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FULL PAPER

Computed tomography findings in Epstein–Barr virus (EBV)-positive diffuse large B-cell lymphoma (DLBCL) of the elderly: comparison with EBV-negative DLBCL

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Objective: This study aimed to compare CT findings in patients with Epstein–Barr virus positive (EBV+) diffuse large B-cell lymphoma (DLBCL) of the elderly with CT findings in patients with Epstein–Barr virus negative (EBV–) DLBCL.

Methods: We retrospectively identified 9 consecutive patients with EBV+ DLBCL (6 males and 3 females; aged 72–83 years, mean: 76.2 years) and 39 consecutive patients with EBV– DLBCL (19 males and 20 females; aged 53–91 years, mean: 71.3 years) who had undergone CT examinations between September 2007 and August 2016. In each type of disease, clinical and CT findings were evaluated.

Results: No significant differences in B symptom incidence or serum lactate dehydrogenase levels were

found between the two diseases. However, the prognosis of patients with EBV+ DLBCL was significantly poorer than that of those with EBV– DLBCL ($p < 0.05$). Nodal and extranodal necrosis was found in 6 (66.7%) of 9 patients with EBV+ DLBCL and in 6 (15.4%) of 39 patients with EBV– DLBCL ($p < 0.005$).

Conclusion: The CT finding of nodal and extranodal necrosis was significantly more frequent in patients with EBV+ DLBCL than in patients with EBV– DLBCL.

Advances in knowledge: This is the first report on the CT findings in patients with EBV+ DLBCL of the elderly. Different CT findings are present in EBV+ DLBCL and EBV– DLBCL.

INTRODUCTION

Epstein–Barr virus (EBV) is one of the most common viruses in humans. In Western countries, approximately half of all 5-year-old children and 90–95% of adults have serologic evidence of an infection. Most people become infected with EBV during childhood or adolescence and gain adaptive immunity against the virus. In addition to Burkitt lymphoma, EBV has been associated with the aetiology of several lymphoproliferative disorders, such as a subtype of classical Hodgkin lymphoma, lymphomatoid granulomatosis, human immunodeficiency virus-associated lymphomas of the central nervous system, epithelial cancers and nasopharyngeal carcinoma.¹

Epstein–Barr virus positive (EBV+) diffuse large B-cell lymphoma (DLBCL) of the elderly has been included in the 2008 World Health Organization classification of tumours of haematopoietic and lymphoid tissues as a new provisional entity.² This disease is characterized by

proliferation of atypical large B-cells including Hodgkin and Reed–Sternberg-like cells with reactive inflammatory components, occurring in patients >50 years of age and sharing features of EBV+ B-cell neoplasms seen in patients with immunologic impairment, despite the absence of any predisposing immunodeficiency.^{3,4}

Clinically, this disease may present with lymphadenopathy and is often extranodal, frequently involving the skin, gastrointestinal tract or lung. In addition, B symptoms and poor performance status are common, and prognosis is significantly inferior compared with Epstein–Barr virus negative (EBV–) cases.^{4–6}

There have been several reports on pathological features of EBV+ DLBCL of the elderly.^{3–13} However, to the best of our knowledge, no English language studies have documented the CT findings in patients with this disease. Furthermore, no studies have compared CT findings in

patients with EBV + DLBCL of the elderly with those in patients with EBV– DLBCL.

We aimed to assess CT findings in patients with EBV+ DLBCL of the elderly and to compare them with those of patients with EBV– DLBCL.

METHODS AND MATERIALS

Patients

Our institutional review boards approved this study and, because of its retrospective format, waived the requirement for informed consent.

Analyzing the patient population at our institutions, we retrospectively identified 9 consecutive patients with EBV+ DLBCL (6 males and 3 females; aged 72–83 years, mean: 76.2 years) and 39 consecutive patients with EBV– DLBCL (19 males and 20 females; aged 53–91 years, mean: 71.3 years) for patients who had undergone CT examinations between September 2007 and August 2016 and were clinically suspected to have EBV+ DLBCL of the elderly. EBV positivity in >50% of tumour cells was required to diagnose a case as EBV+ DLBCL.⁴ The present study included no patients with predisposing immunodeficiency such as human immunodeficiency virus infection or a past history of immunosuppressive agents, according to the definition of the 2008 World Health Organization lymphoma classification of EBV+ DLBCL of the elderly.²

In cases of each type of disease, we evaluated the chart for a history of B symptoms and serum lactate dehydrogenase (LDH) levels.

