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ORIGINAL RESEARCH

A Clinicopathological Study of Cytomegalovirus Lymphadenitis and Tonsillitis and Their Association with Epstein–Barr Virus

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ABSTRACT

Introduction: Histopathological characteristics of cytomegalovirus (CMV) lymphadenitis have been well described. Rare studies have reported the immune status and clinical features. Clinically, experts believed that CMV lymphadenitis develops in immunocompromised and immunocompetent patients. Infectious mononucleosis (IM)-like syndrome is the most well-known clinical presentation.

Methods: We reviewed archived CMV immunohistochemical stains on lymphoid tissues. The clinicopathological features of CMV-positive cases were studied.

Results: For lymph nodes, we detected CMV in 29% (5/17) allogeneic peripheral blood hematopoietic stem cell transplantation

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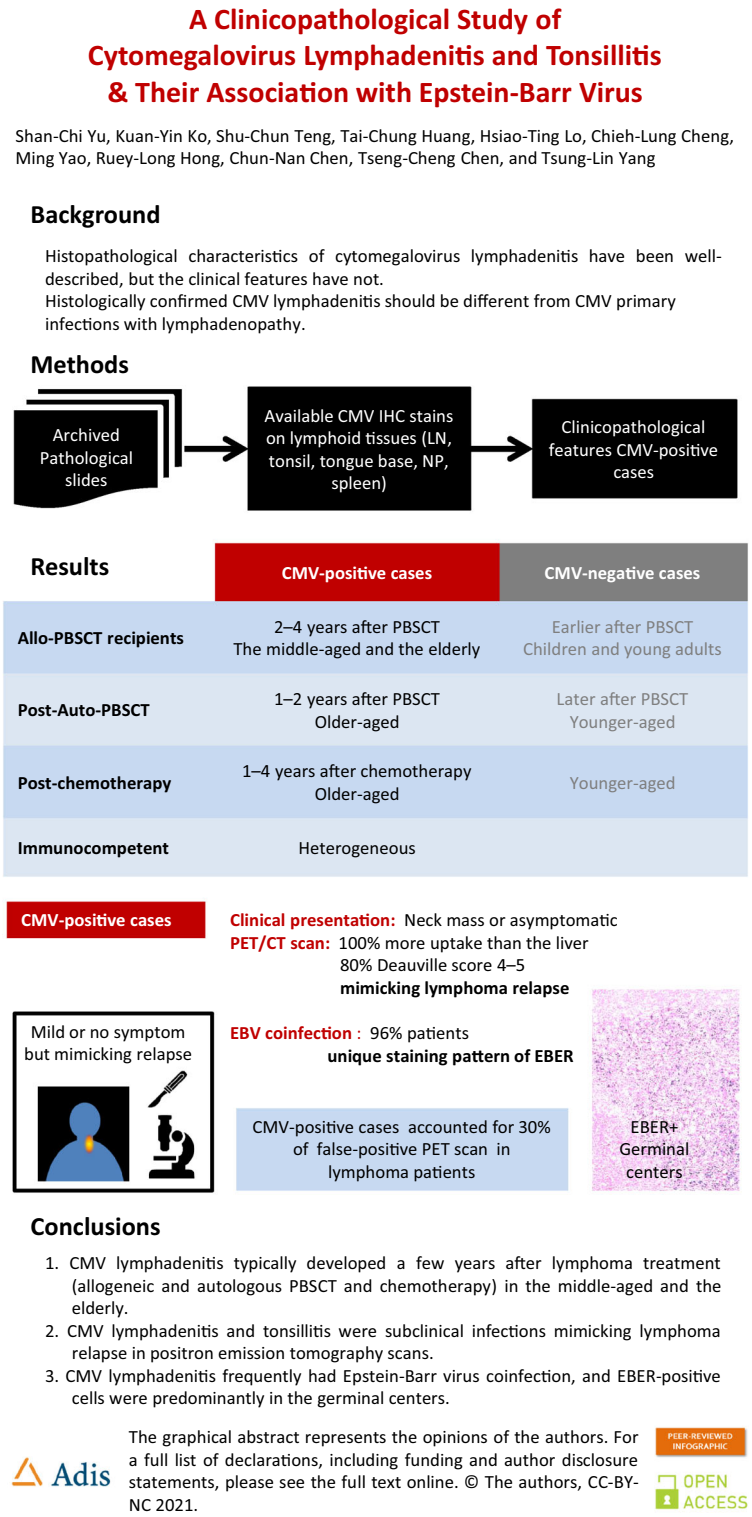
(PBSCT) recipients, 29% (4/14) post-autologous PBSCT patients, 13% (6/47) patients treated with intravenous chemotherapy, and 9% (9/96) immunocompetent patients. We detected CMV in 7% (2/24) of tonsils but not in the nasopharynx, tongue base, or spleen specimens. The patients with iatrogenic immunodeficiency ranged from 37 to 76 years old. CMV infections developed a few years after lymphoma treatment (median duration after allogeneic PBSCT, 932 days; after autologous PBSCT, 370 days; and after chemotherapy, 626 days). The most common clinical presentation was neck mass (13/25, 42%), followed by asymptomatic image finding (10/25, 40%). Positron emission tomography/computed tomography (PET/CT) scan showed increased uptake compared to the liver in all patients (11/11, 100%). Of 10 lymphoma patients, 8 (80%) had a Deauville score of 4–5; they accounted for 30% (8/27) of lymphoma patients with false-positive PET/CT scan results. All cases were self-limiting. 96% (23/25) cases had Epstein–Barr virus coinfection, and EBER-positive cells were predominantly in a few germinal centers.

