Int J Clin Exp Pathol 2014;7(6):3363-3369
www.ijcep.com /ISSN:1936-2625/IJCEP0000367

Case Report

Intravascular large B-cell lymphoma with pontine involvement successfully treated with R-CHOP therapy and intrathecal administration: a case report and review of literature

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Received March 28, 2014; Accepted May 25, 2014; Epub May 15, 2014; Published June 1, 2014

Abstract: A 46-year-old man developed a fever and cough, and computed tomography showed multiple, nodular infiltrative shadows in lungs. He was diagnosed as having intravascular large B-cell lymphoma (IVLBCL). Brain magnetic resonance imaging (MRI, T2W1) showed an abnormal signal area in the pons, which was IVLBCL involvement. R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) therapy and intrathecal (I.T.) injection of methotrexate, cytarabine and prednisolone were selected. Complete remission (CR) was achieved and pontine involvement disappeared. A total of 8 courses of R-CHOP therapy and 4 courses of I.T. were performed. CR has been maintained for 1 year and 2 months.

Keywords: Intravascular large B-cell lymphoma, central nervous system involvement, rituximab, CHOP therapy, intrathecal administration

Introduction

According to the World Health Organization (WHO) classification as revised in 2008, intravascular large B-cell lymphoma (IVLBCL) is classified as "a rare type of extranodal large B-cell lymphoma", which is a disease concept independent of diffuse large B-cell lymphoma (DLBCL) [1]. In general, its prognosis is poor [2]. In addition, 25% of patients with IVLBCL have central nervous system (CNS) lesions at the first onset in Japan [2].

According to a retrospective study in Japan, the 3-year progression-free survival rate was 27% and the overall survival rate was 41% in the chemotherapy group before the introduction of rituximab, but these rates improved to 54% and 60%, respectively, after concomitant use of rituximab, suggesting the efficacy of rituximab [3]. Likewise, the usefulness of concurrent rituximab was also reported in Italy [4].

However, the CNS progression/recurrence rate did not differ greatly according to the presence or absence of the concomitant use of rituximab (the 3-year CNS progression/recurrence rate was 22% and 29% in groups with and without concurrent rituximab, respectively), suggesting a limitation of rituximab [5]. In addition, the prognosis of IVLBCL is extremely poor after CNS progression/recurrence, with a 2-year survival rate of 12% [5], suggesting that the establishment of optimal prevention and treatment of CNS progression/recurrence is indispensable for improving the prognosis.

Case report

The patient was a 46-year-old man. He developed a fever of 38°C to 39°C and a cough in May 2012 and visited the Department of Respiratory Medicine of our hospital in late July. Multiple nodular shadows and granular shadows in the bilateral lung fields (**Figure 1A**) and