CT examinations

CT examinations were performed with a variety of scanners. These examinations were performed volumetrically with a multidetector CT scanner with 1-mm section reconstruction. The scans were obtained with the patient in the supine position at full inspiration. Intravenously administered contrast material was used in 6 patients with EBV+ DLBCL and in 29 patients with EBV– DLBCL, while unenhanced CT scans were performed in 3 patients with EBV+ DLBCL and 10 patients with EBV– DLBCL. For the contrast-enhanced CT scans, 100 ml of 300–350 mgI/ml iodinated contrast material was injected intravenously at a rate of 2–3 ml s^{−1}, with a scan delay of 80–100 s.

Interpretation of CT images

We assessed the CT scans performed from 1 to 40 days (mean: 10.7 days) before or after the diagnosis of EBV+ DLBCL and CT scans performed from 1 to 20 days (mean: 10.7 days) before or after the diagnosis of EBV– DLBCL. Two radiologists (with 28 and 6 years' experience in chest CT image interpretation), who were unaware of the underlying diagnoses, retrospectively and independently interpreted the CT scans. Conclusions were reached by consensus.

CT images were evaluated for the following findings: (1) the sites of abnormalities such as lymphadenopathy or extranodal lesion (s); (2) the size of the short axis of the largest lymph node or extranodal lesion; and (3) the presence of necrosis.

Accepted criteria for the CT diagnosis of necrosis have been defined as focal or diffuse areas of non-enhancing parenchyma depicted during an examination with i.v. bolus administration of contrast material.¹⁴ In the 3 cases with EBV+ DLBCL and 10 cases with EBV– DLBCL with unenhanced CT scans, mean CT numbers were measured in Hounsfield units by placing a circular region of interest in the largest lymph node or extranodal lesion while avoiding areas of calcification, on the slice at the largest cross-sectional area of the lesion. The areas of low attenuation (10–18 HU) were considered evidence of necrosis.¹⁵

Statistical analysis

Statistical analysis for the frequency of symptoms and CT findings was conducted using Fisher's exact test and the χ^2 test. Comparison of mean age was conducted using Student's *t*-test.

Table 1. Patient characteristics

Characteristics	EBV+ DLBCL (<i>n</i> = 9)	EBV– DLBCL (<i>n</i> = 39)
M, F	6, 3	19, 20
Age (year) (range)	72–83	53–91
Mean	76.2	71.3
B-symptom, presence	2 (22.2)	4 (10.3)
LDH level	199–1468	145–5940
Mean	531.2	641.2
Ann Arbor Stage I/II/III/IV	0/3/4/2	1/13/8/17
Extranodal involvement	3 (33.3)	20 (51.3)
Extranodal sites		
Parotid gland	0	1
Thyroid gland	0	1
Nasal cavity	0	3
Breast	0	1
Lung	1	0
Liver	1	3
Pancreas	0	2
Stomach	0	2
Adrenal gland	0	2
Kidney	1	1
Uterus	0	1
Testis	1	1
Skin/subcutaneous tissue	2	5
Bone marrow	1	4

DLBCL, diffuse large B-cell lymphoma; EBV+, Epstein-Barr virus positive; EBV–, Epstein-Barr virus negative; F, female; LDH, lactate dehydrogenase; M, male.

Data in parentheses are percentages.

Figure 1. A 73-year-old male patient with Epstein-Barr virus positive diffuse large B-cell lymphoma of the elderly: the transverse CT image (1-mm thickness) shows multiple necrotic enlarged lymph nodes with well-defined margins (arrows) in the left side of the neck.

RESULTS

Patient characteristics

The clinical characteristics of all patients are summarized in Table 1. There were three patients with Stage II, four patients with Stage III and two patients with Stage IV EBV+ DLBCL. There was 1 patient with Stage I, 13 patients with Stage II, 8 patients with Stage III and 17 patients with Stage IV EBV- DLBCL. The patients with EBV- DLBCL had more frequent Stage IV than those with EBV+ DLBCL.

B symptoms occurred in 2 (22.2%) of 9 patients with EBV+ DLBCL and in 4 (10.3%) of 39 patients with EBV- DLBCL. There were no significant differences in B symptom incidence between patients with EBV+ DLBCL and those with EBV- DLBCL. In addition, no significant differences in serum LDH levels were found between the two groups.

CT findings

CT scans showed abnormalities in all of the 9 patients with EBV+ DLBCL of the elderly (Figures 1–3) and the 39 patients with EBV- DLBCL (Figure 4) (Table 1).

Figure 2. A 77-year-old female patient with Epstein-Barr virus positive diffuse large B-cell lymphoma of the elderly: the transverse CT image (1-mm thickness) at the level of the thigh shows an irregular necrotic nodule with a well-defined margin (arrow) under the skin.

Figure 3. A 76-year-old female patient with Epstein-Barr virus positive diffuse large B-cell lymphoma of the elderly: the transverse CT image (1-mm thickness) at the level of the axillae shows multiple necrotic enlarged axillary lymph nodes with well-defined margins (arrows).

