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EBV-positive mucocutaneous ulcers: a presentation of two cases and a brief literature review

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Abstract

Mucocutaneous ulcers associated with the Epstein Barr virus constitute an EBV-induced B-cell lymphoproliferative disorder first described in 2010 by Stefan D. Dojcinov et al. These lesions can occur in association with a spectrum of immunosuppressive conditions, including primary immune deficiency, Human Immunodeficiency Virus (HIV) infection, post-transplantation and the use of methotrexate or tumor necrosis factor-alpha (TNF-a) antagonists. Patients clinically present with slowly developing indurated cutaneous and/or mucosal ulcers, especially in the oropharynx. Histopathology reveals circumscribed ulcers containing a mixture of lymphocytes, plasma cells, histiocytes, eosinophils and large transformed cells resembling Hodgkin and Reed-Sternberg cells. The adjacent squamous epithelium presents reactive nuclear atypia and pseudoepitheliomatous hyperplasia. The large transformed cells show positivity for CD20, CD30, Oct-2, PAX5 and EBV. These cells are also positive for MUM1, yet lack CD10 expression, with absent or focal positivity for BCL6. Despite the presence of highly atypical cells, the clinical course is indolent, without progression to disseminated disease. We report herein two cases of diagnosed EBV-positive mucocutaneous ulcers to add to the relatively few cases previously described in the literature.

Keywords: Epstein Barr Virus, EBV positive mucocutaneous ulcer, Immunosuppression, Lymphoproliferative

Resumo

A úlcera mucocutânea associada ao Vírus Epstein Barr é uma doença linfoproliferativa indolente de linfócitos B que foi descrita em 2010 por Stefan D. Dojcinov e cols. Pode ocorrer em associação com etiologias imunossupressoras, incluindo deficiência imune primária, infecção pelo vírus da Imunodeficiência Humana (HIV), pacientes pós transplantes e em uso de metotrexato ou antagonistas TNF-alfa. Os pacientes apresentam quadro clínico de úlcera de surgimento insidioso, com localização cutânea ou de mucosas, preferencialmente de orofaringe. Os achados histopatológicos da lesão revelam áreas ulceradas com infiltrado polimórfico de linfócitos, plasmócitos, histiócitos e eosinófilos em meio a células grandes, pleomórficas que lembram células de Hodgkin e de Reed-Sternberg. O epitélio adjacente geralmente mostra núcleos atípicos e hiperplasia pseudoepiteliomatosa. As células grandes pleomórficas mostram positividade para CD20, CD30, Oct-2, PAX5 e EBV. Estas células podem ser também positivas para MUM1, focalmente positivas para Bcl-6 e não costumam expressar CD10. Apesar da presença de células muito atípicas, o curso clínico é indolente, sem progressão para doença disseminada, sendo essencial diferenciá-la de doenças linfoproliferativas malignas. Descrevemos dois casos de pacientes com diagnóstico de úlcera mucocutânea associada ao vírus Epstein Barr (EBV) para adicionar aos poucos casos já descritos na literatura.

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Background

Mucocutaneous ulcers positive for the Epstein Barr Virus (EBVMCU) are a newly recognized clinicopathological entity in the 2017 revision to the World Health Organization diagnostic criteria. (Swerdlow et al., 2017) This condition was described as a lymphoproliferative lesion associated with isolated skin or mucosal ulcers in elderly or immunosuppressed patients. Since 2010, 53 cases have been published. (Dojcinov et al., 2010; Au et al., 2006; Kalantzis et al., 1997; Deeming et al., 2005; Del Pozo et al., 2001; Kazlow et al., 2003; Nalesnik et al., 1988; Warner et al., 2008; Lawrence & Dahl, 1984; Hashizume et al., 2012; Au et al., 2011; Kleinman et al., 2014; Moran et al., 2015; Yamakawa et al., 2014; Attard et al., 2012; Matnani & Peker, 2014; McGinness et al., 2012; Di Napoli et al., 2011; Hart et al., 2014; Kanemitsu et al., 2015; Sadiku et al., 2012; Magalhaes et al., 2015; Soni et al., 2014; Mendes et al., n.d.; Roberts et al., 2016)