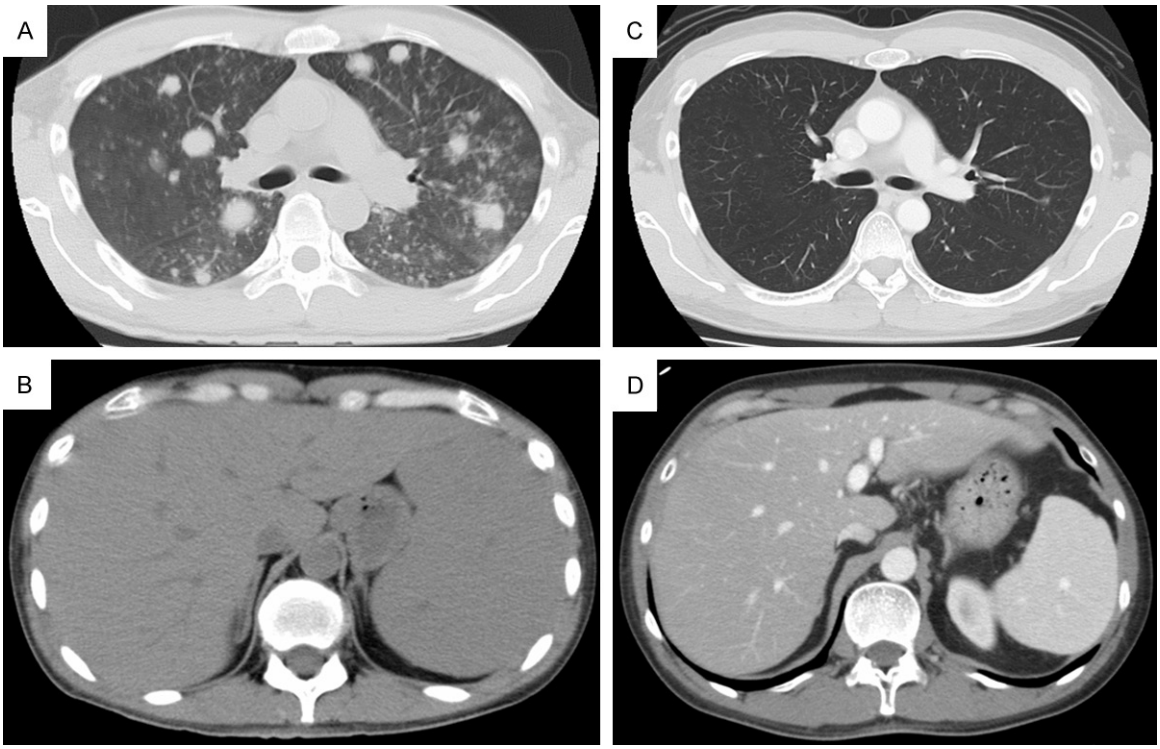

Figure 1. Computed tomography (CT) findings. A: Multiple, smooth-bordered, well-defined, large and small nodular shadows and granular shadows can be seen in both lung fields before treatment. B: Marked hepatosplenomegaly is present before treatment. C: The nodular shadows and granular shadows have disappeared after 4 courses of R-CHOP (rituximab, cyclophosphamide hydrate, doxorubicin hydrochloride, vincristine sulfate, and prednisolone). D: The hepatosplenomegaly improved after 4 courses of R-CHOP.

hepatosplenomegaly (**Figure 1B**) were observed, and he was admitted to our hospital.

At the time of admission, his height and weight were 177 cm and 67.9 kg, respectively, his temperature was 38.0°C, blood pressure 104/56 mmHg, regular pulse rate 92/minute, arterial oxygen saturation 100% under oxygen supply of 3 L/minute, clear consciousness, and he demonstrated anemic palpebral conjunctiva, mild jaundice of the bulbar conjunctiva, no intraoral abnormalities, rales in both lung fields, normal heart sounds, abdominal distention, no palpable liver, palpable spleen 3 finger-breadths below the left hypochondrium, no abnormal neurological findings, and no palpable superficial lymph nodes.

Laboratory findings at the time of admission are shown in **Table 1**. He had pancytopenia and elevated levels of transaminase, biliary enzymes, and lactate dehydrogenase (LDH). The soluble interleukin (IL)-2 receptor level was as remarkably high at as 19,100 U/mL. Various bacterial cultures were negative.

His clinical course after admission is shown in **Figure 2**. A transbronchial lung biopsy (right B4[a], B2[b], and B3[a]) led to the diagnosis of IVLBCL (**Figure 3**). He was transferred to the Department of Hematology in early August. The bone marrow and cerebrospinal fluid examination did not reveal IVLBCL involvement. However, his brain magnetic resonance imaging (MRI, T2W1) showed an abnormal signal area in the pons, raising the suspicion of IVLBCL involvement (**Figure 4A**). A brain biopsy could not be performed, because the lesion was located where biopsy was not possible. The clinical stage was IVB, and he was classified as high risk according to the International Prognostic Index (LDH, performance status, stage, and the number of extranodal lesions). The choice of chemotherapy including high-dose methotrexate (MTX) was considered because of the suspicion of CNS involvement. However, because the patient's general condition was extremely poor and he also had respiratory disorder, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and pred-