Conclusions: Cytomegalovirus (CMV) lymphadenitis and tonsillitis were subclinical infections, not primary CMV infection with IM-like syndrome. The lymphadenopathy typically developed a few years after lymphoma treatments in the middle-aged and the elderly. The lesions mimicked lymphoma relapse in PET scans. Therefore, recognizing CMV infection in lymphoid tissues is of clinical importance.

Graphic abstract:



Keywords: Cytomegalovirus; Epstein–Barr virus; Lymphoma; Lymphadenopathy; Positron emission tomography; Reactive lymphoid hyperplasia

Key Summary Points

Why carry out this study?

Histopathological characteristics of cytomegalovirus lymphadenitis have been well described, but the clinical features have not.

Histologically confirmed CMV lymphadenitis should be different from CMV primary infections with lymphadenopathy.

What was learned from the study?

CMV lymphadenitis typically developed a few years after lymphoma treatment (allogeneic and autologous peripheral blood stem cell transplantation and intravenous chemotherapy) in the middle-aged and the elderly.

CMV lymphadenitis and tonsillitis were subclinical infections mimicking lymphoma relapse in positron emission tomography scans.

CMV lymphadenitis frequently had Epstein–Barr virus coinfection, and EBER-positive cells were predominantly in the germinal centers.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract, to facilitate understanding of the article.To view digital features for this article go to https://doi.org/10.6084/m9.figshare.16432620.

INTRODUCTION

Cytomegalovirus (CMV) is a ubiquitous human herpesvirus [1]. CMV infections occur in both immunocompetent and immunocompromised patients [2, 3]. In immunocompetent hosts, primary CMV infection is normally asymptomatic, and some patients develop infectious mononucleosis (IM)-like syndrome [2–4]. CMV infection is potentially fatal in immunocompromised patients, such as allogeneic peripheral blood stem cell transplantation (PBSCT) recipients [5].

CMV can infect a broad range of human tissues [6]. Most studies have focused on end-organ diseases, such as pneumonitis, gastrointestinal (GI) disease, hepatitis, retinitis, encephalitis, myocarditis, nephritis, cystitis, and pancreatitis [7, 8]. CMV infections are also observed in lymph nodes; both hematopoietic cells and connective tissue cells can be infected [9–11].

The histopathology of CMV lymphadenitis has been well described [9–12]. Microscopically, CMV lymphadenitis is characterized by follicular hyperplasia, monocytoid cell proliferation, and paracortical hyperplasia [9–12]. CMV immunohistochemical (IHC) staining can highlight CMV-positive cells in the monocytoid cell regions [9–12].

In contrast, the clinical aspect of CMV lymphadenitis is vague. Although lymphadenopathy is a common finding in primary CMV infections [13, 14], lymph node biopsy is unnecessary in most circumstances. CMV infections are common, but histologically confirmed cases of CMV lymphadenitis are rare cases [15, 16]. Histologically confirmed CMV lymphadenitis should not be equivalent to primary CMV infection with lymphadenopathy.

Until now, research on CMV lymphadenitis has been rare [15, 16]. Most experts believe that CMV lymphadenitis occurs in either the immunocompromised or the immunocompetent [9–12]. However, no study has clarified the risk of different immune status. An IM-like syndrome is the most well-known clinical presentation of CMV lymphadenitis [9–12], but the frequency remains entirely unclear.

In this study, we conducted a comprehensive clinicopathological study to clarify the clinical

Table 1 Results of cytomegalovirus immunohistochemical staining

	Lymph node	Pharyngeal tonsil	Nasopharynx	Tongue base	Spleen	Total
Iatrogenic immunodeficiency						
Allo-PBSCT	5/17 (29%)	0/2 (0%)				5/19 (26%)
Solid organ transplantation	0/3 (0%)	0/2 (0%)				0/5 (0%)
Auto-PBSCT	4/14 (29%)					4/14 (29%)
Intravenous chemotherapy	6/47 (13%)	2/18 (11%)	0/1 (0%)	0/4 (0%)	0/7 (0%)	8/77 (10%)
Radiotherapy	0/9 (0%)					0/9 (0%)
Oral chemotherapy	0/7 (0%)					0/7 (0%)
Prolonged steroid therapy	0/5 (5%)					0/5 (5%)
HIV infection	0/2 (0%)					0/2 (0%)
Immunocompetent patients	9/96 (9%)	0/5 (0%)	0/1 (0%)	0/1 (0%)	0/5 (0%)	9/108 (8%)
Total	24/200 (12%)	2/27 (7%)	0/2 (0%)	0/5 (0%)	0/12 (0%)	26/246 (11%)