Ninety percent of the adult population become infected with the Epstein Barr virus via the oral route, (Aldridge et al., 2017) and most infections occur early in life. In adulthood, EBV can persistently infect B-cells. The viral genes can upregulate a variety of cellular antigens and pathways, such as NF-kappaB. Physiologically, the proliferation of B cells induced by EBV infection is generally controlled by the immune system. In patients suffering from various causes of immunosuppression (IS), EBV has been associated with B-cell lymphoproliferative disorders (LPD). (Dojcinov et al., 2010)

EBV-LPD is associated with many etiologies, including primary immunodeficiency, HIV infection, post-transplantation (Gru & Jaffe, 2016), immunosenescence owing to aging and iatrogenic causes, such as methotrexate and TNF-alfa antagonists. The spectrum of age-related EBV-positive lymphoproliferative disorders was first described by Oyama and colleagues, and can occur in elderly patients without a history of immunosuppression. (Oyama et al., 2003)

EBVMCU was described, in 2010, as localized sharply circumscribed ulcerative lesions, typically solitary (83%), that can occur in the oropharynx (52%), skin (29%) or gastrointestinal tract (19% - 40% colon, 30% esophagus, 20% rectum and 10% terminal ileum) (Roberts et al., 2016). It occurs more commonly in women, around a mean age of 77. Isolated regional lymphadenopathy can accompany these ulcers, yet usually in the absence of systemic findings. (Gru & Jaffe, 2016) The diagnosis of EBVMCU requires a combination of clinical, morphological and immunophenotypic parameters.

The histopathologic features of EBVMCU usually consist of a well-circumscribed ulcer with a polymorphous infiltrate containing histiocytes, eosinophils and plasma cells, large pleomorphic blasts resembling Hodgkin Reed Sternberg (HRS)-like cells, numerous medium-sized T-cells, plasmacytoid apoptotic bodies, as well as angioinvasion and necrosis. The large pleomorphic blast cells express CD20, CD30, CD15, PAX5, OCT2, MUM1, BOB1 and CD45, with a background of lymphocytes positive for CD3, CD4 and CD8. Reduction or absence of CD20 expression is observed in 33% of cases. These large atypical cells are positive for the latent membrane protein-1 of EBV (LMP-1). The presence of a high Ki67 proliferative index does not exclude the diagnosis of EBVMCU. (Gratzinger & Jaffe, 2016)

Although considered a self-limited disorder, monoclonality studies investigating immunoglobulin and T-cell receptor (TCR) gene rearrangements by PCR-based genotyping showed monoclonal immunoglobulin heavy chain or kappa light chain gene rearrangement and monoclonal TCR gene rearrangement in some cases. (Dojcinov et al., 2010; Au et al., 2006; Moran et al., 2015; McGinness et al., 2012; Hart et al., 2014; Kanemitsu et al., 2015; Roberts et al., 2016; Gru & Jaffe, 2016; Gratzinger & Jaffe, 2016; Stojanov & Woo, 2015; Asano et al., 2009; Shimoyama et al., 2009). Patients with EBVMCU present typically undetectable EBV DNA in peripheral blood, in contrast to many other types of EBV-associated LPDs. (Hart et al., 2014)

Typically, EBVMCU presents an indolent course. While no treatment guidelines exist, management tends to be conservative and, in cases related to the use of immunosuppressants, the withdrawal or decrease in immunosuppressant dosages is common. Nearly two-thirds of immunosuppressive-associated cases evolved to complete clinical remission exclusively by dosage reduction, with a median time to lesion resolution of four weeks (range: 2-12 weeks). A lack of response to immunosuppressant dosage reduction or withdrawal within three months should prompt the reevaluation of an EBVMCU diagnosis. (Hujoel et al., 2018)

The differential diagnosis of EBVMCU includes secondary involvement by Classic Hodgkin Lymphoma (cHL), diffuse large B-cell lymphoma (DLBCL) associated or not with EBV, primary cutaneous anaplastic large cell lymphoma, lymphomatous granulomatosis (LyG) and aggressive Posttransplant Lymphoproliferative Disease (PTLD). (Gru & Jaffe, 2016) Distinctions based solely on pathological findings can prove extremely difficult due to considerable overlap in morphology and immunophenotype; consequently, making correlations with clinical parameters is essential.

