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【 CASE REPORT 】

High-grade Primary Central Nervous System Lymphomatoid Granulomatosis: Successful Rituximab Monotherapy

Sakiko Harada[1], Jun Ando[1,2], Miki Ando[1], Hideaki Nitta[1], Tadaaki Inano[1], Yusuke Hirasawa[3], Yoshiki Furukawa[1], Shintaro Kinoshita[1], Akihide Kondo[4], Koichi Ohshima[5] and Norio Komatsu[1]

Abstract:
The primary central nervous system (CNS) presentation of lymphomatoid granulomatosis (LYG) is rare, and no standard therapy for LYG with primary CNS symptoms exists. CNS-LYG patients usually survive for only less than a year from diagnosis. This is the first report of high-grade primary CNS-LYG with monoclonality that was successfully treated with rituximab monotherapy, resulting in a durable remission for more than 1 year in a 66-year-old woman with pemphigus vulgaris who was also on immunosuppressive therapy.

Key words: central nervous system, high-grade lymphomatoid granulomatosis, pemphigus vulgaris, rituximab

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Introduction

Lymphomatoid granulomatosis (LYG) is a rare Epstein-Barr virus (EBV)-driven B-cell lymphoproliferative disease, which is angiocentric and angiodestructive involving extranodal sites [skin, lung, liver, kidney, central nervous system (CNS)] (1, 2). Although CNS involvement is seen in around one-third of all LYG patients, the initial presentation of LYG with primary CNS symptoms (primary CNS-LYG) is very rare (3, 4). However, since randomized treatment trials have not been conducted in primary CNS-LYG due to its scarcity - although it admittedly may be under-diagnosed owing to reluctance to conduct brain biopsies - no therapy for this form of LYG has yet been established (3, 5, 6).

Case Report

A 66-year-old woman was diagnosed with pemphigus vulgaris in May 2001. Initial treatment with corticosteroids and mycophenolate mofetil (MMF) was ineffective, and azathioprine, cyclosporine, and cyclophosphamide were sequentially substituted. None was fully effective. In April 2010, despite undergoing plasma exchange and prednisolone, the disease worsened, with buccal mucosal ulceration. In August 2010, supplemental intravenous immunoglobulin (IVIG) was initiated. Thereafter pemphigus vulgaris was controlled with prednisolone 20 mg/day, MMF 1,500 mg/day, and biweekly plasma exchange with IVIG 15 g/day for 4 days. Cytomegalovirus esophagitis was diagnosed in June 2018 and was satisfactorily controlled with ganciclovir 5 mg/kg twice a day for 2 weeks.

In September 2019, involuntary movements of both lower limbs and left lower limb pain while sleeping appeared. Physical examination revealed no new skin changes, no lymphoadenopathy, and no hepatosplenomegaly. Tendon reflexes could not be elicited in the lower limbs. Slight iliopsoas weakness was noted. Although her hemogram values were unremarkable (WBC 3,400/μL, RBC 350×10^4/μL, Hb 12.0 g/dL), the lymphocyte number clearly decreased to 210/μL.

[1]Department of Hematology, Juntendo University School of Medicine, Japan, [2]Department of Transfusion Medicine and Stem Cell Regulation, Juntendo University School of Medicine, Japan, [3]Department of Dermatology, Juntendo University School of Medicine, Japan, [4]Department of Neurosurgery, Juntendo University School of Medicine, Japan and [5]Department of Pathology, School of Medicine, Kurume University, Japan
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Correspondence to Dr. Miki Ando, m-ando@juntendo.ac.jp