A total of 26 specimens were CMV-positive. The patient number was 25. One patient had a lymph node specimen and a pharyngeal tonsil specimen

Allo-PBSCT allogeneic peripheral blood stem cell transplantation, *Auto-PBSCT* autologous peripheral blood stem cell transplantation, *HIV* human immunodeficiency virus

features of histologically confirmed CMV lymphadenitis.

METHODS

The study was approved by the National Taiwan University Hospital (NTUH) Research Ethics Committee (REC No. 202101069RINA) and performed in accordance with the Helsinki Declaration of 1964 and its later amendments. We retrospectively reviewed lymphoid tissues with archived CMV IHC stains in the pathological archives of the Department of Pathology, NTUH. The lymphoid tissues we studied included lymph nodes, pharyngeal tonsils, nasopharynx, tongue base, and spleens. Specimens with at least two convincing CMV-positive cells were considered as CMV-positive.

For clinical data, we reviewed age, sex, biopsy site, clinical presentation, underlying disease, history of chemotherapy and PBSCT, CMV serology and blood viral load, prior history of CMV infection, hemogram, hepatic and renal function, treatment after biopsy, and the subsequent clinical course.

We reviewed the images of positron emission tomography/computed tomography (PET/CT) scan to assess the maximum standardized uptake values (SUVmax) of the lesion and the liver. The patients with lymphoma were evaluated according to the Deauville 5-point scoring system [17].

We reviewed the hematoxylin-and-eosin (HE)- and IHC-stained slides. For CMV-positive cells, we evaluated the distribution (focal or diffuse) and cell morphology. We compared the IHC stains with corresponding HE stains to

Table 2 Patients of cytomegalovirus lymphadenitis and tonsillitis

Case no.	Biopsy site	Infection type	Viremia	Prior chemotherapy or PBSCT	History of other CMV infections
1	Neck LN	Primary infection	(+)	Allo-PBSCT, 12 yrs ago (aplastic anemia)	(−)
2	Neck LN	Reactivation	NA	Allo-PBSCT, 1 yr ago (T-ALL)	(+)
3	Neck LN	Reactivation	(−)	Allo-PBSCT, 5 yrs ago (aplastic anemia)	(+)
4	Neck LN	Reactivation	NA	Allo-PBSCT, 2 yrs ago (BPDCN)	(+)
5	Neck LN	Reactivation	(−)	Allo-PBSCT, 2.5 yrs ago (DLBCL)	(+)
6	Neck LN	Uncertain	NA	Auto-PBSCT, 1 yr ago (FL)	(−)
7	Axillary LN	Reactivation	(−)	Auto-PBSCT, 10 mos ago (HL)	(−)
8	Neck LN	Reactivation	(−)	Auto-PBSCT, 6 mos ago (HL)	(−)
9	Neck LN	Reactivation	NA	Auto-PBSCT, 1.5 yrs ago (HL)	(−)
10	Retroperitoneum LN	Uncertain	NA	Chemotherapy (HL)	(−)
11	Neck LN	Uncertain	NA	Chemotherapy (DLBCL)	(−)
12	Tonsil	Uncertain	NA	Chemotherapy (DLBCL)	(−)
13	Neck LN	Uncertain	NA	Chemotherapy (DLBCL)	(−)
14	Neck LN, tonsil	Uncertain	NA	Chemotherapy (DLBCL)	(−)
15	Neck LN	Uncertain	NA	Chemotherapy (AML)	(−)
16	Neck LN	Uncertain	NA	Chemotherapy (Breast cancer)	(−)
17	Splenic hilar LN	Uncertain	NA	(−)	(−)
18	Neck LN	Uncertain	NA	(−)	(−)
19	Neck LN	Uncertain	NA	(−)	(−)
20	Neck LN	Uncertain	NA	(−)	(−)
21	Neck LN	Uncertain	NA	(−)	(−)
22	Neck LN	Uncertain	(−)	(−)	(−)
23	Neck LN	Uncertain	NA	(−)	(−)
24	Neck LN	Uncertain	(−)	(−)	(−)
25	Neck LN	Reactivation	(−)	(−)	(−)

ALL acute lymphoblastic leukemia, *Allo* allogeneic, *AML* acute myeloid leukemia, *Auto* autologous, *BPDCN* blastic plasmacytoid dendritic cell neoplasm, *CMV* cytomegalovirus, *DLBCL* diffuse large B-cell lymphoma, *FL* follicular lymphoma, *HL* classic Hodgkin lymphoma, *LN* lymph node, *mos* months, *NA* not assessed, *PBSCT* peripheral blood stem cell transplantation, *yrs* years

determine the histological location of CMV-positive cells. Cases with CMV-positive cells in more than ½ monocytoid cell regions were considered diffuse, and those with CMV-positive cells in less than ½ monocytoid cell regions were considered focal. We also counted the maximal cell number of CMV-positive cells per high power field (HPF) (×400, eyepiece diameter, 22 mm).

