

Case Report

Safe and effective induction therapy with CHASER for primary testicular lymphoma with central nervous system involvement

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Abstract: Primary testicular lymphoma (PTL) is a rare, aggressive form of non-Hodgkin's lymphoma (NHL) with a poor prognosis. The standard treatment strategy for cases of PTL with advanced stage at diagnosis, especially those with central nervous system (CNS) involvement, remains to be established. Here, we report the case of a 63-year-old Japanese man who developed PTL with CNS involvement, and was safely and effectively treated with CHASER (cyclophosphamide, high-dose cytarabine, dexamethasone, etoposide, and rituximab). CHASER led to the improvement of the neurological symptoms, and no signs of lymphoma were detected by fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT), including in the cerebrospinal fluid. In addition, peripheral blood stem cell harvest was successfully completed after four courses of CHASER. The present case suggests the possibility of CHASER as a safe and effective induction therapy for advanced NHL with CNS involvement at diagnosis.

Keywords: Primary testicular lymphoma, CHASER therapy, non-hodgkin's lymphoma, diffuse large b-cell lymphoma, central nerve system involvement

Introduction

Primary testicular lymphoma (PTL) comprises 1-2% of non-Hodgkin's lymphoma (NHL) cases, and generally has a poor prognosis. The treatment outcome of localized PTL has recently improved due to the use of at least 6 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) every 21 days, with central nervous system (CNS) prophylaxis and radiotherapy to the contralateral testis [1]. However, there is no standard treatment strategy for cases of PTL in the advanced stage at diagnosis, particularly for those with CNS involvement. In general, NHL patients with CNS involvement are aggressively treated, according to a previous study showing that approximately half of these cases experience CNS relapse [2]. Aggressive treatment includes both intra-cerebrospinal fluid (CSF) and systemic chemotherapy with drugs able to penetrate the blood-brain barrier (BBB) to achieve a therapeutic drug concentration in all CNS com-

partments [3]. A previous report demonstrated that diffuse large B-cell lymphoma (DLBCL) patients with CSF infiltration who received CNS-specific treatment had no relapse in or out of the CNS [4]. Although this approach has been proposed for treatment of NHL patients with CNS involvement, it has not been established as a standard induction therapy.

Fujimaki et al. reported a case of lymphomatoid granulomatosis (LYG), a rare subtype of NHL with CNS and lung involvement, which was successfully treated with cyclophosphamide, high-dose cytarabine, dexamethasone, etoposide, and rituximab (CHASER), followed by whole-brain irradiation [5]. Their case showed the efficacy of CHASER for the treatment of NHL with CNS involvement. Here, we describe a case of PTL with CNS involvement that achieved complete remission with CHASER therapy, suggesting the possibility of CHASER as an induction therapy for advanced NHL with CNS involvement at diagnosis.

