Lymphomatoid Granulomatosis with Central Nervous System Involvement Successfully Treated with Cyclophosphamide, High-dose Cytarabine, Dexamethasone, Etoposide, and Rituximab (CHASER therapy) Followed by Brain Irradiation: A Case Study

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Lymphomatoid granulomatosis (LYG) is a rare subtype of diffuse large B-cell lymphoma. It is an extranodal angiocentric and angi-destructive lymphoproliferative disease involving the lungs, skin, and central nervous system (CNS), including abundant reactive T cells with varying numbers of atypical clonal Epstein-Barr virus (EBV)-infected B cells [1]. Clinical diagnosis of LYG is difficult because of a lack of characteristic manifestations, suitable laboratory tests, and imaging findings. No optimal treatment for LYG has yet been established, especially in cases involving the CNS. Several previous reports of rituximab monotherapy, rituximab-containing chemotherapy, interferon alpha-2b, or hematopoietic stem cell transplantation have been published [2], as well as a report of cyclophosphamide (CPM), high-dose cytarabine, dexamethasone, etoposide, and rituximab (CHASER therapy) for lung lesions of LYG [3]. Spontaneous remission has also been reported in patients with LYG involving the CNS and lungs [4]. Here, we describe a case of LYG with lung onset responsive to corticosteroid treatment, but with subsequent CNS involvement resistant to corticosteroid and rituximab monotherapy, which was successfully treated with CHASER therapy followed by brain irradiation. We also propose the value of repetitive evaluation of specimens and gradient-echo T2*-weighted magnetic resonance imaging (T2*-MRI) for diagnosis of CNS involvement in LYG (CNS-LYG).

A healthy 40-year-old woman presented with persistent fever, cough, and dyspnea 2 years before admission to our

hospital. Thoracic computed tomography (CT) performed at a local hospital revealed diffuse ground-glass opacity with nodular lesions in both lungs (Figure 1A). Blood examination showed highly elevated soluble interleukin-2 receptor (11,726 U/ml), and slightly elevated aspartate aminotransferase (86 IU/L) and alanine transaminase (131 IU/L). EBV antiviral capsid antigen (VCA) IgG and Epstein-Barr nuclear antigen (EBNA) were positive, and EBV anti-VCA IgM was negative, indicating past EBV infection. Pathological diagnosis was performed using video-assisted thoracic surgery (VATS), revealing atypical large lymphoid cells infiltrating the regions around the blood vessels (Figure 2A). These infiltrating lymphocytes comprised a large number of CD3-positive T cells and a few large CD20-positive B cells (Figure 2B). However, the lymphocytes were negative for EBV-encoded small RNA (EBER) according to *in situ* hybridization. Although LYG was suspected from the results, a definitive diagnosis was not made at the time. Prednisolone (50 mg/day; 1 mg/kg/day) was administered orally. The patient's fever and respiratory symptoms disappeared and thoracic CT revealed disappearance of the bilateral nodular lesions (Figure 1B). However, 1 month after initiation of steroid therapy, prednisolone was tapered to 30 mg/day and she developed neurological deficits, including left facial dysesthesia, dysarthria, and gait disturbance due to left dominant spastic paraplegia, limb ataxia, and sensory disturbance. CPM (100 mg/day) was added and prednisolone was repeatedly increased or decreased from 50 to 2.5 mg/day, with no improvement. The patient was therefore

Figure 1 Computed tomography (CT) of the lung and magnetic resonance imaging (MRI) of the head. **(A)** Numerous nodular high-density lesions and ground-glass opacity were observed in bilateral lungs before the administration of prednisolone. **(B)** Nodular lesions disappeared after steroid therapy. **(C)** Fluid-attenuated inversion recovery (FLAIR) image revealed high-intensity lesions in the pons, middle cerebellar peduncle, splenium of the corpus callosum, and left corona radiata. **(D)** Gadolinium-enhanced T1-weighted MRI showed enhancement in the pons and cerebellar peduncle. **(E)** Gradient-echo T2*-weighted MRI showed low-intensity lesions in the pons. **(F)** After CHASER therapy, high-intensity lesions in the pons, middle cerebellar peduncle, splenium of the corpus callosum, and left corona radiata were reduced on FLAIR image.

Figure 2 Histopathological examination of lung specimen. **(A)** Hematoxylin and eosin staining showed lymphocytes infiltrating around the small pulmonary vessels at the initial evaluation (original magnification $\times 100$). **(B)** Large CD20-positive B cells were detected by immunostaining for CD20 at the initial evaluation (original magnification $\times 200$). **(C)** A few large B cells were detected as positive for EBER by *in situ* hybridization at the second evaluation (original magnification $\times 400$).