EBER in situ hybridization (ISH) was conducted according to the routine of the Department of Pathology, NTUH. We evaluated the histological location of EBER-positive cells and counted the maximal number of EBER-positive cells per HPF (×400, eyepiece diameter, 22 mm).

Statistical analyses were conducted using the R language. Categorical data were compared using the Fisher's exact test or chi-square test. The normality of continuous data was examined using Shapiro–Wilk test. Continuous data were compared using the Student's *t* test. A two-tailed P value < 0.05 was considered significant. The median duration was estimated using the Kaplan–Meier method and compared by using the log-rank test.

RESULTS

CMV Prevalence in Lymphoid Tissues

From 2008 to 2020, CMV IHC staining was available in 246 specimens, including lymph nodes ($n = 200$), pharyngeal tonsils ($n = 27$), nasopharynx ($n = 2$), tongue base ($n = 5$), and spleens ($n = 12$). The diagnostic purpose of the archived CMV IHC staining was variable, probably due to suspicious morphology or clinical history. The results of CMV IHC staining are summarized in Table 1. CMV was detected in 12% (24/200) lymph nodes and 7% (2/27) tonsil specimens. None of the nasopharynx (0/4), tongue base (0/5), or spleen (0/12) were CMV-positive.

We further stratified the immune status of patients. The CMV-positive rates of lymph node specimens were 29% (5/17) in allogeneic PBSCT recipients, 29% (4/14) in patients treated with autologous PBSCT, 13% (6/47) in patients treated with intravenous chemotherapy, and 9% (9/96) in immunocompetent patients. CMV was not detected in lymph node specimens from solid organ transplantation recipients (0/3), nor in patients treated with radiotherapy (0/9), oral chemotherapy (0/7), or prolonged steroid therapy (0/5), nor in patients with human immunodeficiency virus (HIV) infection (0/2). The CMV-positive rate of tonsil specimens was 11% (2/18) in patients treated with intravenous chemotherapy. CMV was not detected in tonsil specimens from allogeneic PBSCT recipients (0/2), solid organ transplantation recipients (0/2), or immunocompetent patients (0/5).

Patient Characteristics

The clinical characteristics of CMV lymphadenitis and tonsillitis are listed in Table 2. The 26 CMV-positive specimens (24 lymph nodes and 2 tonsils) were sampled from 25 patients. Case 14 had two CMV-positive specimens. Neck lymph nodes accounted for 88% (21/24) of lymph node specimens.

The male to female ratio was 13:12. The median age was 58 years (range 23–76 years). No patient had CMV detected in the blood, except for Case 1. None of the patients received antiviral therapy after the biopsy. No patient had progression of CMV infection.

Clinical Differences Between CMV-Positive and -Negative Cases

Among allogeneic PBSCT recipients (Cases 1–5), Case 1 was a primary CMV infection (positive serum IgM and negative serum IgG) with viremia, and the other four patients were viral reactivation evidenced by clinical history and serology data. We compared CMV-positive and -negative cases in allogeneic PBSCT recipients. CMV-positive cases were older than CMV-negative cases (mean 52 vs. 26 years, $P = 0.008$). CMV-positive cases occurred in the middle-aged and the elderly (range 37–68 years), but CMV-negative cases occurred in children and young adults (range 8–38 years). After PBSCT, CMV-positive cases developed much later than CMV-negative cases. The median duration from PBSCT to biopsy was 932 days with CMV-

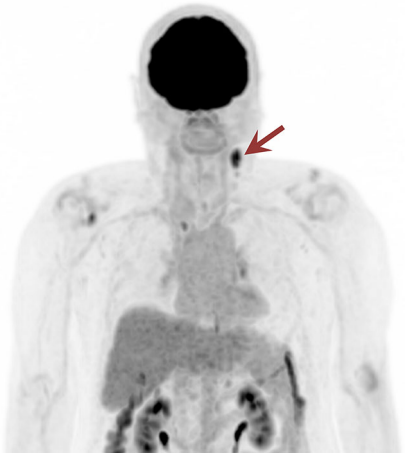


Fig. 1 Positron emission tomography of Case 4 showed high and focal FDG uptake (SUVmax = 7.4) in the left superior jugular node (arrow), suspicious for relapse

