction

Non-Hodgkin's lymphoma (NHL) is a common type of malignant tumor that affects adults. Classified by pathology, diffuse large B-cell lymphoma (DLBCL) is the most common form of NHL, accounting for 47.5% of all NHL cases.[1,2] DLBCL is a high-grade NHL that can invade almost any part of the body.[3] The most common site is the lymph nodes, with 40.0% of primary DLBCLs arising in extranodal sites, such as the gastrointestinal tract, bone, testis, salivary glands, thyroid gland, skin, and central nervous system.[4] The orbit is a rare site of presentation of DLBCL. On the one hand, NHLs rarely involve the orbit, which accounts for just 8.0% to 15.0% of extranodal NHLs.[5] On the other hand, the majority of orbital NHLs are

low-grade lymphomas, whereas only 16.0% are high-grade lymphomas.[6]

Extranodal marginal zone B-cell lymphomas of mucosa-associated lymphoid tissue (MALT) account for 8.0% of NHLs.[7] They have the highest incidence in the stomach, although virtually any mucosal site may be involved.[8] MALT lymphomas of the parotid gland are rare,[9] as are MALT lymphomas of the trachea and bronchus.[10,11]

We report on a rare case of a long-surviving patient (≥10 years) with sequentially diagnosed MALT lymphoma of the parotid gland, DLBCL of lymph nodes of various regions of the body, MALT lymphoma of the bronchus, MALT lymphoma of the trachea, MALT lymphoma of the left thigh, DLBCL of the left orbit, and DLBCL of the right popliteal fossa.

2. Case report

The case report was approved by the Ethnics Committee in West China Hospital of Sichuan University and written informed consent was signed for the patient. A 41-year-old man presented with swelling of the right parotid gland and was referred to the West China Hospital of Sichuan University (Sichuan Province, China) in August 2007. A biopsy of the parotid lymph node detected a MALT-type lymphoma. Positron emission tomography-computed tomography (CT) showed no abnormal uptake in other regions of the body. Local irradiation was administered to the right parotid lesion and remission was achieved.

In July 2008, the patient exhibited systemic multifocal lymphadenopathy and was diagnosed with DLBCL by inguinal lymph node biopsy. A CT scan of the cervix, chest, and abdomen showed superior and inferior mediastinal lymphadenopathy, accompanied by a gastric occupying lesion. A bone marrow biopsy was performed at the same time, revealing Stage IV germinal cells, which accounted for 10.5%. The patient received 6 courses of combination chemotherapy with rituximab, cyclophosphamide, epirubicin, vincristine, and prednisone, 2 courses of monotherapy with rituximab, a single course of monotherapy with cyclophosphamide, and autologous hematopoietic stem cell transplantation, resulting in remission.

In February 2009, no swelling of the lymph nodes was detected on physical examination. No cytological abnormalities were observed and the bone marrow biopsy was normal. The patient subsequently underwent allogeneic hematopoietic stem cell transplantation and myeloablative pretreatment with rituximab, carmustine, etoposide, cytarabine, and melphalan. The patient was also administered an infusion of gamma globulin once a month for 6 months. During the following 4 years, repeated physical examinations, chest CT scans, and positron emission tomography-CT scans detected no obvious signs of a relapse of lymphoma. The patient was well until February 2013 when he developed a dry cough. An enhanced chest CT scan detected anterior mediastinal lymphadenopathy (Fig. 1A). Positron emission tomography-CT revealed a high signal intensity in the mediastinum. Bronchoscopic biopsy exhibited diffuse infiltration of small- to medium-sized lymphoid cells that stained positive for cluster of differentiation (CD) 20, but negative for CD3-epsilon, CD5, CD23, CD43, and cyclin D1. The Ki67 labeling index was 10.0%. These characteristics were consistent with a diagnosis of MALT lymphoma. Subsequently, the patient received 6 courses of combination chemotherapy with rituximab, cyclophosphamide, epirubicin, vincristine, and prednisone. Remission was achieved and a reduction in the size of the mediastinal lymph nodes was detected on a chest CT scan (Fig. 1B).