Main text

Patient characteristics and clinical course

We report two cases of EBVMCU compromising the oral mucosa and skin. Both patients were over 65 years and one was undergoing immunosuppressive treatment.

The first patient, a 67-year-old male, complained of weight loss and two cutaneous lesions on his back. Physical examination revealed one sharply demarcated ulcerative lesion measuring 5 cm, with raised edges and a

yellowish center containing fibrin. The other lesion measured 2 cm and presented scarring aspects. His laboratory evaluation was negative for HIV, anti-HBsAg and HCV antibodies. Previous pathological history consisted of splenectomy due to hemorrhaging of unknown etiology.

The second patient, a 74-year-old female, presented to her dentist with fever and a painful ulcer on her lower right alveolar ridge. She had a history of Sjögren's disease and had been taking methotrexate for 18 months. Laboratory examinations were negative for anti-HIV, anti-HBsAg, anti-HCV, VDRL, EBV (IgM), CMV (IgM) and HSV.

In both cases, lesions of the oral mucosa and skin regressed spontaneously without treatment.

Histology

The histopathological examination of the first patient revealed a sharply circumscribed cutaneous ulcer extending to the hypodermis, with large and pleomorphic mononucleate or binucleate cells resembling Hodgkin/Reed-Sternberg cells, associated with an inflammatory background of small lymphocytes, as well as some eosinophils, plasma cells and histiocytes. Apoptotic cells and foci of necrosis were also observed (Fig. 1).

The histopathological examination of the second patient revealed a necrotic mucosal ulcer and angioinvasion by large cells, some with Hodgkin/Reed Sternberg-like features, in an inflammatory background of small lymphocytes and rare eosinophils (Fig. 2).

Immunohistochemistry

Immunohistochemistry was performed in paraffin sections using monoclonal antibodies against CD30, LMP-1/EBV, CD45, CD20, CD3, CD4, CD8, PAX5, OCT2, MUM1 and BCL6 (Table 1). Sections were dewaxed in xylene and rehydrated using serial concentrations of ethanol. Heat-mediated antigen retrieval was performed, and endogenous peroxidase activity was blocked with 5% alcoholic hydrogen peroxide for 30 minutes. Slides were then incubated overnight with the primary antibodies. After primary antibody binding was detected by the EnVision® + Dual Link/Peroxidase system (Dako, Carpenteria, Ca, USA), sections were counterstained using Harris haematoxylin. (Table 1).

Immunohistochemical analysis of the first patient depicted large pleomorphic cells positive for CD30, OCT-2, CD20, MUM-1, CD45 and EBV (LMP1). The base of the ulcer showed a dense rim of small lymphocytes positive for CD3, CD4, CD8 and CD45. CD8 positive T-lymphocytes were more abundant than CD4. (Tables 2 and 3) (Fig. 1).

Immunohistochemical analysis of the second patient demonstrated large pleomorphic cells positive for CD30, OCT-2, CD20, MUM-1, CD45, PAX5 and EBV (LMP1).

Table 1 Immunohistochemistry – Primary Antibodies

Antibody	Dilution	Manufacturer
CD45	1:3000	Dako
CD3	1:400	Dako
CD4	1:300	Spring
CD8	1:300	Dako
CD20	1:1000	Cell Marque
MUM 1	1:300	Dako
PAX 5	1:50	Spring
Oct-2	1:100	Spring
LMP-1	1:5000	Dako
CD30	1:300	Dako
BCL6	1:2400	Cell Marque

Dako, Carpenteria, CA, USA; Cell Marque, Rocklin, CA, USA; Spring/Abcam, Cambridge, MA, USA

The base of the ulcer showed small lymphocytes positive for CD3, CD4 and CD8, with some cells positive for OCT-2, CD45 and EBV (LMP1). CD8 positive T-lymphocytes were more abundant compared to CD4. (Tables 2 and 3) (Fig. 2).