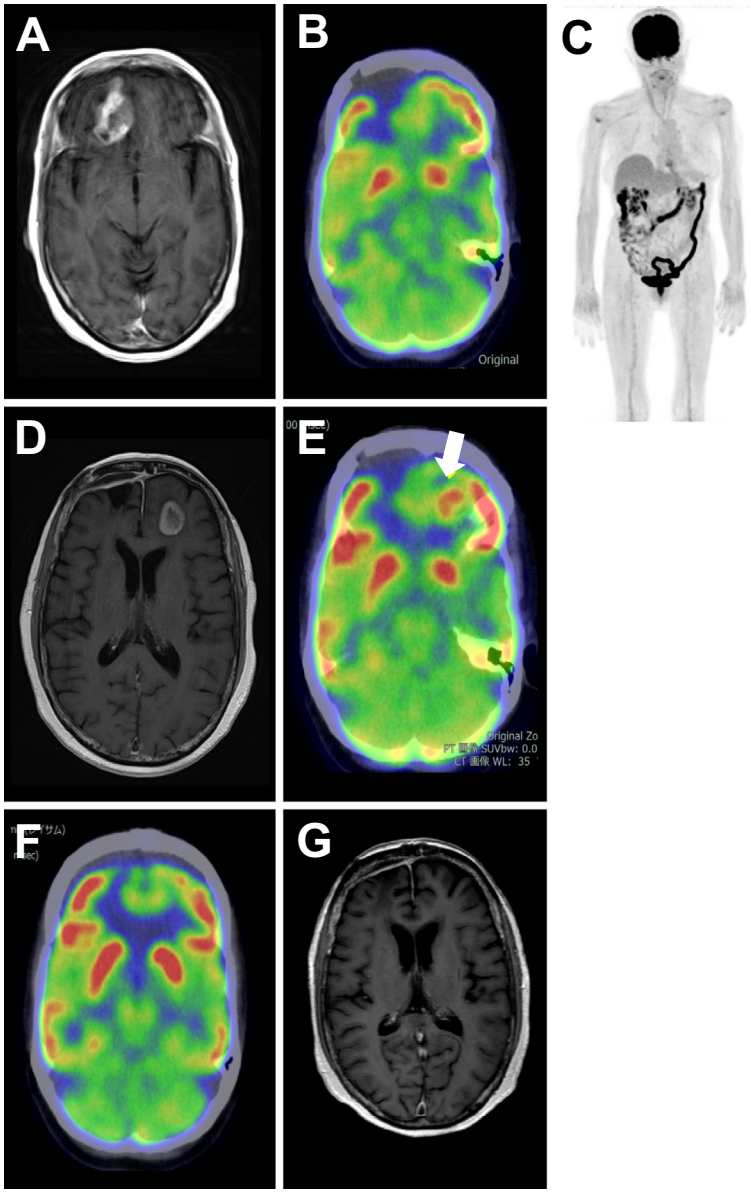

Figure 1. **Changes over time on magnetic resonance imaging (MRI) and positron emission tomography-computed tomography (PET-CT). (A) Hyperintense lesion, right frontal lobe, on presentation for evaluation of involuntary, painful lower-limb movement (MRI, gadolinium-enhanced T1 weighted image). (B, C) No abnormal accumulation of fluorodeoxyglucose (FDG) after surgical excision of the lesion (PET-CT). (D) New hyperintense lesion, left frontal lobe, 3 months after (A) and surgical excision (MRI, gadolinium-enhanced T1 weighted image). (E) Abnormal accumulation of FDG, left frontal lobe, 3 months after (A) and surgical excision (PET-CT). (F) No abnormal accumulation of fluorodeoxyglucose 2 months after (E) (PET-CT). (G) No lesion is observed 15 months after (A) (MRI, gadolinium-enhanced T1 weighted image).**

The lactate dehydrogenase activity in the patient's serum (255 U/L) increased (expected 124-222 U/L), the C-reactive protein value (0.20 mg/dL) was normal (<0.29 mg/dL), and the soluble interleukin-2 receptor value (235 IU/mL) was normal (157-474 IU/mL). A chemiluminescent enzyme immunoassay showed no evidence of human immunodeficiency virus (HIV)-1 and -2 infections. EBV infection was identified, with viral capsid antigen (VCA) IgG X320, VCA IgM <X10, and EBV nuclear antigen X20. A quantitative polymerase chain reaction assessment of whole-blood EBV DNA found 2.3×10^3 copies/μg. No abnormalities were found on urinalysis. Chest roentgenograms did not show any abnormality.

