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Review Article

A review of EBV-positive mucocutaneous ulcers focusing on clinical and pathological aspects

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Epstein-Barr virus (EBV)-positive mucocutaneous ulcers (EBVMCUs) were first described as a lymphoproliferative disorder in 2010. Clinically, EBVMCUs are shallow, sharply circumscribed, unifocal mucosal or cutaneous ulcers that occur in immunosuppressed patients, including those with advanced age-associated immunosenescence, iatrogenic immunosuppression, primary immune disorders, and HIV/AIDS-associated immune deficiencies. In general, patients exhibit indolent disease progression and spontaneous regression. Histologically, EBVMCUs are characterized by the proliferation of EBV-positive, variable-sized, atypical B-cells. According to conventional histopathologic criteria, EBVMCUs may diagnosed as lymphomas. However, EBVMCUs are recognized as pseudomalignant lesions because they spontaneously regress without anti-cancer treatment. Therefore, overtreatment must be carefully avoided and multilateral differentiation is important. In this article, we reviewed previously reported EBVMCUs focusing on their clinical and pathological aspects in comparison with other EBV-positive B-cell neoplasms.

Keywords: EBV-positive mucocutaneous ulcer, clinical features, pathological features, immunosuppression

INTRODUCTION

Epstein-Barr virus (EBV)-positive mucocutaneous ulcers (EBVMCUs) were first described as a distinct clinicopathological entity in 2010 when Dojcinov *et al*. reported 26 patients with ulcerative lesions confined to the oropharynx, skin, and gastrointestinal tract.[1] The lesions were characterized by the proliferation of EBV-positive, variably sized, atypical B-cells that may resemble Hodgkin and Reed-Sternberg (HRS)-like cells. As the patients were immunosuppressed, demonstrating either age-related immunosenescence or iatrogenic immunosuppression, EBVMCUs were later described as a new disease type by the World Health Organization.[2]

EBVMCUs are shallow, sharply circumscribed, mucosal or cutaneous ulcers with underlying polymorphous infiltration. The HRS-like cells that are observed in the lesions, as well as any observed immunoblasts, demonstrate B-cell immunophenotypes, i.e., CD20 expression; therefore, the ulcers were originally classified as EBV-positive diffuse large B-cell lymphomas (EBV-positive DLBCLs), but were later recognized as a unique disease type, pathologically distinct from lymphomas. However, some characteristics of EBVMCUs overlap with those of immunodeficiency-associated lymphoproliferative disorders (LPDs).

In general, patients with EBVMCUs exhibit indolent disease progression and spontaneous regression. Although radiotherapy or chemotherapy may be considered as therapeutic options, most patients have spontaneous regression when their immunosuppression is reduced or discontinued; only one disease-associated death has been reported.[3] In this article, we describe the clinicopathological aspects of EBVMCUs.

EBV BIOLOGY

EBV, also known as human herpes virus 4, is a member of the herpes virus family and is one of the most common human viruses.[4-8] Approximately 95% of people become infected with this virus during childhood because it may be directly transferred between individuals through saliva. Although infections sometimes manifest as infectious mononucleosis, many are asymptomatic.

EBV preferentially infects B lymphocytes through the interaction of the major viral surface glycoprotein (gp350) with a B lymphocyte receptor (CD21); a second viral

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glycoprotein (gp42) also binds the class II major histocompatibility complex molecules on the B lymphocyte, which function as co-receptors for the virus. In most people, EBV infections are transient, but some malignant tumors are associated with EBV infections (Table 1). EBV is also associated with malignant lymphomas and LPDs, including DLBCL, classic Hodgkin lymphoma (cHL), Burkitt lymphoma (BL), immunodeficiency-associated LPDs, and extranodal NK/T cell lymphoma, nasal type.