Discussion/conclusion

EBV-positive mucocutaneous ulcers have been recently described, and are characterized by an ulcerated lesion not associated with lymphadenopathy, hepatosplenomegaly or bone marrow involvement. This condition is usually associated with immunodeficiency. The majority of cases present an indolent course and can regress spontaneously. When associated with immunosuppressive therapy, treatment should be discontinued and/or associated with rituximab. Despite the fact that 30% of cases present clonal rearrangement of immunoglobulin and/or clonal T rearrangement, the prognosis is generally excellent. Clonality has also been observed in both polymorphic and monomorphic cases of PTLD. (Swerdlow et al., 2017; Dojcinov et al., 2010; Au et al., 2006; Kalantzis et al., 1997; Nalesnik et al., 1988; Di Napoli et al., 2011; Gru & Jaffe, 2016)

The distinct localization of EBV-positive mucocutaneous ulcers is not fully understood. It has been suggested that this process might be a consequence of reduced immunosurveillance against EBV in sites rich in EBV-infected B-cells, such as the Waldeyer ring. It has also been speculated that EBV-positive mucocutaneous ulcers may result from chronic irritation, leading to decreased immune resistance and the localized proliferation of EBV-infected B-cells. (McGinness et al., 2012)

The histopathological aspects of EBVMCU may present challenges to pathologists, as the presence of large pleomorphic cells around necrotic foci are suggestive of malignant lymphoproliferative processes. Morphological findings