In November 2013, the patient experienced chest tightness and a shortness of breath that was accompanied by coughing up white mucus. A chest CT scan revealed enlarged mediastinal lymph nodes and a compressed trachea (Fig. 1C). Tracheal biopsy detected confluent dark lymphocytes that were positive for leukocyte common antigen, CD3-epsilon, CD20, and CD43, but negative for CD5, CD10, cyclin D1, cytokeratin, epithelial membrane antigen, chromogranin A, synemin, thyroid transcription factor-1, and the S-100 protein. Polymerase chain reaction detected immunoglobulin heavy chain (*IGH*) gene rearrangements, but not immunoglobulin kappa light chain (*IGK*) gene rearrangements. The number of Ki-67-positive cells was small. Thus, a relapse of the MALT lymphoma was diagnosed. The patient received 10 courses of local radiation, resulting in remission.

The patient was well until March 2015 when an enlarged mass of the left thigh was detected (Fig. 2). An excisional biopsy revealed a MALT lymphoma, which was positive for CD20, CD43, and B-cell lymphoma (Bcl)-2, but negative for CD3-epsilon, CD5, CD10, CD21, CD23, cyclin D1, and Bcl-6. The Ki-67 labeling index was 15.0%. Gene rearrangements of *IGH* and *IGK* demonstrated a clonal amplification peak. The patient was administered 5 courses of local irradiation and a single course of monotherapy with rituximab.

In September 2015, surgical resection of the left orbital masses was performed, approximately 6 months after the detection of the left orbital tumors (Fig. 3A–C). Two tumors were resected during surgery. The largest tumor, measuring $3.0 \times 2.5 \times 1.4$ cm, was located in the inferior orbit, adjacent to the inferior rectus muscle, and the smaller tumor, measuring $1.7 \times 1.2 \times 0.6$ cm, was located on the temporal side of the superior orbit (Fig. 4). An excisional biopsy of the orbital masses revealed diffuse infiltration of large

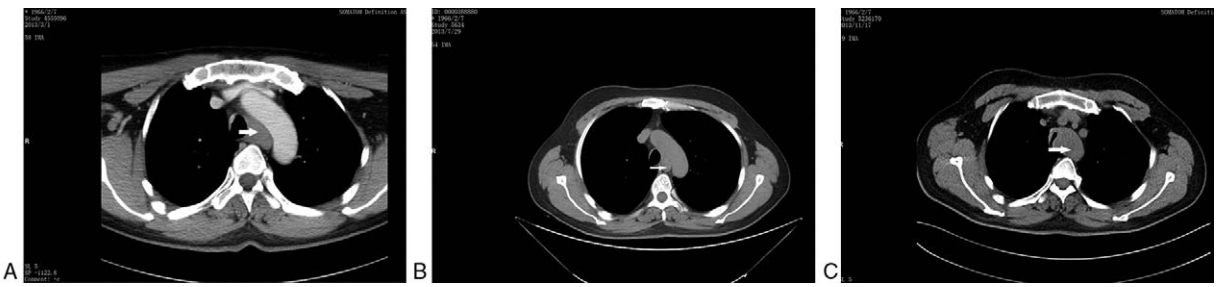

Figure 1. Chest computed tomography scan revealing mediastinal lymphadenopathy. (A) Mediastinal lymphadenopathy in February 2013. (B) A reduction in the size of the mediastinal lymph nodes after treatment in July 2013. (C) Enlarged mediastinal lymph nodes in November 2013.

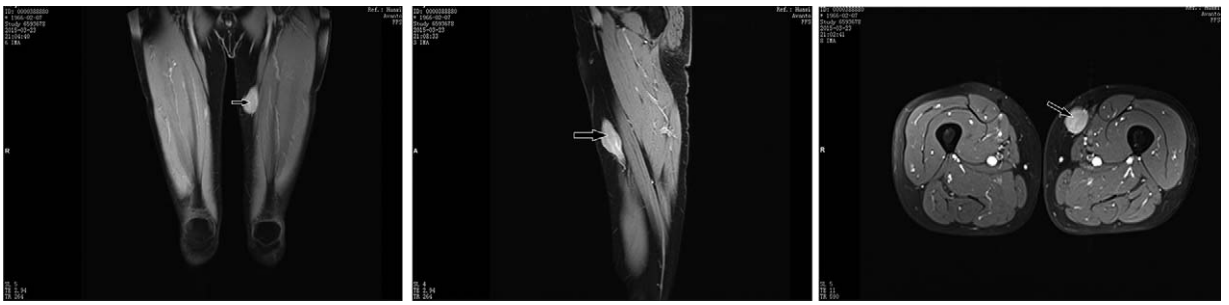

Figure 2. Magnetic resonance imaging revealing an enlarged mass (arrow) of the left thigh.

lymphoid cells that were positive for CD20 and Bcl-2, but negative for CD10, CD30, cyclin D1, Bcl-6, and multiple myeloma oncogene 1. The Ki-67 labeling index was 30.0% to 40.0% (Fig. 5A–I). Gene rearrangements of *IGH* and *IGK* demonstrated a clonal amplification peak. These findings indicated the presence of DLBCL.