Table 3 Results of positron emission tomography/computed tomography scan

Case no.	Lesion SUVmax	Liver SUVmax	Lesion to liver SUV ratio	Deauville score
4	7.40	4.02	1.84	4
5	6.47	4.10	1.57	4
6	12.40	3.98	3.11	5
8	12.90	3.83	3.36	5
9	4.36	2.51	1.73	X
10	6.80	4.12	1.65	4
11	8.30	2.65	3.13	5
12	9.68	3.77	2.56	X
13	8.75	2.88	3.03	5
14 (lymph node)	7.24	2.50	2.89	5
14 (tonsil)	12.60	2.50	5.04	5
25	5.20	3.62	1.43	Not applicable

max maximum, *SUV* standardized uptake value

positive cases and 61 days with CMV-negative cases ($P = 0.020$). We also noted that all CMV-reactivation cases had had other CMV infections during the acute phase after PBSCT, such as retinitis, GI disease, and viremia.

For post-autologous PBSCT patients, CMV-positive cases (Cases 6–9) were older than CMV-negative cases (mean, 58 vs. 45 years, $P = 0.053$). After PBSCT, CMV-positive cases developed earlier than CMV-negative cases. The median duration from PBSCT to biopsy was 370 days with CMV-positive cases and 2593 days with CMV-negative cases ($P = 0.010$). All patients had a history of lymphoma. Hodgkin lymphoma (3/4, 75%) was the most common type in CMV-positive cases, and diffuse large B-cell lymphoma (6/10, 60%) was the most

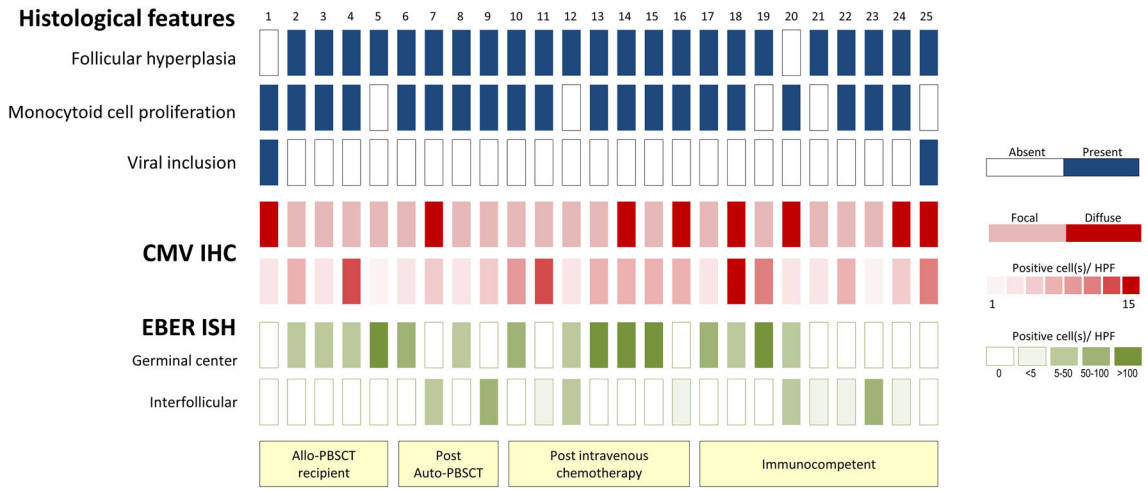


Fig. 2 Pathological findings of the 25 cases (from left to right, Cases 1–25). Hematoxylin-and-eosin staining is shown in the upper three rows (blue); cytomegalovirus (CMV) immunohistochemical (IHC) staining is shown in the middle two rows (red); EBER in situ hybridization (ISH) is shown in the lower two rows (green)

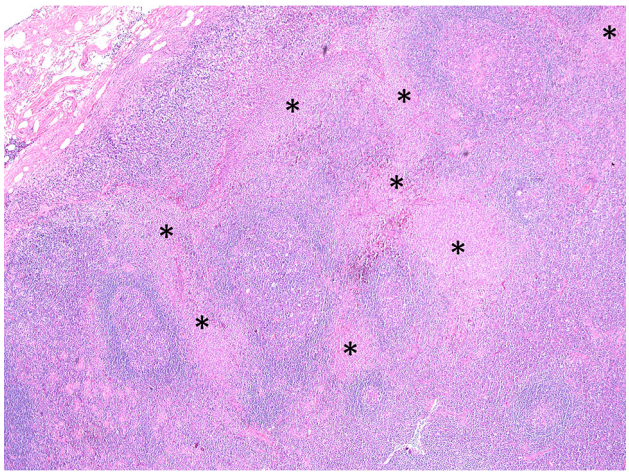


Fig. 3 Hematoxylin-and-eosin staining of Case 9, showing monocytoid cell proliferation (asterisks) and follicular hyperplasia

common type in CMV-negative cases ($P = 0.084$).