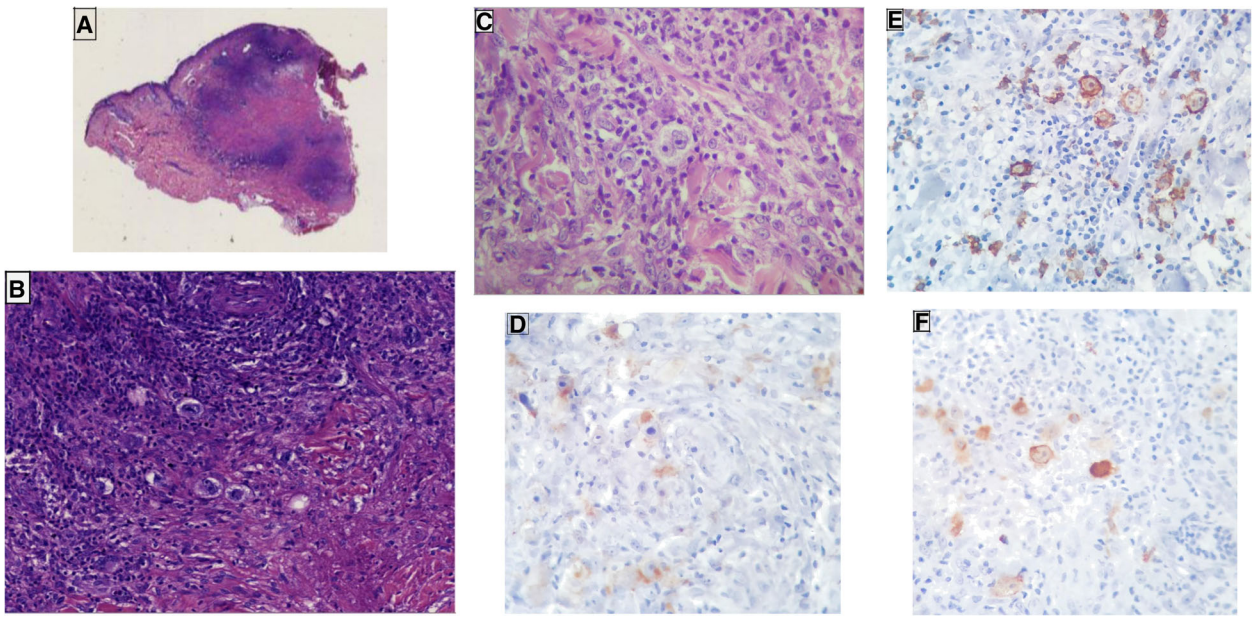

Fig. 1 Patient 1: **a** Cutaneous lesion showing a well-circumscribed ulcer with a dense rim of lymphocytes at the base (25X). **b** and **c** Large and pleomorphic Hodgkin/Reed-Sternberg-like cells in an inflammatory background (B:200X; C:400X). These atypical cells present immunoreactivity for CD30 **d** CD20 **e** and LMP1/EBV **f**. (D, E, F: 400X)

may be suggestive of a diagnosis of cHL, DLBCL associated or not with EBV, anaplastic large cell lymphoma (ALCL) or LyG. Immunophenotyping can also share similarities with these diseases, especially cHL. HRS-like cells typically express CD30, PAX5, LMP1/EBV and, sometimes, CD15. Some immunohistochemical findings could prove helpful in performing differential diagnosis. Firstly, the inflammatory background should contain abundant CD8-positive T-cells and a large number of EBV-positive plasmacytoid apoptotic cells, neither of which is common in cHL. Another important feature not typically seen in cLH but usually found in EBVMCU is positivity for CD45 and CD20 in large pleomorphic cells. Furthermore, LMP1/EBV expression is usually detected in small cells, immunoblasts and large

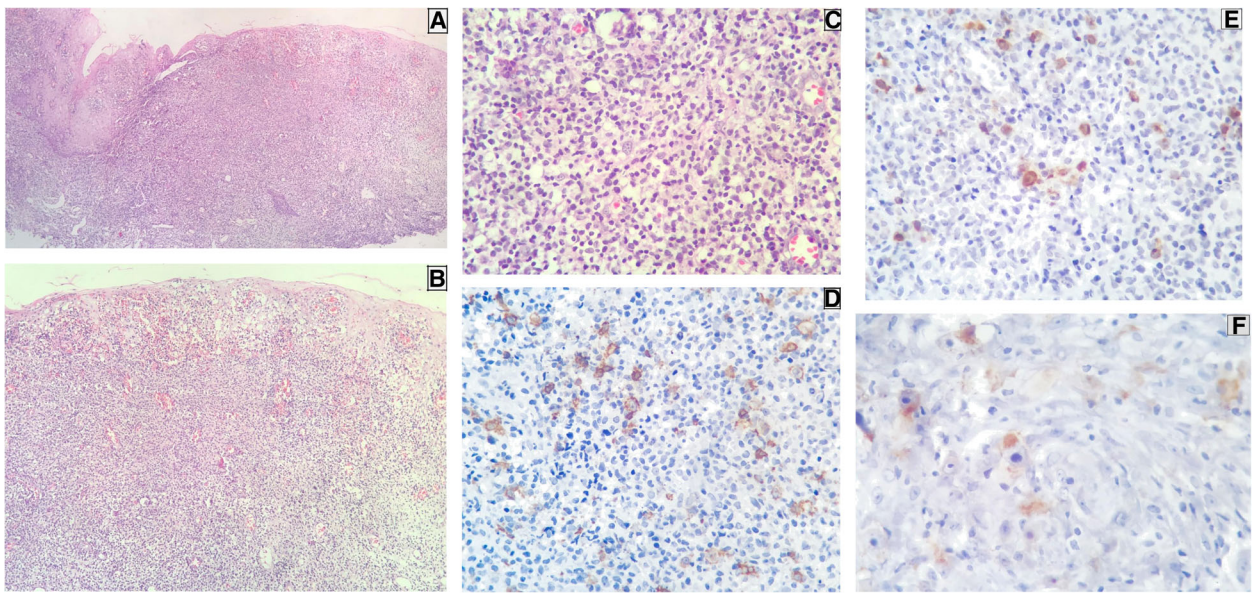

Fig. 2 Patient 2: **a b c** Lesion of the oral mucosa showing large and pleomorphic Hodgkin/Reed-Sternberg-like cells in an inflammatory background (A: 40X; B: 100X; C: 400X). On immunohistochemistry, pleomorphic cells show positivity for CD20 **d** LMP1/EBV **e** and CD30 **f**. (D, E, F: 400X)