Brain magnetic resonance imaging (MRI) revealed a mass lesion in her right frontal lobe in gadolinium-enhanced T1 weighted image (Fig. 1A). To make a precise diagnosis and control brain edema, neurosurgeons removed the mass completely. After surgery, her neurological disorders completely disappeared and no abnormal accumulations of fluorodeoxyglucose (FDG) were found on positron emission

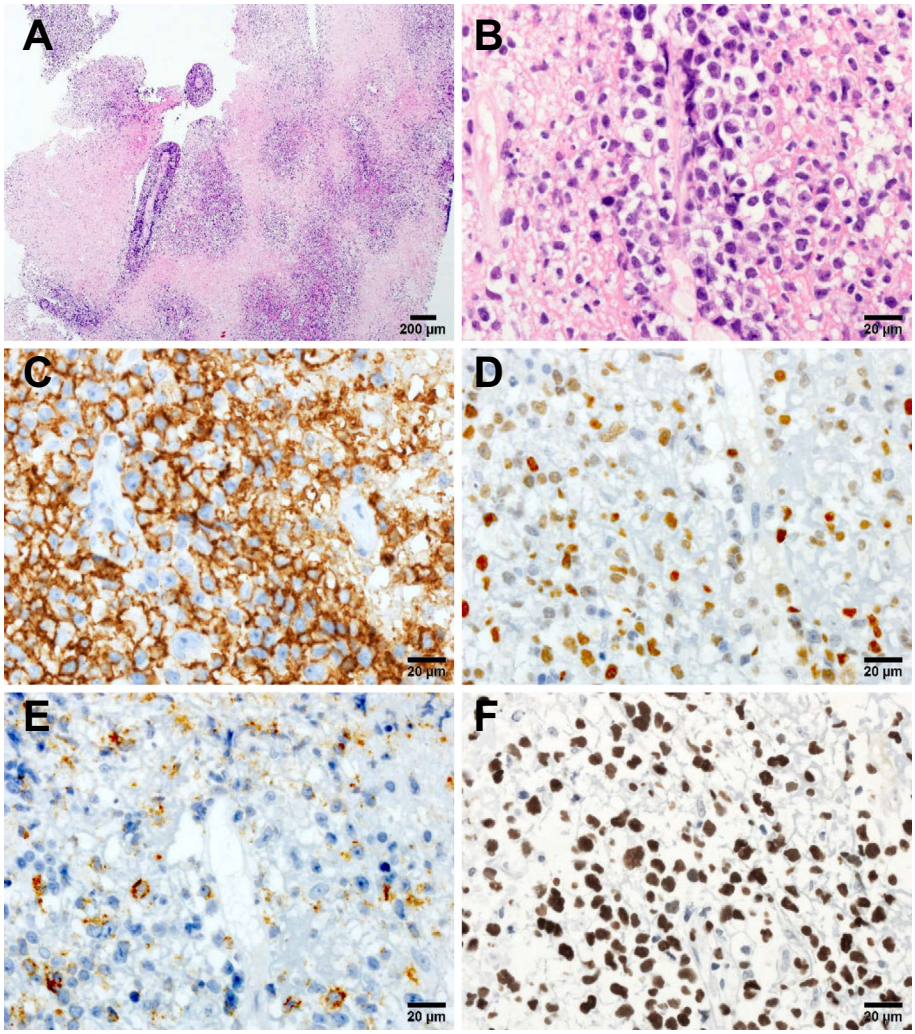

Figure 2. Photomicrographs, histopathologic preparations of a brain right frontal lobe tumor-resection specimen. (A) Infiltration by large to medium-sized abnormal lymphoid cells with angiocentric distribution [Hematoxylin and Eosin (H&E) staining, original magnification (×) 40]. Scale bar, 200μm. (B). As above (H&E staining, ×400). Scale bar, 20μm. Immunohistochemical (C-E) and *in situ* hybridization studies (F), all ×600 with hematoxylin counterstain and diaminobenzidine chromogen: Tumor cells express the B-cell marker CD20 (C), EBV nuclear antigen-2 (D), and Epstein-Barr virus (EBV) latent membrane protein 1 (E). EBV-encoded small RNA *in situ* hybridization detects EBV sequences in >50 cells per high-power field (F). All 4 scale bars, 20μm.