Table 1. Laboratory findings

CBC	WBC	3100/μL ↓
	Myelo	0.5%
	Band	10.5%
	Seg	58.0%
	Ly	12.5% ↓
	Mono	15.0% ↑
	RBC	319×10^4/μL ↓
	Hb	8.6 g/dL ↓
	Ht	27.5% ↓
	MCV	86.2 fl
	MCH	27.0 pg ↓
	Plt	12.1×10^4/μL ↓
	Reti	3.0% ↑
Coagulation	PT activity	60% ↓
	APTT	39.6 sec
	Fbg	450 mg/dL ↑
	DD	1.20 μg/mL ↑
Urinalysis	No abnormalities	
Biochemistry	TP	5.3 g/dL ↓
	Alb	2.0 g/dL ↓
	AST	35 IU/L ↑
	ALT	69 IU/L ↑
	LDH	765 IU/L ↑
	ALP	995 IU/L ↑
	γ-GTP	187 IU/L ↑
	LAP	119 IU/L ↑
	Ch-E	128 IU/L ↓
	T-Bil	0.6 mg/dL
	BUN	15 mg/dL
	Cr	0.83 mg/dL
	CRP	13.3 mg/dL ↑
	Ferritin	940.6 mg/dL ↑
Immunoserological findings	IgG	1359 mg/dL
	IgA	239 mg/dL
	IgM	54 mg/dL
	Antinuclear antibodies	< ×40
	β-D-glucan	5.0 pg/mL
	HBs antigen	Negative
	HCV antibodies	Negative
	Qualitative RPR test	Negative
	TPHA	Negative
	HIV antibodies	Negative
Tumor markers	Soluble IL-2 receptor	19100 U/mL ↑
	AFP	2.1 ng/mL
	CEA	1.2 ng/mL
	CA19-9	2.6 U/mL
Culture	Blood culture	Negative
	Sputum culture	Negative
	Bronchoalveolar lavage fluid culture	Negative
	Blood (QFT)	Negative
	Mycobacterial culture of gastric juice	Negative
	Mycobacterial culture of sputum	Negative
	Mycobacterial culture of bronchoalveolar lavage fluid	Negative
	Cerebrospinal fluid culture	Negative
	Mycobacterial culture of cerebrospinal fluid	Negative

Values higher and lower than the reference values are shown with ↑ and ↓, respectively.

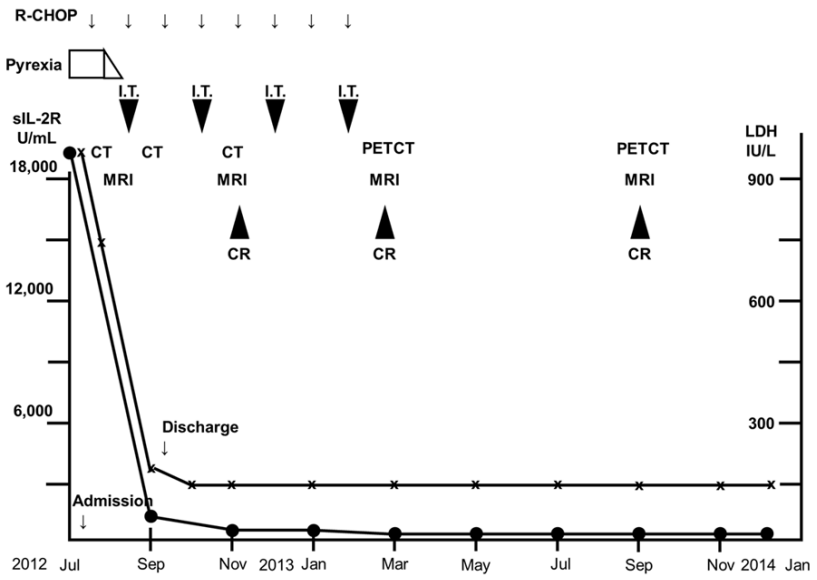

Figure 2. Clinical course. R-CHOP: Rituximab, cyclophosphamide hydrate, doxorubicin hydrochloride, vincristine sulfate, and prednisolone, I.T.: intrathecal, CT: computed tomography, PET CT: positron emission tomography computed tomography, MRI: magnetic resonance imaging, CR: complete remission, sIL-2R: soluble interleukin-2 receptor. CR was achieved after 4 courses of R-CHOP therapy, and a total of 8 courses of R therapy and 6 courses of CHOP therapy were performed. CR has been maintained for 1 year and 2 months.

nisolone) therapy and I.T. administration were chosen after obtaining informed consent from the patient and his family. The treatment was started in mid-August. His clinical symptoms improved markedly, and he was discharged in early September. When 4 courses of R-CHOP therapy and 2 courses of I.T. were completed, complete remission (CR) was confirmed (**Figure 1C**, **1D**). In addition, MRI showed disappearance of the lesion in the pons (**Figure 4B**). Thus, the lesion in the pons disappeared on MRI after 4 courses of R-CHOP therapy and 2 courses of I.T., suggesting IVLBCL involvement. After that, 8 courses of R-CHOP therapy and 4 courses of I.T. were completed in mid-January 2013. As of March 2014, positron emission tomography computed tomography (PET CT) and brain MRI confirmed that CR had been maintained for 1 year and 2 months.

