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

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Epstein-Barr virus (EBV)-positive mucocutaneous ulcers (EBVMCU) were first described as a lymphoproliferative disorder in 2010. Clinically, EBVMCU 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, EBVMCU are characterized by the proliferation of EBV-positive, variable-sized, atypical B-cells. According to conventional histopathologic criteria, EBVMCU may be diagnosed as lymphomas. However, EBVMCU 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 EBVMCU 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 (EBVMCU) were first described as a distinct clinicopathological entity in 2010 when Dojcinov et al.1 reported 26 patients with ulcerative lesions confined to the oropharynx, skin, and gastrointestinal tract. 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, EBVMCU were later described as a new disease type by the World Health Organization.2

EBVMCU 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 DLBCL), 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 EBVMCU 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 EBVMCU.

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 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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latency II is an intermediate pattern involving the expression of a variety of B-cell genes. EBV-infected cells express only six types of nuclear proteins (EBNA1, 2A-C, and LP) and three types of membrane proteins (LMP1, LMP2A, and LMP2B), which mediate the transforming role 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 BamHI 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.

EBV-associated diseases

| B-cell lymphoproliferations |
|-----------------------------|
| Infectious mononucleosis    |
| EBV-positive diffuse large B-cell lymphoma, NOS |
| 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 |

EBVMCU clinical features

Among EBVMCU case reports to date, the median patient age was 66.4 years (range, 16-101 years, Table 2), 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
or cutaneous ulcers, 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. 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. 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. After their report, EBVMCUs were also reported in patients with primary immunodeficiencies, solid organ or bone marrow transplant recipients, and in those with HIV/ acquired immune deficiency syndrome (AIDS). 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. 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, but only 3 developed progressive disease.

Before EBVMCUs were defined, there were several cases reported, and Table 2 summarizes the case reports and series from 2010 to 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) |
| Primary Immunodeficiency-Associated EBVMCU | | | |
| Gingiva | 45-year-old female with T-cell deficiency |
| Esophagus | 61-year-old male with hypogammaglobulinemia |
| Nasopharyngeal | 16-year-old male with CHARGE syndrome |
| Chronic Antigenic Stimulation-Associated EBVMCU | | | |
| Sinus | 59-year-old female |
| EBVMCU of Unclear Etiology | | | |
| Oropharyngeal | 2 cases (49-year-old female, 49-year-old female) |
| Total | 121 | 66.4 | 16-101 | 50/71 |

*EBVMCU cases in 2010 to 2018.1, 3, 6, 14-48*

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).
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
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 Dojcicov 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, 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. 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. 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.

CONCLUSION
EBVMCUs are a newly described entity in the World Health Organization classification. 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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