tomography-computed tomography (PET-CT) (Fig. 1B, C).

A neuropathologic examination found vascular-invasive infiltration by large to medium-sized atypical lymphocytes (Fig. 2A, B) that expressed the B-cell marker CD20 (Fig. 2C) as well as EBV nuclear antigen-2 (Fig. 2D) and EBV latent membrane protein 1 (Fig. 2E), exhibiting a type III latency pattern. T cell infiltration was not prominent. EBV-encoded small RNA (EBER) sequences were demonstrable by *in situ* hybridization, with >50 EBER-positive cells per high-power field (Fig. 2F). A southern blot analysis revealed clonality of immunoglobulin heavy chain (IgH) gene rearrangement and no clonality of T cell receptor. High-grade LYG (grade 3, World Health Organization 2016) was diagnosed, which was thought to have arisen as EBV-associated lymphoproliferative disease, with EBV reactivation caused by the long-term usage of immunosuppressants. MMF was discontinued and prednisolone was gradually reduced from October 2019. No other sites except for CNS were involved by LYG.

CNS-LYG recurrence was identified 3 months later (January, 2020) with a high-intensity lesion observed contralaterally on brain MRI (Fig. 1D). An abnormal accumulation of FDG was observed on PET-CT only in the left frontal lobe (Fig. 1E). We diagnosed the recurrence of LYG in the CNS. Patient fragility precluded the administration of combination immunochemotherapy such as DA-EPOCH-R (dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, and rituximab) or R-CHOP (cyclophosphamide, doxorubicin, vincristine and rituximab) (3); thus IV rituximab 375 mg/m^2 every 7 days was initiated. In March 2020, after 4 rituximab treatments, FDG accumulation abnormalities were no longer found on PET-CT (Fig. 1F). Remission

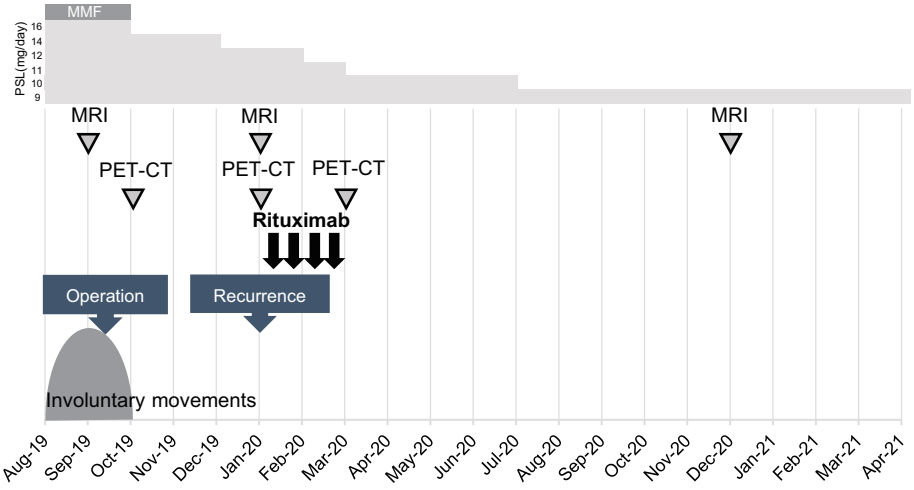

Figure 3. Clinical course. An overview of the symptoms, treatments and time points of magnetic resonance imaging (MRI) and positron emission tomography-computed tomography (PET-CT). MMF: mycophenolate mofetil, PSL: prednisolone

was diagnosed. Remission has continued for >12 months since the start of rituximab treatment, as established by brain MRI in December 2020 (Fig. 1G). The whole-blood EBV DNA copy number declined during therapy, then completely vanished after rituximab treatment. Involuntary movements of legs disappeared after surgery. At present (March 2021), she is clinically doing well (Fig. 3). Her primary skin disorder also has improved.