Discussion

Because no treatment for IVLBCL has been prospectively investigated, there is no established treatment for IVLBCL, regardless of the presence or absence of CNS involvement. R-CHOP therapy and preventive I.T. seem to be mainly used for IVLBCL without CNS involvement in actual clinical practice. A phase II clinical trial of the combination of R-CHOP therapy, which is the standard treatment for DLBCL, and treatment to prevent CNS recurrence (high-dose MTX therapy with rituximab and intrathecal administration of anticancer drugs) for IVLBCL without CNS involvement is in progress, and its results are awaited. However, no clinical trials for IVLBCL with CNS involvement are in progress.

The efficacy of chemotherapy including high-dose MTX, which is the standard treatment for primary CNS DLBCL and DLBCL with CNS involvement [6], I.T., and irradiation is unknown.

Nakazato et al. reported that a patient with IVLBCL with pontine involvement was successfully treated with R-hyper-CVAD/R-MTX-Ara-C (rituximab, hyper-fractionated cyclophosphamide, vincristine, adriamycin, and dexamethasone/rituximab, methotrexate, and cytarabine) and intrathecal MTX administration and had maintained CR for 2 years, and that this treatment was useful as an initial treatment option [7]. R-hyper-CVAD/R-MTX-Ara-C therapy was reported to give good results in patients with mantle cell lymphoma or Burkitt's lymphoma [8]. However, it is difficult to perform this therapy in elderly patients and in patients with organ dysfunction or poor general condition due to the high toxicity, and it is inevitable that its indications are limited.

There have been no large-scale studies on the evaluation of fluorodeoxyglucose (FDG) PET CT in IVLBCL. It has been reported that FDG PET CT is useful [9], but it has also been reported that FDG PET CT may give false-negative results in IVLBCL lesions with low tumor cell density [10] and that FDG PET CT is not suitable for detecting lesions in the brain [11]. Therefore, it was considered necessary to follow up the brain lesion in the present patient by periodically performing MRI.