referred to our hospital. Her general laboratory examinations were normal. Anti-VCA IgG and EBNA were positive, and anti-early antigen diffuse type and restricted type IgG and EBV-DNA were negative, confirming past EBV infection. Cerebrospinal fluid revealed elevated protein concentration (113 mg/dL) with normal glucose and cell counts. Oligoclonal IgG bands were absent. Brain MRI revealed T2-hyperintense areas at the pons, middle and superior cerebellar peduncles, splenium of the corpus callosum, and left corona radiata (Figure 1C), with punctate and linear gadolinium enhancement at the pons (Figure 1D). Furthermore, T2*-MRI showed hypointensity in these enhanced areas, indicating microbleeds (Figure 1E). Thoracic CT showed no relapse. The patient received pulse steroid therapy, subsequent oral prednisolone (50 mg/day; 1 mg/kg/day), and continuation of CPM, with only slight improvement in the above-mentioned neurological deficits and no improvement in brain

MRI findings, although no new symptoms appeared. We performed EBER *in situ* hybridization using the same specimens previously obtained by VATS. A few large B cells were positive for EBER in this second evaluation, confirming a diagnosis of grade 1 LYG, at 21 months after the first suspected diagnosis of LYG (Figure 2C). We administered rituximab monotherapy (375 mg/m², once weekly for 1 month), again with only slight neurological improvement and no improvement in brain MRI findings. We therefore discontinued oral prednisolone for the first time as its initiation at 22 months after the first suspected diagnosis of LYG. Two cycles of CHASER therapy were administered, with considerable reductions in the size of the brain lesions on MRI (Figure 1F). All CHASER drugs were administered at their full doses for the first cycle, but were reduced to 75% doses for the second cycle because of detection of serum *Aspergillus* antigen and cytomegalovirus DNA. Subsequent focal

and whole-brain radiation therapy (46 Gy total) was initiated for the remaining brainstem lesions, eventually leading to complete remission. Accordingly, neurological findings including dysarthria, limb ataxia, and sensory disturbance were improved, although she was unable to walk without assistance because of disuse muscle weakness. The patient remained in remission for 12 months.

This case report highlights several interesting points with regard to the treatment, definitive diagnosis, and MRI findings of LYG. First, we demonstrated the successful long-term treatment of CNS-LYG with CHASER therapy followed by brain irradiation. Although one previously reported case achieved spontaneous remission [4], CNS-LYG has generally been treated by corticosteroids, rituximab, CPM, adriamycin, vincristine, and prednisolone (CHOP therapy), and radiation [2,5]. However, corticosteroids, CPM, and rituximab monotherapy were not fully effective in the current case. Although CHASER therapy, which is relatively less toxic, has previously only been reported for LYG of the lungs without CNS involvement [3], we selected it for the following reasons: (1) high-dose cytarabine is likely to cross the blood–brain barrier and is used as a standard therapy for lymphoma of the CNS; (2) etoposide has been reported to be effective in EBV-associated lymphoproliferative disorders [6]; and (3) CPM dosage actually increases. Although we initially planned four cycles of CHASER therapy, only two were actually administered to reduce the risk of severe infections. However, even two cycles of CHASER therapy significantly ameliorated the patient's neurological symptoms and radiological lesions. We also administered radiation therapy as consolidation therapy. Several cases of CNS-LYG treated with chemotherapy and/or steroid therapy followed by radiation therapy have been reported [5,7], including one case of CNS-LYG with lung onset in which radiation therapy was effective after failure of immunosuppressive therapy [7]. These results indicate that radiation therapy following CHASER therapy may be beneficial, and we therefore suggest that patients with long-standing CNS-LYG could achieve a better prognosis with CHASER therapy followed by brain irradiation.

Notably, although the EBER results were initially negative, they were positive at a subsequent evaluation. This may be because LYG activity was low, and only a few cells were positive for EBER

when VATS was performed. Although there have been several reports of patients diagnosed after repetitive biopsies [8], we propose that the same specimens should be re-evaluated before performing additional biopsies in patients with suspected LYG.

This case highlights the value of T2*-MRI for the diagnosis of LYG and its differentiation from other similar diseases. Our case demonstrated two characteristic MRI findings: punctate and linear gadolinium enhancements, and hypointensity of T2*-MRI indicating microbleeds. Multiple punctate and linear enhancements in LYG have been reported to indicate abnormal perivascular tissues and walls of small vessels [9]. However, similarly enhanced lesions can be seen in diseases other than LYG–CNS, such as chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS), lymphoma, primary angitis of the CNS, and sarcoidosis [9,10]. The gadolinium enhancement pattern is thus not sufficient to differentiate CNS-LYG from other diseases. However, LYG may tend to cause microbleeds more frequently than these above-mentioned diseases because it shows pathological characteristics of angiocentric and angi destructive progression. T2*-MRI may thus represent a useful modality for the differential diagnosis of CNS-LYG.

To the best of our knowledge, this case provides the first evidence for the efficacy of CHASER therapy followed by brain irradiation in a patient with CNS-LYG. We therefore conclude that it is appropriate to consider CHASER therapy for treatment-resistant CNS-LYG, that the same specimens should be re-evaluated before performing additional biopsies, and that T2*-MRI has the potential to distinguish LYG from other diseases because of its ability to detect microhemorrhages.

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Conflict of interest

The authors declare no conflict of interest.

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