Extranodal involvement was found in 3 (33.3%) of 9 patients with EBV+ DLBCL of the elderly, most frequently observed in the skin/subcutaneous tissue ($n = 2$; 22.2%) (Figure 2), followed by the lung, liver, kidney, testis and bone marrow. In 20 (51.3%) of 39 patients with EBV- DLBCL, extranodal involvement was

Figure 4. A 62-year-old male patient with Epstein-Barr virus negative diffuse large B-cell lymphoma: the transverse CT image (1-mm thickness) at the level of the piriform fossa shows multiple smooth-walled enlarged lymph nodes without necrosis, with well-defined margins (arrows).

found, which was most frequently observed in the skin/subcutaneous tissue ($n = 5$; 12.8%), followed by the bone marrow ($n = 4$; 10.3%), the nasal cavity ($n = 3$; 7.7%) and the liver ($n = 3$; 7.7%).

The short axis of the largest mass/lymph node was 15.5–51.2 mm (mean, 27.6 mm) in patients with EBV+ DLBCL and 8.8–224.1 mm (mean, 41.6 mm) in patients with EBV– DLBCL (Table 2). Necrosis was often observed in the largest lesions. Necrosis was found in 6 (66.7%) of 9 patients with EBV+ DLBCL (Figures 1–3) and in 6 (15.4%) of 39 patients with EBV– DLBCL (Figure 4) ($p < 0.005$). In patients with EBV+ DLBCL, necrosis tended to involve the axillary lymph nodes ($n = 3$) (Figure 3), mediastinal lymph nodes ($n = 2$), pelvic lymph nodes ($n = 2$), cervical lymph nodes ($n = 1$) (Figure 1), lung ($n = 1$) and skin ($n = 1$). With regard to the range/mean age of the patients with necrosis and the sites of necrosis, there were no significant differences between the two groups. There was no correlation between the duration between diagnosis and CT examination and the incidence of nodal necrosis.

Follow-up

All of the patients underwent chemotherapy. Kaplan–Meier survival curves for the two groups are shown in Figure 5. Patients with EBV– DLBCL had a longer survival than those with EBV+ DLBCL ($p < 0.05$).

DISCUSSION

According to current published studies from Asia on EBV+ DLBCL of the elderly, the prevalence has ranged from 8% to 11.4% in patients with DLBCL who are immunocompetent.^{6,16,17} Only very limited data are available on the disease in Western countries.

Hoeller et al¹¹ identified only 8 (3.1%) EBV+ cases in 258 DLBCL cases analyzed in patients >50 years of age from Central Europe. In the present study on Japanese, 9 (18.8%) of 48 patients with DLBCL of the elderly were EBV+, higher than that in the previous reports, which may be explained by the fact that the mean age of our population was older than that in the other reports.^{4,6,17} Another interpretation may be that, as with other EBV-associated disorders, there is a geographically and/or ethnically determined distribution pattern of EBV+ DLBCL of the elderly.

Pathogenic mechanisms of EBV+ DLBCL of the elderly have remained to be completely elucidated; however, it has been estimated that a physiological ageing process of hosts results in immunological deteriorations and subsequent outgrowth of EBV-infected B-cells. It has been postulated that the development of EBV+ DLBCL is preceded by subclinical expansion of EBV+ B-cells.¹⁸ EBV DNA has been more frequently observed in peripheral blood mononuclear cells of elderly persons than in those of younger subjects.¹⁹

The clinical course of the patients with EBV+ DLBCL of the elderly is often aggressive. The following independent prognostic factors for EBV+ DLBCL have been identified: B symptoms, elevated LDH and age ≥ 70 years. In the present study, B symptoms occurred in 2 (22.2%) patients with EBV+ DLBCL and in 4 (10.3%) patients with EBV– DLBCL. There were no significant differences in B symptom incidence between patients with EBV+ DLBCL and those with EBV– DLBCL. In addition, there was no significant difference in serum LDH levels between the two groups, which was similar to that in the previous reports described by Park et al.⁶ The poorer prognosis of patients with EBV+ DLBCL is similar to the findings of previous reports.^{4,6,9,10}

Table 2. CT findings for each type of disease

Findings	EBV+ DLBCL ($n = 9$)	EBV– DLBCL ($n = 39$)	p -value
Short axis in the largest mass/lymph node (mm)	15.5–51.2 (27.6)	8.8–224.1 (41.6)	NS
Necrosis	6 (66.7)	6 (15.4)	$p < 0.005$
M, F	3, 3	5, 1	
Age (year) (range)	73–83	70–84	
Mean	78	76.8	
Sites of necrosis			
Cervical lymph node	1	1	
Axilla lymph node	3	1	
Mediastinal/hilar lymph node	2	1	
Abdominal lymph node	0	1	
Pelvic lymph node	2	0	
Parotid gland	0	1	
Lung	1	0	
Ileocecum	0	1	
Uterus	0	1	
Skin/subcutaneous tissue	1	0	

DLBCL, diffuse large B-cell lymphoma; EBV+, Epstein–Barr virus positive; EBV–, Epstein–Barr virus negative; F, female; M, male; NS, not significant.