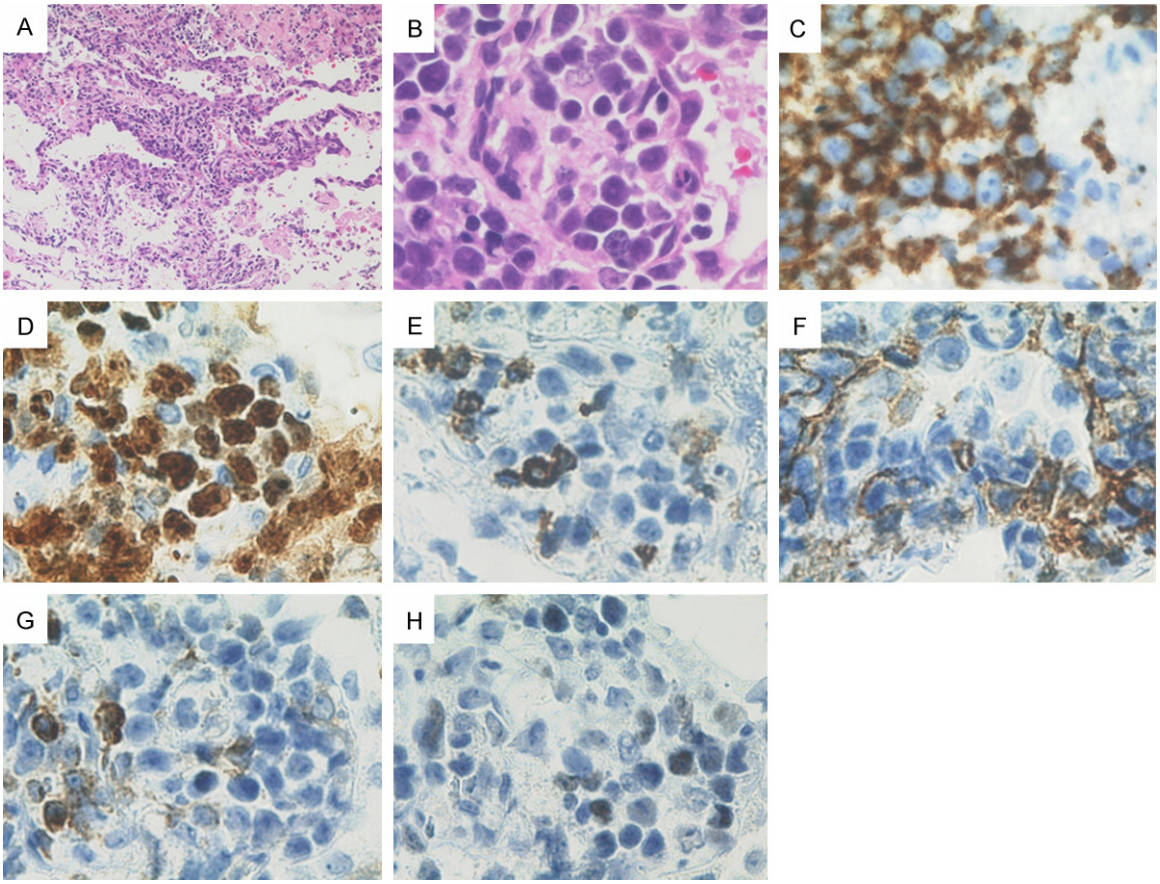

Figure 3. Histopathological findings of transbronchial lung biopsy (TBLB) specimens. A: Low magnification of a specimen from the alveoli shows many infiltrating cells (×100 with hematoxylin and eosin staining). B: High magnification of a specimen from the alveoli shows proliferation of large atypical cells in some small vessels in the alveolar septa (×600 with hematoxylin and eosin staining). C: Cluster of differentiation antigen 20 (CD20), positive (×600). D: Ki-67, 90% positive (×600). E: CD5, negative (×600). F: CD10, negative (×600). G: B-cell lymphoma (BCL)-2, negative (×600). H: BCL-6, negative (×600).

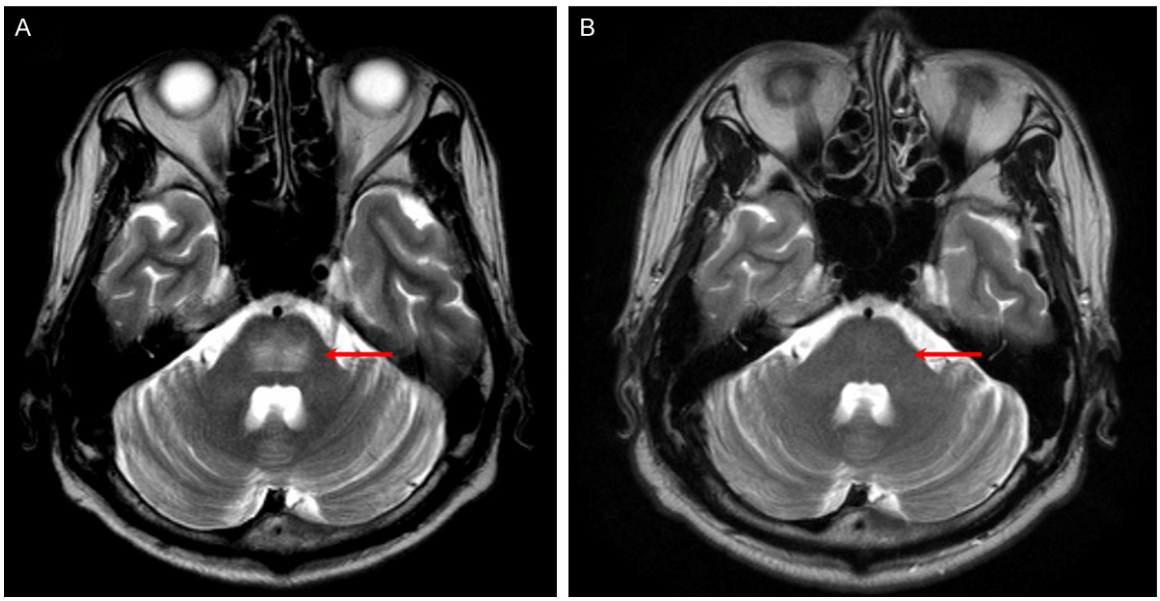

Figure 4. Brain MRI findings (T2W1). A: Before treatment, a high-intensity area can be seen in the central pons on the T2-weighted image, but the surrounding areas remained normal. No contrast enhancing effect is evident, and diffusion-weighted images also show no signal abnormalities (red arrow). B: The abnormal signal in the pons has disappeared after 4 courses of R-CHOP therapy (red arrow).

This is the first reported case of IVLBCL with CNS involvement in which CR was maintained only with R-CHOP therapy and I.T. It was suggested that R-CHOP therapy plus I.T. may be useful as an initial treatment option for IVLBCL with CNS involvement. In particular, R-CHOP therapy plus I.T. was considered to be indicated for elderly patients and for patients with organ dysfunction or poor general condition.

IVLBCL is a rare disease, and IVLBCL with CNS involvement is even rarer, with an incidence of 25% at the first onset. In the future, it is considered necessary to accumulate cases of IVLBCL with CNS involvement and to conduct clinical studies in other institutions.