By minimizing viral gene transcription, EBVs can avoid the host immune response; however, the mechanism by which the virus is able to avoid the host immune response has not been elucidated. The EBV infection process has two phases, a lytic and a latent phase. First, during the lytic phase, the virus particles are amplified. Then, during the latent phase, the viral genome is maintained within the host cell. During the latent phase, viral gene products upregulate the expression of a variety of B-cell genes. EBV-infected cells express only six types of nuclear proteins (EBNA1, 2, 3A-C, and LP) and three types of membrane proteins (LMP1, LMP2A, and LMP2B), which mediate the transforming role of EBV in B cells. The latency phase of the infection may be described as one of three types, each determined by the specific viral gene expression pattern. In Latency I, EBV expresses only EBNA1, which is expressed in all infected cells, and causes viral genome maintenance and replication. Latency II is an intermediate pattern involving the expression of many proteins. Latency IIa is a transitional form of Latency III that helps the infected cells avoid cytotoxic T lymphocytes. This form is characterized by the expression of LMP1, LMP2A, and EBNA1, and the expression of EBV-encoded small RNAs and *Bam*HI fragment A rightward transcript microRNA. Latency IIb is a form that precedes the transition to Latency III and is characterized by the expression of EBNA2 without LMP1 expression.[9] Latency III is a phase during which all gene products are expressed. Latency I is associated with BL, Latency II is associated with cHL and NK/T cell lymphoma, and Latency III is associated with immunodeficiency-associated LPDs.

During EBV infection, the molecular pathways that control the cell cycle and suppress apoptosis are activated; LMP1 is one of the important factors involved in activating these pathways. LMP1 activates the nuclear factor-κB (NF-κB) pathway, and NF-κB transcription factors control lymphoid cell proliferation and hyperactive NF-κB signaling promotes malignant transformation. EBV-infected cells also express the bcl-2 protein, which may enable the cells to become resistant to apoptosis.

Table 1. EBV-associated diseases.

B-cell lymphoproliferations
Infectious mononucleosis
EBV-positive diffuse large B-cell lymphoma, NOS
EBV-positive mucocutaneous ulcer
Diffuse large B-cell lymphoma associated with chronic inflammation
Lymphomatoid granulomatous
Plasmablastic lymphoma
Burkitt lymphoma
Classical Hodgkin lymphoma
Immunodeficiency-associated lymphoproliferative disorders
LPD associated with primary immune deficiencies
Lymphomas associated with HIV
Post-transplant lymphoproliferative disorders
Other iatrogenic immunodeficiency-associated lymphoproliferative disorders
T-cell lymphoproliferations
EBV-positive T-cell and NK cell lymphoproliferative diseases of childhood
Aggressive NK-cell leukemia
Extranodal NK/T-cell lymphoma, nasal type
Primary EBV-positive nodal T- or NK-cell lymphoma
Epithelial cell malignant tumors
Nonglandular nasopharyngeal carcinoma
Lymphoepithelioma-like carcinoma (salivary, thymus, lungs, stomach)
Breast carcinoma
Hepatocellular carcinoma
Mesenchymal malignant tumors
Leiomyosarcoma
Follicular dendritic cell sarcoma

EBV-ASSOCIATED LPDs

Among the EBV-associated LPDs, immunodeficiency-associated LPDs have been garnering attention in recent years.[10-12] Immunosuppression is believed to affect the homeostasis of the persistent infection state, enabling the appearance of EBV-associated LPDs. In the World Health Organization disease classification, there are four categories of immunodeficiency-associated LPDs: LPDs associated with primary immune disorders, lymphomas associated with human immunodeficiency virus (HIV) infections, post-transplant LPDs (PTLDs), and other iatrogenic immunodeficiency-associated LPDs (Oii-LPDs). Some Oii-LPD cases fulfill the pathological concept of DLBCLs, NK/T cell lymphomas, and cHL. For example, Oii-LPDs sometimes exhibits HRS cells that are positive for CD30. In Asia, including in Japan and Korea, there are many reports of Oii-LPDs following methotrexate (MTX) treatment. Oyama *et al*. reported EBV-positive DLBCLs in elderly (>60 years old) Japanese patients without predisposing immunodeficiencies.[11] They suggested that EBV-positive DLBCLs are related to the immune depression resulting from the aging process. Thus, in 2010, ulcerative lesions related to iatrogenic immunosuppression or age-related immunological deterioration were recognized as EBVMCUs.[1,13]