Figure 5. Kaplan-Meier curves show survival of patients with Epstein-Barr virus positive (EBV+) diffuse large B-cell lymphoma (DLBCL) of the elderly and of those with Epstein-Barr virus negative (EBV-) DLBCL aged >50 years. Patients with EBV+ DLBCL had a worse prognosis than those with EBV- DLBCL ($p < 0.05$).

EBV+ DLBCL of the elderly has a variety of clinical features including nodal or extranodal involvement.^{3,8,9,12,13} In the present study, 6 (66.7%) of 9 cases presented with nodal involvement. This result was similar to the report by Hofscheier et al.⁹ They found that 9 (69.2%) of 13 cases presented with mainly nodal involvement, whereas 4 (30.8%) cases were diagnosed at extranodal sites.⁹

There are a few reports on CT findings in patients with EBV+ DLBCL; however, the articles are mostly case reports. Tokuyama et al.²⁰ reported a case of methotrexate-associated EBV+ DLBCL in a patient with rheumatoid arthritis. The chest CT revealed a large pulmonary mass containing prominent areas of central necrosis and a CT angiogram sign. However, to the best of our knowledge, no English language studies on CT findings of patients with EBV+ DLBCL of the elderly have appeared. Moreover, no studies have compared CT findings of EBV+ DLBCL of the elderly with EBV- DLBCL. In the present study, we retrospectively identified 48 consecutive patients (9 patients with EBV+ DLBCL and 39 patients with EBV- DLBCL) aged >50 years. There were no significant differences between the two diseases in terms of B symptom frequency, the sites of extranodal involvement and the staging. However, in patients with EBV+ DLBCL of the elderly, necrosis was significantly more frequently observed than in those with EBV- DLBCL ($p < 0.005$). In terms of the sites of necrosis, there was no significant difference between the two diseases.

There are a few reports documenting pathological features of EBV+ DLBCL of the elderly.³⁻¹³ The most common lesion is composed of tumour cells with a broad range of B-cell maturation including centroblasts, immunoblasts and plasmablasts, admixed with a reactive infiltrate of small lymphocytes, plasma cells and epithelioid histiocytes. Moreover, large areas of “geographical” necrosis are considered to be characteristic and important for the diagnosis of EBV-associated lymphoma.^{2,3,7-9,11,12} Oyama et al.³ evaluated 22 patients with EBV+ LPD without predisposing immunodeficiencies. In all 9 patients with large-cell lymphoma, extensive necrosis was found and 8 of the remaining 13 patients with polymorphic LPD had extensive necrosis. 4 (67%) of 6 cases of EBV+ DLBCL of the elderly analyzed by Hoeller et al.¹² showed at least focal necrosis pathologically. Hofscheier et al.⁹ also reported that in 3 (33.3%) of 9 EBV+ DLBCL in Mexican patients, extensive necrosis was found. The mechanisms of tissue necrosis and vascular damage characteristic of EBV-associated LPDs are unknown. However, Teruya-Feldstein et al.²¹ revealed high levels of interferon- γ -inducible protein-10 and the monokine induced by interferon- γ gene expression in tissue with necrosis and vascular damage from EBV + LPD, suggesting that monokine induced by interferon- γ and interferon- γ -inducible protein-10 play an important role in the pathogenesis of tissue necrosis and vascular damage associated with EBV+ LPD.

There are several limitations to this study. First, this was a retrospective study, and interpretation of CT images was performed by consensus. Second, this study included only a small number of patients. However, we hope this preliminary study of this rare entity will contribute to the understanding of the interrelationships between age, EBV and lymphoproliferative disorders. Third, intravenously administered contrast material was not used in all patients, because six of the patients had allergic histories for contrast materials and five patients were in poor general health. Fourth, no pathologic correlation with CT findings of enlarged necrotic lymph nodes was possible. Finally, the CT images were obtained at two institutions using different protocols.

In summary, we identified 9 (18.8%) of 48 patients with DLBCL of the elderly with EBV positivity. Comparing the CT findings in patients with EBV+ DLBCL of the elderly with those with EBV- DLBCL aged ≥ 50 years, CT findings of necrotic lesions were significant more frequently observed in patients with EBV+ DLBCL than in patients with EBV- DLBCL. Radiologists should be aware that enlarged necrotic lymph nodes may indicate EBV+ DLBCL of the elderly in patients aged ≥ 50 years.

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