Disclosure of conflict of interest

None.

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References

[1] Nakamura S, Ponzoni M, Campo E. Intravascular large B-cell lymphoma. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW, eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Fourth Edition. Lyon: IARC; 2008. pp. 252-253.

[2] Shimada K, Kinoshita T, Naoe T, Nakamura S. Presentation and management of intravascular large B-cell lymphoma. Lancet Oncol 2009; 10: 895-902.

[3] Shimada K, Matsue K, Yamamoto K, Murase T, Ichikawa N, Okamoto M, Niitsu N, Kosugi H, Tsukamoto N, Miwa H, Asaoku H, Kikuchi A, Matsumoto M, Saburi Y, Masaki Y, Yamaguchi M, Nakamura S, Naoe T, Kinoshita T. Retrospective analysis of intravascular large B-cell lymphoma treated with rituximab-containing chemotherapy as reported by the IVL study group in Japan. J Clin Oncol 2008; 26: 3189-95.

[4] Ferreri AJ, Dognini GP, Govi S, Crocchiolo R, Bouzani M, Bollinger CR, D'Incan M, Delaporte E, Hamadani M, Jardin F, Martusewicz-Boros M, Montanari M, Szomor A, Zucca E, Cavalli F, Ponzoni M. Can rituximab change the usually dismal prognosis of patients with intravascular large B-cell lymphoma? J Clin Oncol 2008; 26: 5134-6.

[5] Shimada K, Murase T, Matsue K, Okamoto M, Ichikawa N, Tsukamoto N, Niitsu N, Miwa H, Asaoku H, Kosugi H, Kikuchi A, Matsumoto M, Saburi Y, Masaki Y, Yamamoto K, Yamaguchi M, Nakamura S, Naoe T, Kinoshita T; IVL Study Group in Japan. Central nervous system involvement in intravascular large B-cell lymphoma: a retrospective analysis of 109 patients. Cancer Sci 2010; 101: 1480-6.

[6] Ferreri AJ, Reni M, Foppoli M, Martelli M, Pangalis GA, Frezzato M, Cabras MG, Fabbri A, Corazzelli G, Ilariucci F, Rossi G, Soffietti R, Stelitano C, Vallisa D, Zaja F, Zoppegno L, Aondio GM, Avvisati G, Balzarotti M, Brandes AA, Fajardo J, Gomez H, Guarini A, Pinotti G, Rigacci L, Uhlmann C, Picozzi P, Vezzulli P, Ponzoni M, Zucca E, Caligaris-Cappio F, Cavalli F; International Extranodal Lymphoma Study Group (IELSG). High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: a randomised phase 2 trial. Lancet 2009; 374: 1512-20.

[7] Nakazato T, Suzuki K, Mihara A, Sanada Y, Yoshida S, Kakimoto T. Intravascular large B-cell lymphoma with pontine involvement successfully treated with R-hyper-CVAD/R-MTX-Ara-C regimen. Rinsho Ketsueki 2010; 51: 148-152. Japanese.

[8] Romaguera JE, Fayad L, Rodriguez MA, Broglio KR, Hagemeister FB, Pro B, McLaughlin P, Younes A, Samaniego F, Goy A, Sarris AH, Dang NH, Wang M, Beasley V, Medeiros LJ, Katz RL, Gagneja H, Samuels BI, Smith TL, Cabanillas FF. High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine. J Clin Oncol 2005; 23: 7013-23.

[9] Hoshino A, Kawada E, Ukita T, Itoh K, Sakamoto H, Fujita K, Mantani N, Kogure T, Tamura J. Usefulness of FDG-PET to diagnose intravascular lymphomatosis presenting as fever of unknown origin. Am J Hematol 2004; 76: 236-9.

[10] Shimada K, Kosugi H, Shimada S, Narimatsu H, Koyama Y, Suzuki N, Yuge M, Nishibori H, Iwata Y, Nakamura S, Naoe T, Kinoshita T. Eval-

uation of organ involvement in intravascular large B-cell lymphoma by 18F-fluorodeoxyglucose positron emission tomography. Int J Hematol 2008; 88: 149-53.

[11] Kawai N, Okada M, Haba R, Yamamoto Y, Tamiya T. Insufficiency of positron emission tomography and magnetic resonance spectroscopy in the diagnosis of intravascular lymphoma of the central nervous system. Case Rep Oncol 2012; 5: 339-46.