EBVMCU CLINICAL FEATURES

Among EBVMCU case reports to date, the median patient age was 66.4 years (range, 16-101 years, Table 2[1,3,6,14-48]), with a slight female predominance; female patients comprised 58.3% of cases. Factors contributing to the female prevalence may include some that are involved in rheumatoid arthritis, which is also more common among females than males. Patients demonstrate sharply circumscribed mucosal

Table 2. Case reports and series. (2010-2018)

	Cases	Mean age (years)	Age range (years)	Sex (male/female)
Other Iatrogenic Immunodeficiency-Associated EBVMCU				
Oropharyngeal	46	65.2	17-84	17/ 29
Skin	14	66.2	49-81	3/ 11
Gastrointestinal	20	59.9	26-81	11/ 9
EBVMCU due to age-associated immunosenescence				
Oropharyngeal	23	76.7	51-101	10/13
Skin	7	81.3	74-89	5/2
Gastrointestinal	3	69.3	64-79	1/ 2
HIV/AIDS-Associated EBVMCU				
Palate	2 cases (54-year-old male, 36-year-old female)[20]			
Primary Immunodeficiency-Associated EBVMCU				
Gingiva	45-year-old female with T-cell deficiency[14]			
Esophagus	61-year-old male with hypogammaglobunemia[15]			
Nasopharyngeal	16-year-old male with CHARGE syndrome[3]			
Chronic Antigenic Stimulation-Associated EBVMCU				
Sinus	59-year-old female[46]			
EBVMCU of Unclear Etiology				
Oropharyngeal	2 cases (49-year-old female, 49-year-old female)[3, 6]			
Total	121	66.4	16-101	50/71

EBVMCU cases in 2010 to 2018.[1, 3, 6, 14-48]

or cutaneous ulcers,[49] with >70% of the ulcers occurring in the oral mucosa (Figure 1). As EBVs are secreted into saliva and local trauma or inflammation is likely to occur in the oral cavity, there is a possibility of EBVMCUs developing intraorally.[50] Some cases result in eating disorders without any systemic symptoms, including lymph node swelling or B symptoms, i.e., fever, night sweats, and weight loss.

EBVMCUs emerge when the host-virus homeostasis is not maintained, i.e., when the virus overwhelms the host's immune response. Specifically, ulcer eruption may result from immune abnormalities caused by inflammation and immunosuppression. Dojcinov *et al*. first reported the ulcers in patients characterized by advanced age who were undergoing iatrogenic immunosuppression using MTX, azathioprine, cyclophosphamide, or tumor necrosis factor-α inhibitor.[1] Patients with EBVMCUs who were not using immunosuppressants were elderly (>60 years old), leading to the suggestion that EBVMCUs also develop as a result of age-associated immunodeficiency that is mainly caused by T cell hypofunction.[1] After their report, EBVMCUs were also reported in patients with primary immunodeficiencies,[14,15] solid organ or bone marrow transplant recipients,[16-19] and in those with HIV/ acquired immune deficiency syndrome (AIDS).[20] One case of ulceration was reported in an immunosuppressed patient with inflammatory bowel disease; therefore, the possibility of EBVMCUs being involved in such cases needs to be considered.[21] Among the previously reported cases, 80 (66.1%) were iatrogenic immunodeficiency-associated EBVMCUs and 33 (27.3%) were associated with age-associated immunosenescence. EBVMCUs have also been reported in patients with primary immunodeficiencies (3 cases) and in those with HIV/AIDS (2 cases). During follow-up (1-180 months), spontaneous regression was observed in 6 cases and complete remission was observed in 79 cases following the reduction of immunosuppression, chemotherapy, or radiotherapy; 7 cases relapsed,[1,3,38] but only 3 developed progressive disease.[3,15,22]