The patients treated with intravenous chemotherapy (Cases 10–16) included five lymphoma patients and two other malignancies. For patients treated with intravenous chemotherapy, CMV-positive cases were older-aged than CMV-negative cases (mean 64 vs. 54 years, $P = 0.008$). For CMV-positive cases, we found differences between patients with lymphoma and other malignancies. First, lymphoma patients were older than patients with other malignancies (mean 66 vs. 56 years, $P = 0.049$). Second, lymphadenopathy developed earlier in patients with lymphoma than with other malignancies ($P = 0.040$). The median duration from the most recent chemotherapy to biopsy was 604 days (around 1.7 years) in lymphoma patients. In contrast, CMV lymphadenitis developed 4 years and 11 years after the most recent chemotherapy in acute myeloid

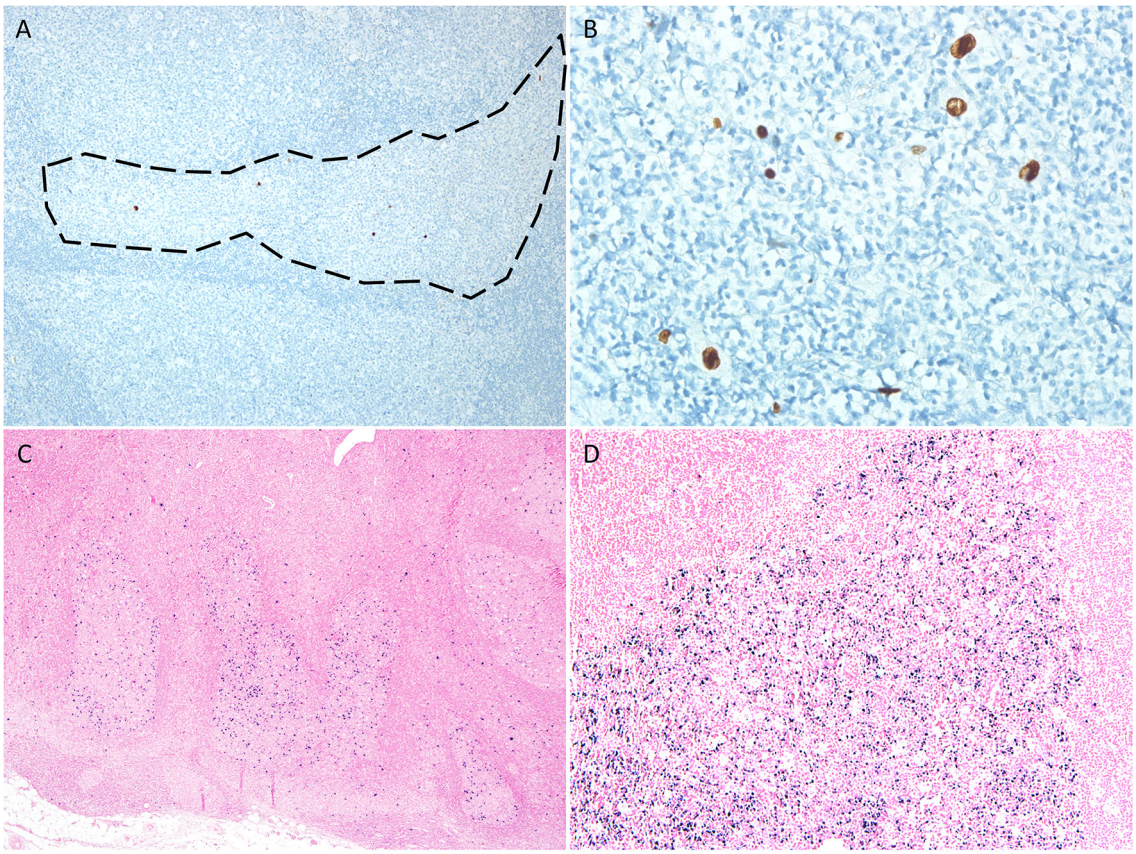


Fig. 4 **A** Cytomegalovirus (CMV) immunohistochemical staining revealed positive cells in the monocytoid cell region (circled with dashed lines) (Case 10). **B** The CMV-positive cells were variable in size and shape (Case 16). **C** EBER-positive cells predominantly in the germinal centers (Case 14). **D** a germinal center with numerous positive cells (Case 13)

leukemia (Case 15) and breast cancer (Case 16) patients, respectively.

For the immunocompetent patients (Cases 17–25), there was no difference in age, sex, or lymph node site between CMV-positive and -negative cases. There was no difference in the frequency of cancer history, hepatitis, autoimmune disease, diabetes mellitus, hypertension, heart disease, liver cirrhosis, renal disease, chronic obstructive lung disease, central nervous system disease, or congenital anomaly.