In October 2015, lymphadenopathy was palpated in the right anterior region of the neck (diameter, approximately 1.5 cm). A mass of approximately 6.0 cm in diameter was palpated in the lower left region of the umbilicus. Additionally, an oval mass of 5.0 cm in diameter was detected in the left calf. Bone marrow biopsy revealed no invasion of the lymphoma. The patient received 5 courses of chemotherapy with rituximab and lenalidomide. The multifocal lymphadenopathy shrunk rapidly after chemotherapy was administered.

In March 2016, the patient underwent surgical resection for a right popliteal mass that had been detected for >5 months (Fig. 6). An excisional biopsy revealed diffuse infiltration of large lymphoid cells that were positive for CD20 and Bcl-2, but negative for CD3-epsilon, CD5, CD10, CD30, and tumor protein p53. The Ki-67 labeling index was approximately 40.0%. Gene rearrangements of *IGH* and *IGK* demonstrated a clonal amplification peak. Thus, a diagnosis of DLBCL was confirmed. To date, the patient is still alive.

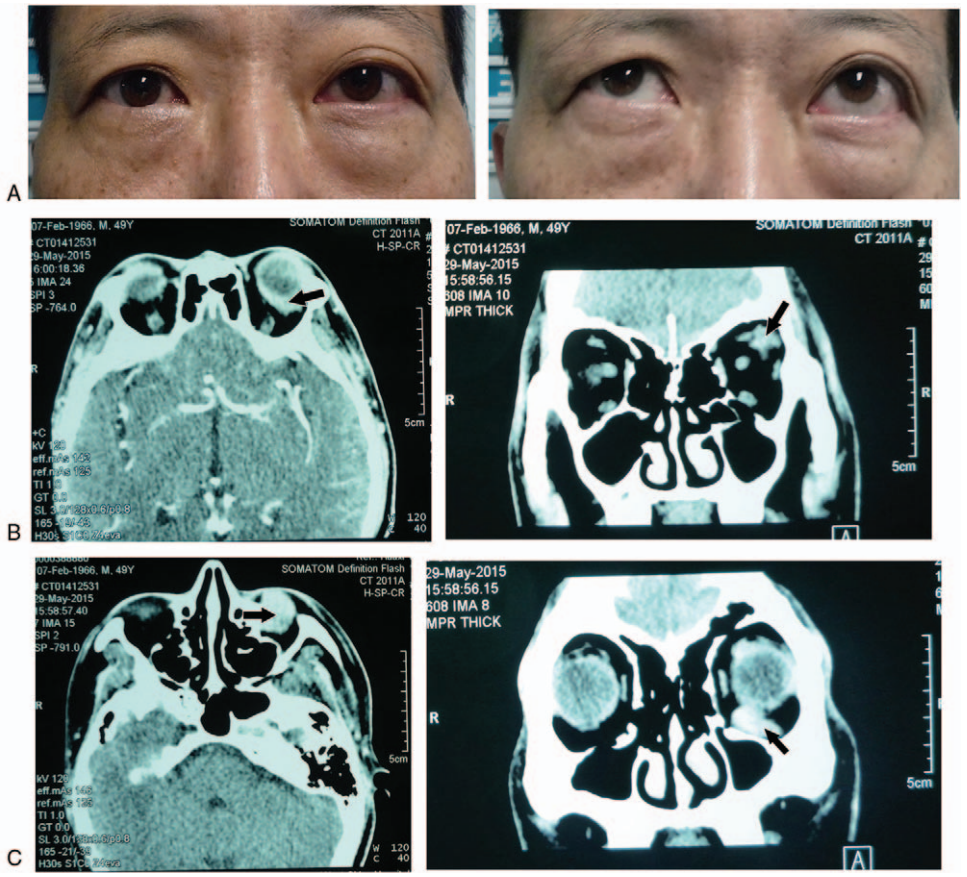

Figure 3. (A) The appearance of the eyes with left orbital tumors. (B and C) Computed tomography scans revealing the location of the orbital tumor (arrows) in the superior orbit (B) and the inferior orbit (C).