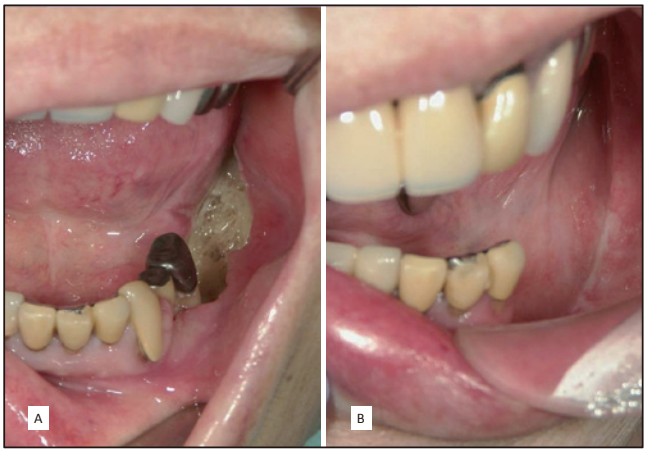

Fig. 1.
Macroscopic findings of a gingival Epstein-Barr virus-positive mucocutaneous ulcer.
The ulcer appearance while the patient was undergoing methotrexate treatment (***A***). After reducing the methotrexate dose, the lesion spontaneously resolved (***B***).

Before EBVMCUs were defined, there were several

reports of oral ulcerations occurring as a side effect of MTX therapy.[51] In such cases, the ulcers regressed following reductions in the immunosuppression regimes. Thus, these ulcers were not considered to be EBV-related, but rather the result of treatment-associated toxicity. These ulcers were also regarded as being nonspecific based on microscopic observations; however, most of the case reports only described the associated clinical features without histological evaluation.

CLINICAL MANAGEMENT AND PROGNOSIS

Almost all EBVMCU cases have some degree of spontaneous regression following cessation or reduction of the immunosuppressive treatment for autoimmune disorders such as rheumatoid arthritis. Some patients with these lesions have been treated by radiotherapy and rituximab or other forms of chemotherapy, and often demonstrate complete remission. However, whether the lesions responded to the treatment or spontaneously resolved remains unknown.

The ulcers rarely spread to distant sites, but they have been observed to spread locally and relapse after regression. Hodgkin lymphoma (HL)-like EBVMCUs sometimes do not regress.[52] Therefore, the patients in such cases are treated by radio- or chemotherapy; these patients also often exhibit remission. As progressive disease and the subsequent development of HL was observed in a rare case, the ulcers may also be associated with HL.[22] Other than this one case, there has been only one disease-associated death among the reported cases and series.[3] Thus, other EBV-positive LPDs have a poorer prognosis than EBVMCUs.

PATHOLOGICAL FEATURES

The localized mucosal or cutaneous ulcers are characterized by the presence of EBV-positive atypical immunoblasts or HRS-like cells (Figure 5). The atypical cells range in size from small to large, and accompany dense polymorphic infiltration with the variable presence of other inflammatory cells such as plasma cells (polymorphous type) (Figure 2, 4). Some cases have demonstrated histological findings similar to those associated with DLBCL or cHL (Figure 3, 5). Occasionally atypical lymphoid cells demonstrated plasmacytoid features (Figure 6). In these cases, the cells exhibit characteristics of activated B lymphocytes, including (in most cases) CD20 and CD30 expression. These cells are often also positive for CD79a, PAX5, and OCT2, with variable expression of BOB1. CD15 is expressed in approximately half of the cases and MUM1 is typically expressed.[2] These immunohistochemical results strongly support the origination of these atypical cells from B cells. Although these histological findings are similar to those associated with cHL, many of the B lymphocytes being CD20-positive is different from cHL. In addition, extranodal lesions are rare in patients with cHL. Thus, cHL and EBVMCU can be distinguished based on their respective clinicopathological features. HRS-like cells are seen in EBV-positive LPDs, but