Successful induction therapy with CHASER for PTL with CNS involvement

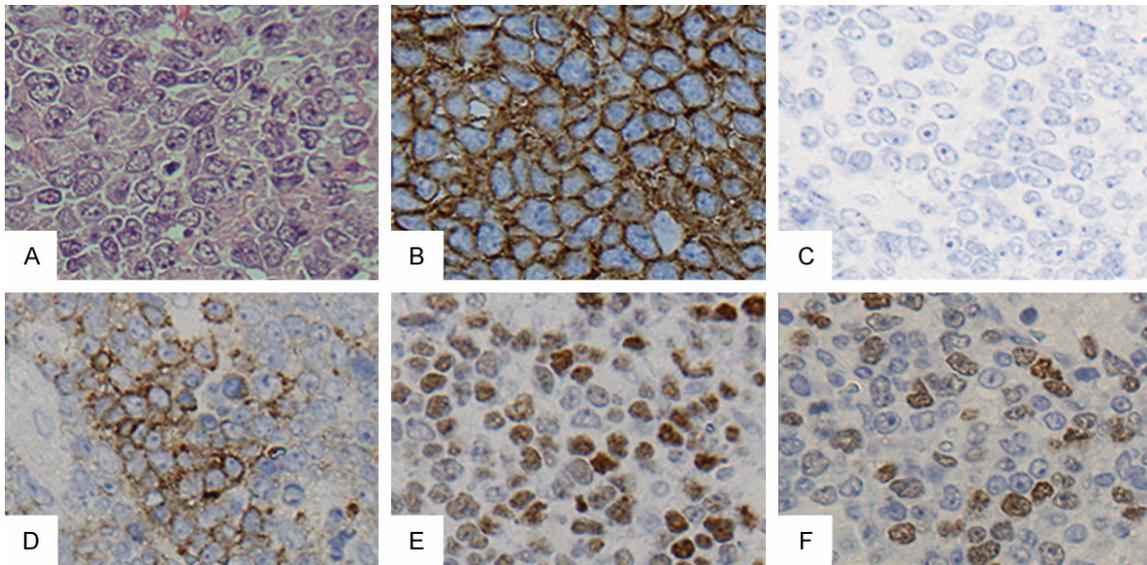


Figure 1. Pathological findings of the right testis (X400). A. HE staining showed diffuse infiltration by large atypical lymphocytes. B. CD20 staining was positive. C. CD5 staining was negative. D. CD10 staining was positive. E. BCL6 staining was positive. F. MUM1 staining was positive.

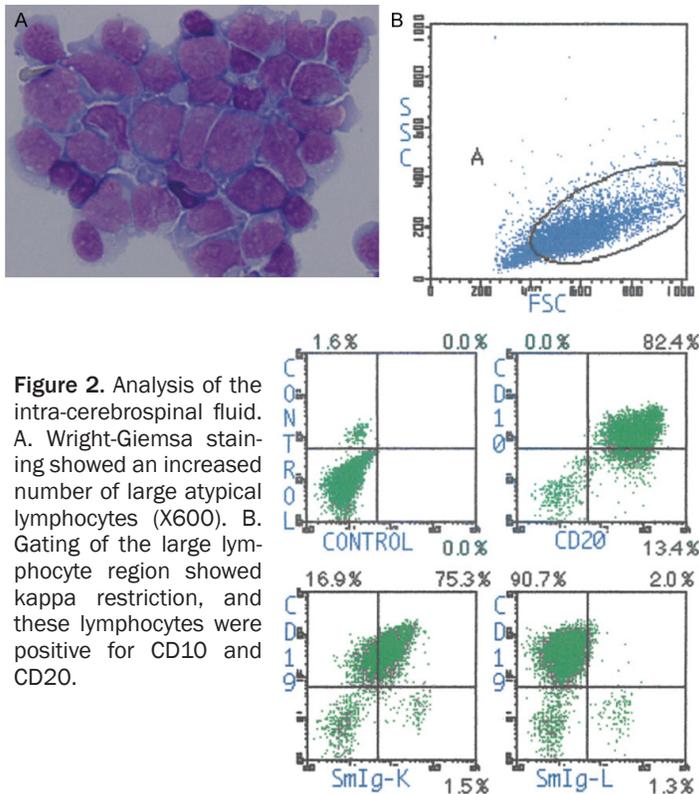


Figure 2. Analysis of the intra-cerebrospinal fluid. A. Wright-Giemsa staining showed an increased number of large atypical lymphocytes (X600). B. Gating of the large lymphocyte region showed kappa restriction, and these lymphocytes were positive for CD10 and CD20.

Case report

A 63-year-old Japanese man was admitted to our hospital exhibiting lower extremity sensory

disturbance and gait disorder. After admission, his neurological symptoms steadily worsened with right hemiparesis, right facial palsy, diplopia, and dysarthria. At the same time, right scrotal enlargement was observed, and a total right orchiectomy was immediately performed. Histopathology of the right testis revealed diffuse infiltration by large atypical lymphocytes that were positive for CD10, CD19, CD20, BCL2, BCL6, and MUM1, and negative for CD5, CyclinD1, TdT, and EBER. The Ki-67 labeling index was approximately 90%, and c-myc-positive cells were approximately 60% by immunohistochemical staining (**Figure 1**). Chromosome analysis revealed a complex karyotype, and southern blot analysis showed rearrangement of the immunoglobulin gene (IgHJH). Cytological evaluation of the CSF revealed an increased number of atypical lymphocytes that were positive for CD10, CD20, and kappa chain (**Figure 2**). Bone marrow examination showed no evidence of infiltration. Fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT)