Clinical Presentation and PET/CT Scan Results

For CMV-positive patients, the most common clinical presentation was neck mass (13/25, 42%), followed by asymptomatic image findings during cancer follow-up (10/25, 40%). Among the patients with neck lymphadenopathy, 43% (9/21) were solitary, 29% (6/21) were multiple unilateral, and 29% (6/21) were bilateral.

Only one patient presented with fever (½5, 4%). The hemogram showed mild abnormalities, like anemia (9/25, 36%), thrombocytopenia (8/25, 32%), and atypical lymphocytes in the peripheral blood (2/25, 8%). Slightly elevated aspartate aminotransferase was noted in 8% (2/25) patients. Just 36% (9/25) patients had no abnormalities in their laboratory data. The extent of fever and laboratory abnormalities was all mild. More specifically, none achieved any individual criterion of CMV syndrome [7].

Many asymptomatic patients had a positive PET/CT scan mimicking lymphoma relapse and

thus underwent biopsy. A representative image is shown in Fig. 1. We reviewed the available pre-biopsy PET/CT scan images (Table 3). SUV-max of lesions ranged 4.36–12.90 (mean 8.51). All the cases had a lesion to liver SUV ratio of > 1 (range 1.43–5.04). In other words, all lesions showed increased FDG uptake compared to the liver. By the Deauville scoring system, 80% (8/10) of lymphoma patients had positive PET/CT results (Deauville score 4–5).

We further calculated the CMV-positive rate in PET/CT false-positive cases. From 2008 to 2020, we found 36 lymphoma patients who had a negative biopsy but a positive PET/CT finding (Deauville score 4 or 5), of whom 75% (27/36) had available CMV IHC stains. The CMV-positive rate was 30% (8/27) in these lymphoma patients with false-positive PET/CT results.

Histopathological Characteristics

The histopathological findings of individual cases are plotted in the upper panel of Fig. 2 (in blue). Morphologically, CMV lymphadenitis is characterized by follicular hyperplasia (22/24, 92%) and monocytoid cell proliferation (20/24, 83%). A representative photograph of CMV lymphadenitis is shown in Fig. 3. The two cases of CMV tonsillitis showed follicular hyperplasia and intraepithelial lymphocyte proliferation. Viral inclusions were observed in 8% (2/25) of patients.

CMV IHC staining demonstrated positive cells, commonly among the monocytoid cells (Fig. 4A). The results are plotted in the middle panel of Fig. 2 (in red). The CMV-positive cells were distributed diffusely (8/25, 32%) or focally (17/25, 68%). The CMV-positive cells ranged from 1 to 14 cells/HPF. The presence or absence of viral inclusion in HE stain is irrelevant to the positive cell amount in IHC stain. The cell size and morphology of CMV-positive cells were considerably diverse (Fig. 4B), suggesting that multiple cell types were infected.

By EBER ISH, we found that the majority (23/25, 92%) of CMV-positive cases had Epstein–Barr virus (EBV) coinfection. The results of EBER ISH are plotted in the lower panel of Fig. 2 (in green). The distribution of EBER-positive cells was peculiar. The EBER-positive cells were frequently located in few germinal centers (Fig. 4C, D). Thirteen cases had EBER-positive cells predominantly in the germinal centers, and five of them had more than 100 EBER-positive cells/HPF.

DISCUSSION

The current understanding of CMV lymphadenitis is based on expert opinions and rare studies. There have been only two small-scale case series (3 and 7 cases, respectively) published in the 1990s [15, 16] and a few cases in the 2000s [18–20]. Our work has been the most comprehensive study of CMV lymphadenitis, and the case number exceeded the total of the previous case series.

CMV has a broad tissue tropism [6]. Results of CMV IHC staining have been extensively investigated in gastrointestinal tissues [21, 22], but the data on other tissues remain limited. In one study, CMV-positive cells were noted in rare head and neck specimens but were absent in any hematological specimens [23]. Among lymphoid organs, we found that CMV was the most common in the lymph nodes, followed by the pharyngeal tonsils. We did not detect CMV in any nasopharynx, tongue base, or spleen specimen.

CMV causes infections in immunocompetent and immunocompromised hosts. In immunocompetent patients, the clinical features of CMV lymphadenitis were heterogeneous. The risk was not higher in patients of old age or with chronic diseases. In the other patients, we detected CMV in allogeneic PBSCT recipients, post-autologous PBSCT patients, and post-chemotherapy patients, but not in any solid organ transplantation recipients or patients with HIV infection.

The most common reason for iatrogenic immunodeficiency was treatments for malignant lymphoma. Other malignancies were relatively uncommon. CMV lymphadenitis typically developed a few years after cancer treatment (2–4 years after allogeneic PBSCT, 1–2 years after autologous PBSCT, and 1–4 years after the most recent chemotherapy), most

commonly in the middle-aged and the elderly (range 37–76 years). The patient characteristics are helpful for recognizing CMV lymphadenitis in a diagnostic setting.