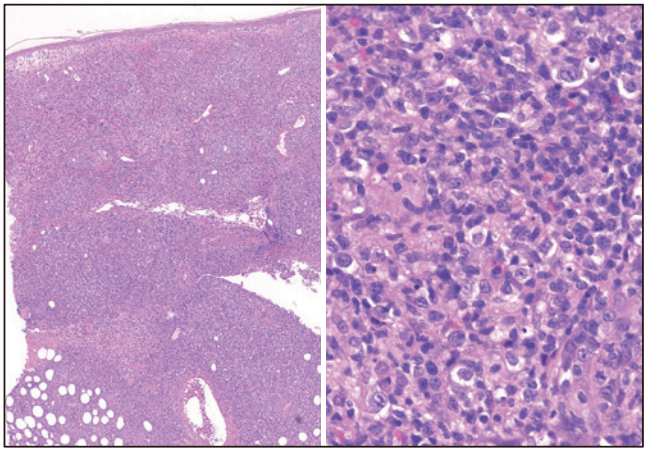

Fig. 2.
A cutaneous Epstein-Barr virus-positive mucocutaneous ulcer (polymorphous type) on the lower leg of a 72-year-old female undergoing methotrexate treatment.
Atypical lymphoid cells with a polymorphous morphology are infiltrating the epidermal, dermal, and subcutaneous tissues.
After reducing the methotrexate dose, the lesion spontaneously resolved.

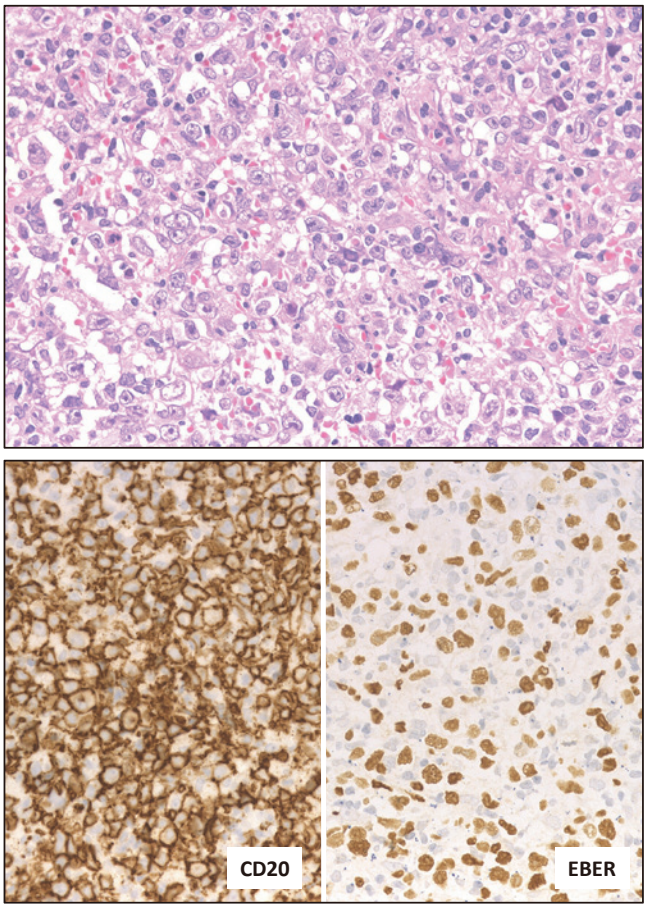

Fig. 3.
An Epstein-Barr virus-positive mucocutaneous ulcer (diffuse large B-cell lymphoma [DLBCL] type) in the nasopharyngeal mucosa of an 80-year-old female undergoing methotrexate treatment.
This case resembles DLBCL morphology.
The lymphoid cells are positive for CD20 and Epstein-Barr virus-encoded small RNA.
Following chemotherapy that included rituximab, the lesion showed complete remission.