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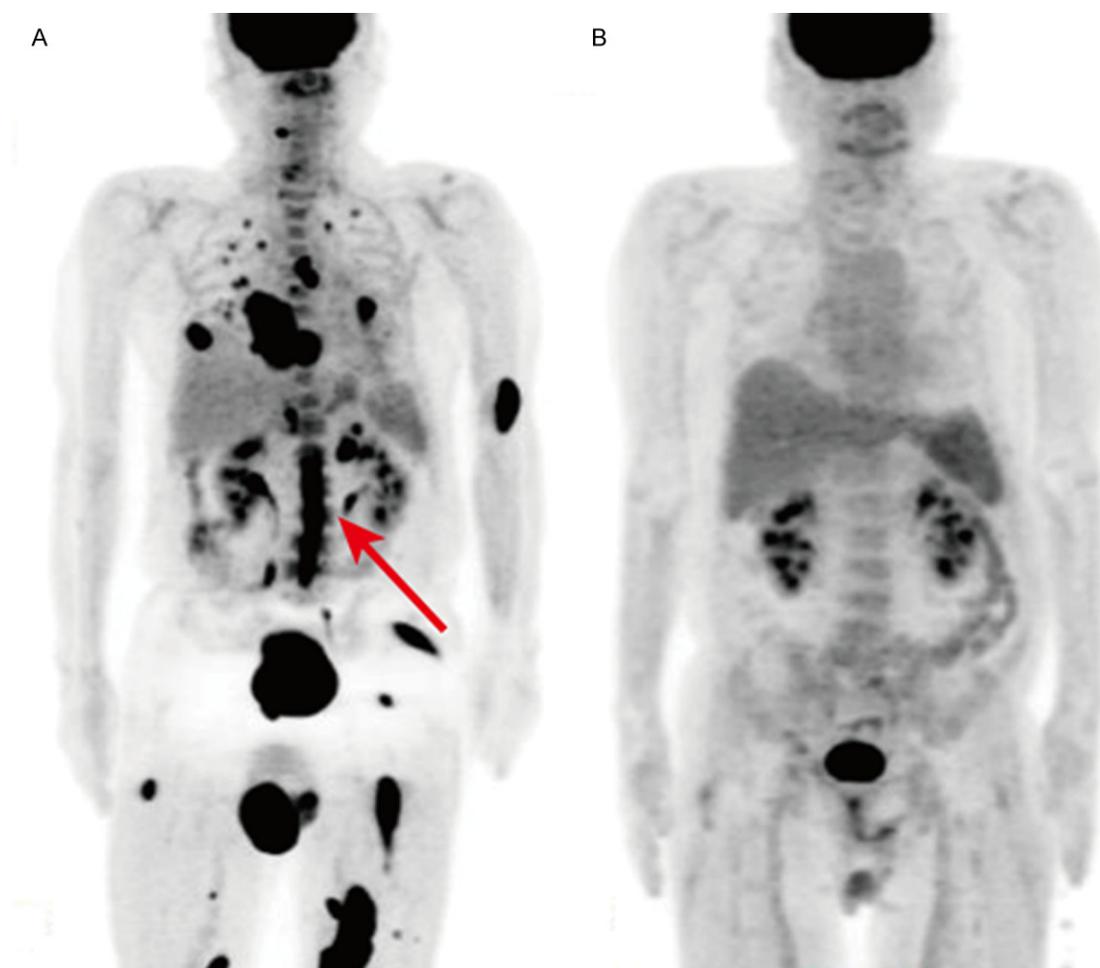