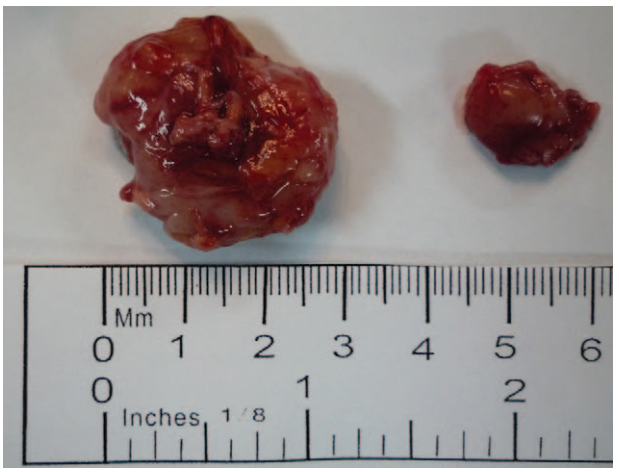

Figure 4. Resection of 2 tumors during surgery, with one larger in the inferior orbit and the other smaller in the superior orbit.

3. Discussion

Sequential development of MALT lymphoma in the right parotid gland, multifocal systemic lymph node DLBCL, MALT lymphoma in the anterior mediastinum, MALT lymphoma in the left thigh, DLBCL in the left orbit, and DLBCL in the right popliteal fossa suggests that the morphological and immunohistochemical phenotypes of the same clonal B-cells may change during long-term follow-up.

MALT lymphomas rarely occur in the parotid gland, trachea, or bronchus. In this patient, however, multifocal regions, including the parotid gland, trachea, bronchus, and thigh, were sequentially involved in MALT lymphoma. Orbital DLBCL is also rare. It is even more rare for orbital DLBCL to be accompanied by the sequential development of systemic MALT lymphoma and DLBCL, as is the case in our patient. Although it has been well documented that DLBCL can be caused by a relapse of MALT lymphoma,[12] our patient presented with alternating MALT lymphoma and DLBCL. To the best of our knowledge, this is the first case of orbital DLBCL to present with MALT lymphoma and DLBCL alternately in multifocal regions.

In our patient, MALT lymphoma of the parotid gland was treated with local irradiation. Systemic lymph node DLBCL was treated with combination chemotherapy (rituximab, cyclophosphamide, epirubicin, vincristine, and prednisone) and autologous hematopoietic stem cell transplantation. MALT lymphoma of the anterior mediastinum was treated with combination chemotherapy (rituximab, cyclophosphamide, epirubicin, vincristine, and prednisone). Relapse of MALT lymphoma of the anterior mediastinum was treated with local irradiation and monotherapy with rituximab. Multifocal lymphadenopathy of the neck, abdomen, and calf was treated with combination chemotherapy with rituximab and lenalidomide. Could there be a relationship between therapeutic approach and the alternate development of MALT lymphoma and DLBCL? Two case studies[13,14] have reported on the sequential development of MALT lymphoma, Hodgkin lymphoma, and DLBCL in patients with similar courses of treatment. It was postulated that standard treatments, such as combination chemotherapy, autologous hematopoietic stem cell transplantation, and irradiation, might be driving factors for these phenotypic changes in neoplastic cells. The correlation between MALT and DLBCL may represent a Richter transformation,[15] wherein a low-grade lymphoma (such as MALT) transforms into an aggressive type (such as DLBCL).