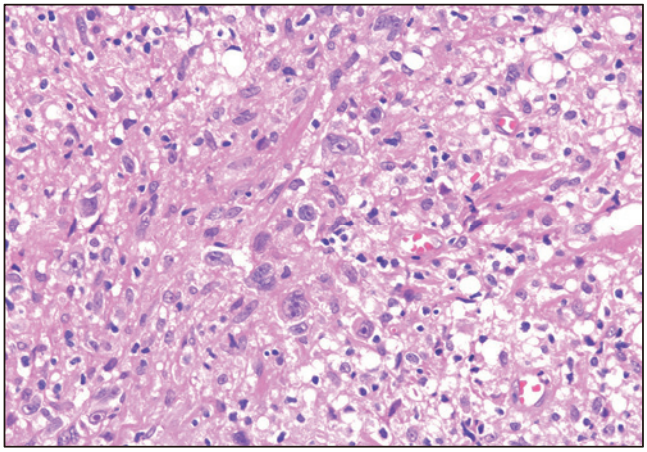

Fig. 4.
A gingival Epstein-Barr virus-positive mucocutaneous ulcer (polymorphous type) in a 91-year-old male undergoing methotrexate treatment.
The lesion showed polymorphous morphology with Hodgkin and Reed-Sternberg-like cells.

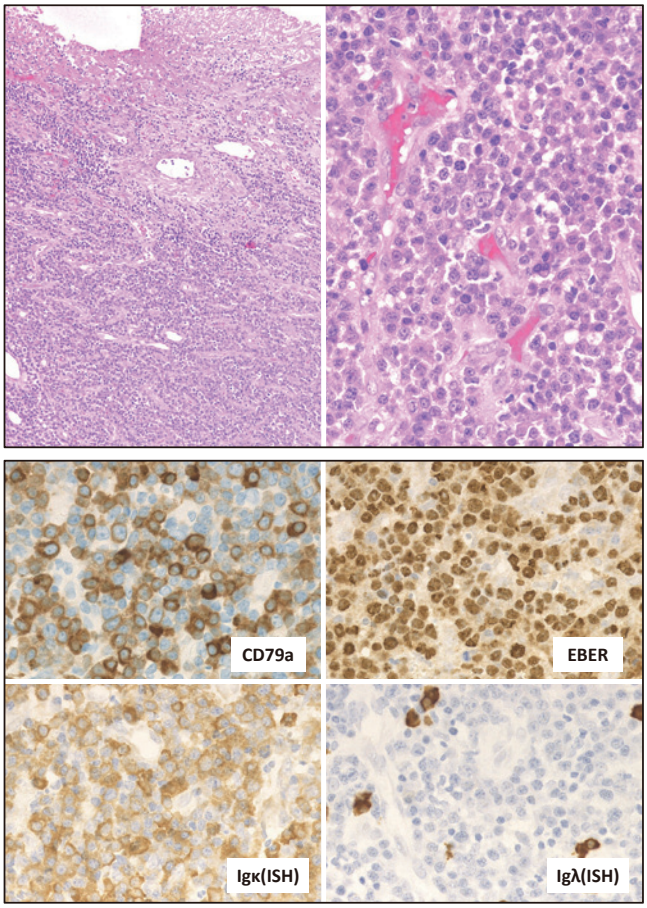

Fig. 5.
A gingival Epstein-Barr virus-positive mucocutaneous ulcer (diffuse large B-cell lymphoma [DLBCL] type) in a 69-year-old male.
Large, atypical lymphoid cells, with plasmacytoid differentiation are infiltrating the subepithelial lesion.
This lesion is similar to a DLBCL with plasma cell differentiation.
These atypical lymphoid cells are CD20-negative and positive for CD79a and Epstein-Barr virus-encoded small RNA.
Immunoglobulin light chain analysis, using in situ hybridization, showed a κ chain monotype.