Table 2 Summary of Immunophenotype of B-cell Blasts, including Cells with HRS-like Features

Antibody	Patient 1	Patient 2
OCT-2	+	+
CD30	+	+
CD20	+	+
CD3	–	–
CD8	–	–
CD4	–	–
MUM1	+	+
EBV (LMP-1)	+	+
CD10	–	–
CD45	+	+
PAX5	–	+

HRS-like cells. Finally, it is important to note that since Hodgkin's Lymphoma is essentially a lymph node disease, extra-nodal involvement is generally secondary. (Swerdlow et al., 2017; Ohata et al., 2017)

Another important disease to consider in the differential diagnosis of EBVMCU is LyG, a similarly EBV-driven B-cell LPD with angiocentric and angiodestructive features. LyG is rare, also commonly associated with immunosuppression, and is characterized by a background of small T-lymphocytes, with variable numbers of large atypical immunoblast-like cells, admixed with HRS-cells. Cells are positive for LMP1/EBV, CD20 and CD30, but usually not for CD15. Differential diagnosis relies on clinical presentation, as LyG typically compromises the lung, sometimes in association with other organs, more frequently the central nervous system (Swerdlow et al., 2017; Song et al., 2015).

EBV-positive DLBCL is another important differential diagnosis. These tumors occur in apparently immunocompetent individuals, usually older than 50 years of age, and carry a poorer prognosis when compared with EBV-negative DLBCL. Presentation occurs at extra nodal sites in 70% of patients and can involve the skin. Morphologically, large lymphoid cells resembling centroblasts, immunoblasts or HRS-cells are present. The background is reactive with lymphocytes, plasma cells and histiocytes. Neoplastic cells express B-cell antigens, CD30 and EBV. (Swerdlow et al., 2017; Goodlad et al., 2017).

Table 3 Summary of Immunophenotype of Background Small Lymphocytes

Antibody	Patient 1	Patient 2
OCT-2	–	+ some cells
CD30	–	–
CD20	–	+ rare cells
CD3	+	+
CD8	+	+
CD4	+	+
MUM1	–	–
EBV (LMP-1)	–	+
CD45	+	+
PAX5	–	–

In conclusion, EBVMCU poses a diagnostic challenge to the pathologist due to its histopathological similarity with some EBV-associated malignant lymphoproliferative disorders. A combination of clinical history, morphological findings and immunohistochemical features are crucial to achieving a definitive diagnosis, as well as to selecting appropriate therapy for affected patients.

Abbreviations

ALCL: Anaplastic Large Cell Lymphoma; cHL: classic Hodgkin Lymphoma; DLBCL: Diffuse Large B-cell Lymphoma; EBV: Epstein Barr Virus; EBV-LPD: EBV-induced B cell lymphoproliferative disorder; EBVMCU: EBV-positive mucocutaneous ulcer; HIV: Human Immunodeficiency Virus; HRS: Hodgkin and Reed-Sternberg; IS: Immunosuppression; LPD: Lymphoproliferative disorders; LyG: Lymphomatous Granulomatosis; PTLD: Posttransplant Lymphoproliferative Disease; TCR: T-cell receptor

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Availability of data and materials

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Authors' contributions

Authors KCW and CBM were major contributors in writing the manuscript. Authors CBM, JCM and DDA performed histological examinations and diagnosis in the two cases. KCW accompanied the histological examination of each case. Authors TC and DCQ identified the first patient and provided figures depicting histological examinations. Author MR identified the second patient. Authors KCW and CBM wrote the manuscript. DCQ and CBM revised the final manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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