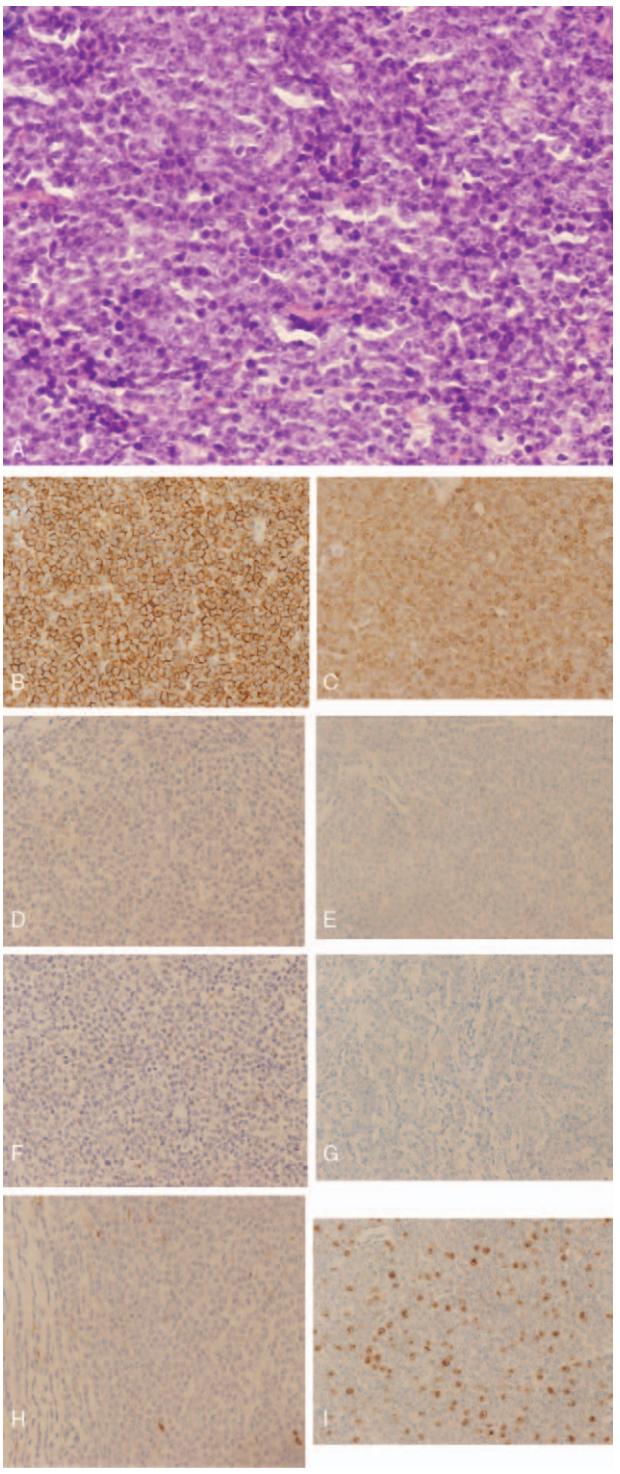

Figure 5. Histopathological and immunohistochemical analysis of the left orbital lesion obtained by excisional biopsy. (A–H) Diffuse infiltration of large lymphoid cells (A) that stained positive for cluster of differentiation (CD) 20 (B) and B-cell lymphoma 2 (C), but stained negative for CD30 (D), CD10 (E), B-cell lymphoma 6 (F), multiple myeloma oncogene 1 (G), and cyclin D1 (H). (I) The Ki-67 labeling index was 30.0% to 40.0%.

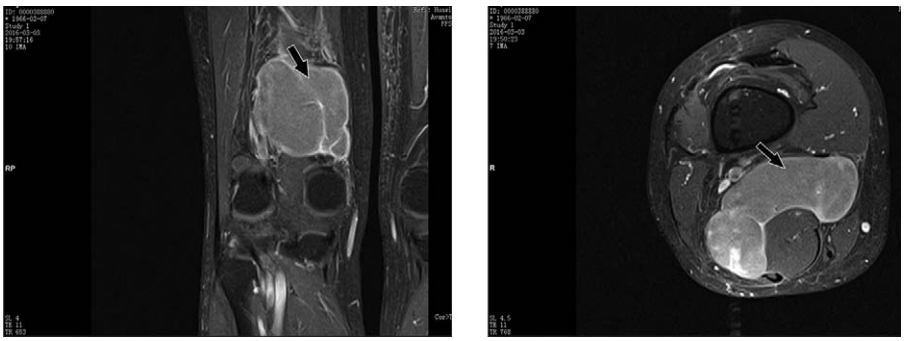

Figure 6. Magnetic resonance imaging revealing a mass (arrow) in the right popliteal fossa.

4. Conclusions

In conclusion, we present a rare case of sequentially diagnosed MALT lymphoma of the parotid gland, DLBCL of lymph nodes of various regions of the body, MALT lymphoma of the bronchus, MALT lymphoma of the trachea, MALT lymphoma of the left thigh, DLBCL of the left orbit, and DLBCL of the right popliteal fossa. The patient remains alive and is still being followed-up. Physicians should pay particular attention to the long-term development of other types of NHL after achieving complete remission of one type of NHL.

Author contributions

Conceptualization: Xubo Yang.
Methodology: Xubo Yang, Weimin He.
Resources: Xubo Yang.
Writing – original draft: Xubo Yang.
Writing – review & editing: Xubo Yang, Weimin He.
Data curation: Xiaoxue Min.
Supervision: Weimin He.

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