The clinical manifestations of most cases were a palpable neck mass in afebrile adults. Many patients were even asymptomatic. The clinical presentation was different from IM. The disease course of our cases was self-limiting, and no patients needed antiviral therapy. These data indicated that our cases were subclinical infections different from reactivation in critically ill or immunocompromised patients [24, 25].

The asymptomatic patients underwent a biopsy because of positive PET/CT scan results. In our study, all the CMV-positive lesions showed more FDG uptake than the liver, which means a Deauville score of 4–5 in lymphoma patients. Active inflammation or infection can cause false-positive results in PET scans [26], and a wide variety of etiologies have been reported. CMV infections can show increased FDG uptake in PET scans. For example, lymphadenitis [20], GI infections [27, 28], and infectious mononucleosis [29]. A case of CMV lymphadenitis mimicking lymphoma relapse in PET scan has been reported [20]. CMV infection was considered a rare cause of false-positive PET scan results. In contrast, we found that CMV infection accounted for 30% of tissue-proved false-positive PET/CT results in lymphoma patients. Our data indicated that CMV infection is a common etiology of false-positive PET scan results during post-treatment follow-up of lymphoma patients.

Furthermore, we found that most CMV-positive cases had EBV coinfection, and that the EBER-positive cells were frequently in germinal centers. These two findings have never been reported in CMV lymphadenitis. Reviewing the photographs of case reports, we found a similar case showing EBER-positive cells in the germinal centers [19]. An EBER-positive germinal center is a unique staining pattern. In reactive lymphoid hyperplasia, most EBER-positive cells are in the interfollicular area [30, 31]. Only a few cases of EBER-positive germinal centers have been reported [32–34]. The high frequency of EBER-positive germinal centers has never been reported in any other diseases.

The cooperation of human herpes viruses has been well known in EBV and human herpesvirus 8 (HHV8) [35]. Different from EBV and HHV8 coinfection, EBV and CMV infect two cell populations in CMV lymphadenitis. The germinal center cells and monocytoid cells do not directly contact each other. The two viruses have to interact indirectly, for example, through cytokines and extracellular vesicles [36, 37]. However, mechanistic studies will need advanced study models like humanized mice [38] or tonsil organoids [39] because CMV and EBV infect only human cells.

In allogeneic PBSCT recipients, CMV lymphadenitis with EBER-positive cells should be distinguished from non-destructive PTLD [40, 41], especially florid follicular hyperplasia PTLD [42]. The distinction between florid follicular hyperplasia PTLD and other reactive lymphoid hyperplasia is extremely vague [41]. We recommend CMV IHC staining in cases with (1) monocytoid cell proliferation or (2) a history of symptomatic CMV infection. If CMV IHC staining is positive, diagnosing CMV lymphadenitis should be more appropriate.

The study has some limitations. The single-center study was based on only Taiwanese patients. We think that two factors may contribute to a high incidence of CMV lymphadenitis in Taiwan. First, the seroprevalence of CMV is high in Taiwan [1]. Second, PET/CT is widely available in Taiwan, where the number of PET/CT scanners per million people is one of the highest in the world [43]. Furthermore, the CMV-positive rate was biased because CMV IHC stains were performed in cases with suspicious morphology or history, not in all cases. We believe that a prospective large-scaled multi-country study in the future will better support the conclusions, especially when CMV quantitative detection can be prospectively applied in the plasma and tissue.

CONCLUSIONS

We report the clinical features of CMV lymphadenitis. These patients were not primary CMV infection with IM-like syndrome. Instead, most cases were subclinical localized

reactivation, with mild or no symptoms. The lymphadenopathy typically developed a few years after lymphoma treatments, such as allogeneic and autologous PBSCT, and intravenous chemotherapy, in the middle-aged and the elderly. The lesions showed increased uptake compared to the liver in PET scans, thereby mimicking lymphoma relapse. Our data indicated that CMV infection was a common reason for false-positive PET scan results in lymphoma patients. CMV-positive cases frequently had EBV coinfection in germinal centers, and hence PTLD is a differential diagnosis in allogeneic PBSCT recipients.

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Author Contributions. S-CY reviewed the pathological slides and wrote the manuscript; K-YK reviewed the PET scan images; S-CT designed the study and interpreted the data; T-CH, C-LC, MY, R-LH, C-NC, T-CC, and T-LY collected the clinical data. H-TL performed immunohistochemistry and in situ hybridization.

Disclosures. Shan-Chi Yu, Kuan-Yin Ko, Shu-Chun Teng, Tai-Chung Huang, Hsiao-Ting Lo, Chieh-Lung Cheng, Ming Yao, Ruey-Long Hong, Chun-Nan Chen, Tseng-Cheng Chen, and Tsung-Lin Yang have nothing to disclose.

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Data Availability. The datasets generated during the current study are available from the corresponding author on reasonable request.

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