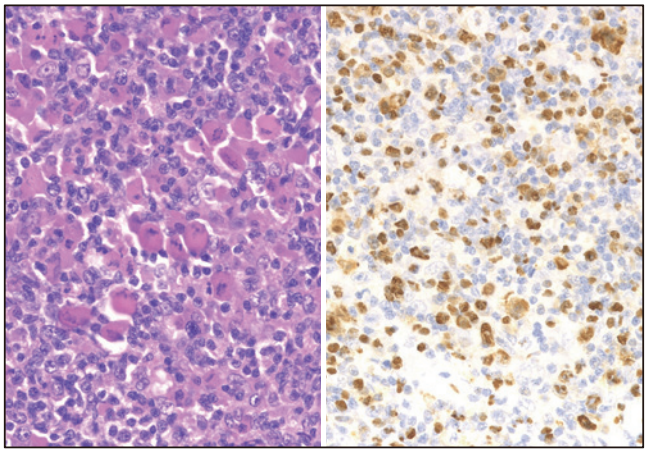

Fig. 6.
A lingual Epstein-Barr virus-positive mucocutaneous ulcer (mucosa-associated lymphoid tissue lymphoma type) in a 66-year-old female undergoing methotrexate treatment.
Atypical, medium-sized lymphoid cells demonstrate plasmacytoid features and Russel bodies.
In situ hybridization shows that the atypical cells are Epstein-Barr virus-encoded small RNA-positive.
After reducing the methotrexate dose, the lesion spontaneously regressed.

the B lymphocytes in patients with infectious mononucleosis or PTLD are CD30-positive and CD15-negative; CD15 expression is also downregulated in cases of EBV-positive, MTX-associated LPD.

Mucosal and cutaneous EBVMCU lesions exhibit dense polymorphic infiltration with the variable presence of inflammatory cells, including plasma cells, histiocytes, lymphocytes, and eosinophils. Apoptotic bodies and necrosis are also often noted. These infiltrating lymphocytes are mainly CD8-positive T cells and 31% of them demonstrate *T cell receptor* (*TCR*) gene rearrangements.[1]

EBV-positive DLBCL is a disease that requires distinction from EBVMCUs based on its histology and prognosis. EBV-positive DLBCLs were initially reported to be associated with aging. This disease is characterized by poor outcomes, and is a high-grade lymphoma that presents with CD20-positive, CD30-positive, and sometimes CD15-positive HRS-like cells. Polymerase chain reaction characterization revealed more clonal *immunoglobulin heavy chain* (*IgH*) gene rearrangements associated with EBV-positive DLBCL than with EBVMCUs.[1,13] However, differentiating between EBVMCUs and EBV-positive DLBCLs is difficult. Aside from EBVMCUs typically being "localized lesions", consideration of the clinical findings is necessary when distinguishing between the two.

GENETIC FEATURES

There are several reports on the search for clonality in age-related and immunodeficiency-related EBVMCUs.[1,23] Dojcinov *et al*. reported that 38% of their cases exhibited *IgH* gene rearrangements and 31% exhibited *TCR* gene rearrangements when evaluated using polymerase chain reaction.

Age-related EBVMCUs have been found to have lower clonality than EBV-positive DLBCLs,[13] suggesting that EBVMCUs are not true tumors.

As EBV-positive cells are B lymphocytes, the *IgH* gene rearrangements of EBVMCUs are associated with B cells. Furthermore, EBVMCUs may present *TCR* gene rearrangements even though EBV-positive cells are B cells. A previous report suggested that *TCR* gene rearrangements are associated with a limited T cell repertoire associated with EBV infections in patients who are aged and immunosuppressed.[1] The T cells responsible for immune responses are the mature memory T cells that are CD8-positive. It is possible that T cells cannot recognize the EBV epitope because T cell epitope recognition is restricted in older patients and in those with other immunodeficiencies.[53] This may enable an increase in the number of EBV-positive cells. As a result, the human body may allow the proliferation of mature memory T cells to elicit an immune response and be involved in clonality.

Ohata *et al*. investigated several gene mutations (*MYD88, CD79A, CD79B, CARD11, and EZH2*), and although none were associated with EBVMCUs, more than 30% of tumor tissues from EBV-negative DLBCLs contained mutations.[24]

CONCLUSION

EBVMCUs are a newly described entity in the World Health Organization classification.[2] They are ulcerative lesions localized to the skin and mucosa that are characterized by the presence EBV-positive variably sized B-cells. To appropriately treat EBVMCUs, clinicians need to be able to distinguish them from DLBCLs and cHL based on their clinicopathological findings. Although there is currently no established treatment regimen due to the lack of evidence, future case studies are expected to rectify this.

CONFLICT OF INTEREST

The authors report no potential conflicts of interest.

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