Figure 3. Whole-body FDG-PET/CT at diagnosis and after two courses of CHASER. A. Systemic FDG uptake, including the right testis (SUVmax=34.1), lumbar cord and cauda equina (SUVmax=18.3), lung tumor (SUVmax=31.2), heart (SUVmax=34.1), left adrenal gland (SUVmax=12.3), bilateral femur (SUVmax=37.3), buttocks (SUVmax=25.8), and sublingual, mediastinal, and hilar lymph nodes (SUVmax=29.9) was observed at diagnosis. Red arrow indicates lymphoma cell involvement in the CNS. B. FDG-PET/CT after two courses of CHASER did not detect any systemic uptake, indicating complete response.

revealed systemic uptake, including in the right testis, lumbar cord, and cauda equina (**Figure 3A**). With these findings, the patient was diagnosed with advanced primary testicular DLBCL with CNS involvement. Steroid pulse therapy with methylprednisolone was followed by CHASER therapy, and intrathecal (IT) chemotherapy with cytarabine and dexamethasone was administered. His neurological symptoms markedly improved, and FDG-PET/CT after two courses of CHASER did not detect systemic FDG uptake (**Figure 3B**). After an additional two courses of CHASER, lymphoma cells in the CSF had completely disappeared, equivalent to a complete response. Moreover, peripheral blood stem cell harvest was successfully completed

with a CD34-positive cell count of 2.3×10^6 /kg body weight after the fourth course of CHASER. Before undergoing autologous stem cell transplantation (SCT), high-dose intravenous methotrexate (HD-MTX) was administered for CNS relapse prophylaxis. However, abducens paralysis was observed on day 21, despite brain magnetic resonance imaging (MRI) and CSF evaluation showing no evidence of lymphoma recurrence. Shortly after, left hemiparesis, tongue deviation, and facial palsy were also observed. FDG-PET/CT revealed systemic FDG uptake, indicating early recurrence. Despite immediate initiation of salvage therapy, the neurological symptoms gradually worsened, and the patient died 9 months after diagnosis.

Discussion

This case report highlights the effectiveness and feasibility of CHASER as an induction therapy for advanced PTL with CNS involvement. Although CHASER has been widely used as a salvage therapy for relapsed and refractory B-cell NHL [6], there has been only one case report indicating the efficacy of CHASER for treatment of an LYG patient with CNS involvement [5]. The present patient completed four courses of CHASER without any adverse effects. As we had initially planned to perform autologous SCT, stem cells were collected after four courses of CHASER, and stem cell harvest was successfully completed with sufficient CD34-positive cells.

PTL with CNS involvement is associated with a poor prognosis due to the hindrance of CNS exposure to the majority of chemotherapeutic agents by the BBB. In addition, advanced PTL patients, particularly those with CNS involvement, often show early recurrence. CHASER was selected for the present case because of its high dosage of cytarabine, which has a high degree of penetration into the CNS, and its prolonged half-life in the CSF [7]. Moreover, etoposide and the high dosage of cyclophosphamide may be effective for systemic NHL lesions. HD-MTX has been shown to be able to penetrate the BBB; however, its efficacy for treatment of systemic disease was shown to be limited and insufficient [8]. In NHL patients with a high tumor burden, an HD-MTX-containing chemotherapeutic regimen may cause tumor lysis syndrome, contributing to critical renal damage and delayed MTX elimination. Therefore, to avoid these risks, intensive chemotherapy including high-dose cytarabine without MTX was used for induction therapy in the present case.

In conclusion, this case suggests that CHASER may be used as an induction therapy for not only PTL with CNS involvement, but also for other subtypes of B-NHL with CNS involvement. However, development of early recurrence after four courses of CHASER therapy should be noted as a limitation in the present case. Adding cytarabine to HD-MTX for CNS relapse prophylaxis [9], or immediately performing autologous SCT may prevent such early relapse and prolong progression-free survival [10]. Further accumulation of cases and investigation by large-scale multicenter clinical trials are warranted to assess the feasibility and effective-

ness of CHASER for first line treatment of advanced NHL with CNS involvement.

Disclosure of conflict of interest

None.

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