Discussion

Immunocompromise (iatrogenic, HIV-infection related, reflecting congenital immune deficiency, e.g.) makes it possible for the reactivation of EBV and the development of LYG (3, 4, 7). In our patient, HIV infection was not relevant and no repeated infection from childhood was observed, thus making congenital immune deficiency unlikely. We ascribe her immunocompromised status, manifested initially in chronic cytomegalovirus esophagitis and resulting in LYG, to the long-term use of immunosuppressants for pemphigus vulgaris.

In general, the prognosis of LYG is considered to be poor, with a median overall survival of only 14 months (4). B cell lymphoma develops in almost 13% of LYG patients (5, 6). Prospective studies have established treatment protocols for LYG that require histopathologic grading, which is based on the number and density of large atypical EBV-positive B cells. The discontinuation of immunosuppressants, corticosteroids, or interferon-alpha is recommended for Grade 1 or 2 LYG, while immunochemotherapy is chosen for Grade 3 LYG because it is often monoclonal and should be treated as EBV-associated lymphoma (3, 8-10). Rituximab has recently been used to treat LYG; in a retrospective study of 11 LYG patients treated with rituximab-based therapies, mainly R-CHOP, approximately two-thirds of patients responded. The median overall survival was ~1 y (3, 11).

Although systemic LYG with CNS involvement has a poor prognosis, with a mortality rate ranging from 65% to 90% at 14 months (5, 6), rituximab was also reported to be to some extent effective (8, 12, 13). However, to the best of our knowledge, this is the first report of high-grade primary CNS-LYG with IgH monoclonality that was successfully treated with rituximab monotherapy, resulting in a durable remission for >12 months. Furthermore, our patient has survived for 17 months from diagnosis, whereas primary CNS-LYG patients usually survive only for <1 year from diagnosis (7). A case whereby rituximab and temozolomide immunochemotherapy was initiated on high-grade primary CNS-LYG with pulmonary involvement, the tumor progressed and the patient is reported to have died 2 months after the initial presentation (14). In our case, the fact that the tumor lesion was confined to the CNS, along with the discontinuation of immunosuppressants may have had the positive effect on the rituximab treatment outcome.

Since the ratio of the cerebrospinal fluid concentration to the serum concentration of administered rituximab is only 0.1 to 4.4%, the rituximab molecule is therefore too large to cross the blood-brain barrier (BBB) readily (15). This is of potential concern in rituximab monotherapy for primary CNS-LYG (15, 16). However, recent clinical trials demonstrate that chemotherapy with rituximab is more effective than chemotherapy alone for primary CNS lymphoma (16).

The malignant disease in our patient, treated with rituximab alone, responded well, with remission at this writing for >1 year. We did not measure rituximab in her CSF and can only speculate that angiodestruction in LYG may have allowed rituximab to cross the BBB. This question may warrant attention in rituximab treatment of other patients with LYG and CNS involvement. We note as of possible interest that rituximab is effective for several autoimmune diseases due to the suppression of antibody generation, including pemphigus vulgaris (17), and indeed in our patient rituximab monotherapy was also found to be associated with

the clearance of her primary skin disorder.

In conclusion, primary CNS-LYG may recur even after complete resection. For cases with high-grade LYG with CNS involvement and monoclonality, aggressive rituximab-based chemotherapy is usually recommended. However, we experienced a case of high-grade primary CNS-LYG in which rituximab monotherapy proved to be effective with a successful 1 year remission.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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