

## Epstein–Barr virus-positive mucocutaneous ulcer: A rare case report from Riyadh, Saudi Arabia

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### ABSTRACT

**Background:** A new ailment, Epstein–Barr virus-positive mucocutaneous ulcer recognized as a B cell lymphoproliferative disorder caused by latent EBV infection that causes distinct ulcerations on the oral cavity, gastrointestinal tract, and skin. There are a number of factors that predispose to this condition, among which are iatrogenic immunosuppressive medications, primary immunodeficiency, or the effects of aging. **Case presentation:** 58-year-old rheumatoid arthritis patient present with pain in the hard palate, palatal demarcated ulceration with raised edges near the right upper premolar, hypertrophic gums, and hypertrophy of the gums. Following he had been diagnosed with EBVMCU on the basis of pathological finding of biopsies that displayed with a surface ulceration of polymorphic lymphoid infiltrate in the submucosa that contained large, atypical cells. **Conclusion:** Diagnosis confirmed as histologic sections show a biopsy of squamous epithelium with an atypical lymphoid infiltrate filling the submucosa. **In situ** hybridization for Epstein–Barr virus encoded RNA (EBER) demonstrated positive results in large cells atypical cells. This condition has been described in immunocompromised patients recently, and an understanding of its etiology is essential for proper diagnosis and treatment.

**Keyword:** Epstein–Barr virus; Epstein–Barr virus-positive mucocutaneous ulcer; age-associated immunosenescence; classic Hodgkin lymphoma, Saudi Arabia.

### 1. INTRODUCTION

Double stranded DNA  $\gamma$  -1 Epstein–Barr virus (EBV) is a highly prevalent herpesvirus. Human herpes virus is one of eight infective members of the herpes family that can be spread directly from one person to another by the saliva. This virus causes latent infection in the host and the ability to transform B lymphocytes (Yao et al., 1985). There are currently 90 percent of adults worldwide infected with this disease (Smatti et al., 2018). B-lymphocytes are targeted by EBV, and it causes a latent infection that can transform normal B cells into those with malignant properties if left untreated. Usually in a normal host, primary infection with EBV asymptomatic and, it

remains unrecognizable in B cells for the rest of one's life after primary infection by EBV (Young and Rickinson 2004).

EBV-positive mucocutaneous ulcers (EBVMCUs) is an exceptional clinical condition occurs in patients with immunosuppression due to iatrogenic causes, alterations in the immune system linked with age, or many types of primary immunodeficiency like agammaglobulinemia, chronic granulomatous disease, etc. Dojcinov et al., (2010), has described it first and they reported how 26 patients with either age-related immune senescence or immune suppression caused by various autoimmune medications such as azathioprine, methotrexate, or cyclosporine A presented with a common clinical presentation. Because of its remarkable features, in 2017 revised World Health Organization (WHO) classification introduced lymphoproliferation disease as new problem (Willemze et al., 2019).

In recent studies, it has been revealed that EBVMCUs are usually caused by iatrogenic immunosuppression (56%), advanced age (40%), and primary immunodeficiency (4%) and are much less likely to be associated with EBV infections (Roberts et al., 2016). In EBVMCU, the skin, mouth and digestive tract are affected with distinct well-demarcated ulcerations. The infiltrated cells consist of scattered lymphocytes and immunoblasts mixed with plasma cells, histiocytes and eosinophils, and the blasts resemble those from Hodgkin Reed-Sternberg (HRS) cancer.

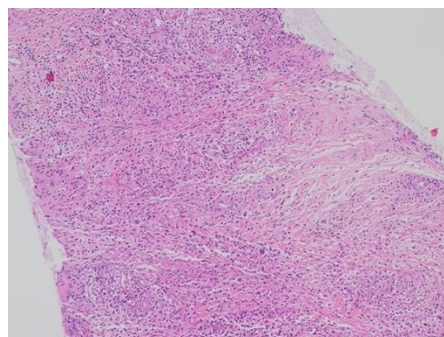
According to prospective studies, the oropharynx is considered as most common site of primary infection and provide the easy way to this virus to enter thorough it (41%), Roberts et al., (2016). In most cases, EBVMCU does not require treatment and has a self-limiting course. There is the possibility that EBVMCU is more aggressively treated in some conditions that gradually develop. Although the lack of current recommendations or knowledge-based opinions is to guide the therapy for this disease, this case report provides a foundation for the formulation of therapeutic decisions and diagnosis.

## 2. CASE PRESENTATION

A 58-year-old male presented with past medical history of rheumatoid arthritis to Prince Sultan Military Medical City visited ENT doctor with chief complaints of oral pain in his hard palate for 7 months, anorexia, and remarkable weight loss. Physical examination was observed in hypertrophic gums and a palatal demarcated ulceration with raised edges near the right upper premolar. The patient experiences tetanic spasm of the mastication muscles, no visible brown-spot on skin and periorbital oedema or uvula deviation. Laboratory evaluation showed negative serologies for HIV, anti-HBsAg and HCV antibodies. A biopsy was done 3 months ago in a private hospital with poor diagnosis of differentiated neoplasm. Patient referred to the doctor and the paraffine block was sent to the laboratory for second opinion. Subsequently patient was transferred to oncology department for biopsy of his right palatal lesion. Figures 1 to 4 showed pathologic findings, that represents histologic and immunohistochemical features of EBV-positive mucocutaneous ulcer.

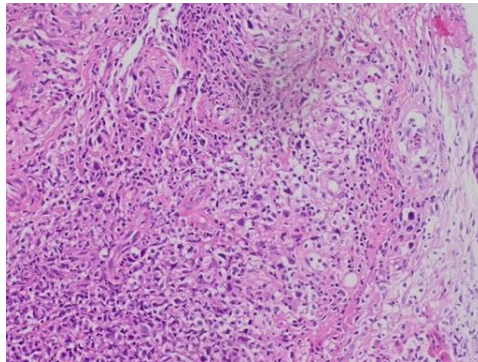
### PET-CT-based targeted biopsy of the palate

Biopsies of EBV-positive mucocutaneous ulcers revealed surface ulceration with atypical lymphoid cell infiltrates. The appearance of this lymphoid component varies. Various studies have shown that it can resemble to both diffuse large B-cell lymphoma (DLBCL) and classic Hodgkin's lymphoma (cHL) in terms of its histological appearance. An inflammatory infiltration could be mixed with histiocytes, plasma cells and lymphocytes; there may also be eosinophils present. Typically, areas of EBV-positive B-cells are surrounded by rim of reactive T-cells. Several immunoblasts have been shown to express antibodies associated with the B-cell immunophenotype.



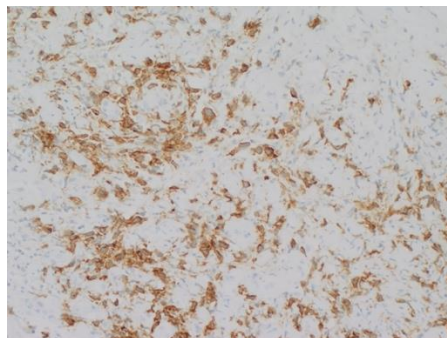
**Figure 1** Histologic sections show a biopsy of squamous epithelium with an atypical lymphoid infiltrate filling the submucosa.

Histologic sections show a biopsy of squamous epithelium with an atypical lymphoid infiltrate filling the submucosa. The infiltrate is composed of scattered large neoplastic cells (mononuclear with large eosinophilic nucleoli, multinuclear and few binucleated Reed-Sternbergs like cells) in a background of small lymphocytes, histiocytes, plasma cells with occasional neutrophils and eosinophils, scattered apoptotic cells are also noted (Fig. 1 & 2).

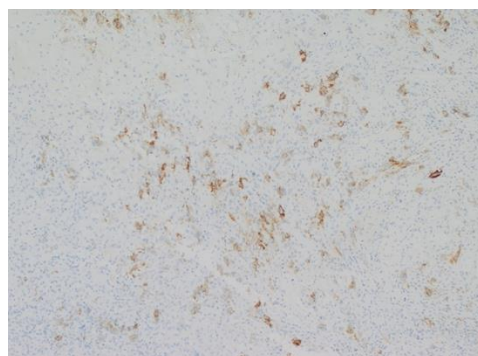


**Figure 2** The underlying infiltrate composed of scattered large neoplastic cells (mononuclear with large eosinophilic nucleoli, multinuclear and few binucleated Reed-Sternbergs like cells) in a background of small lymphocytes, histiocytes, plasma cells with occasional neutrophils and eosinophils.

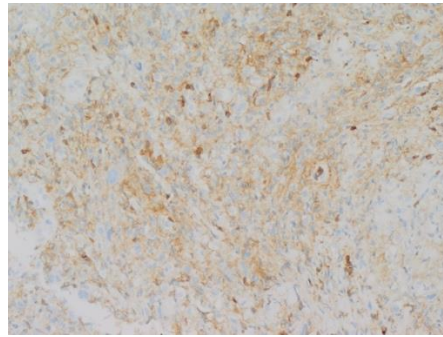
A focal mucosal ulceration was visible at the surface epithelium. The large neoplastic cells show dispersed and steady positive CD30 immunostaining. The B cell markers (CD20, PAX-5, OCT-2, and BOB1) show variable positivity (Fig 3a-d). The large cells are positive for *in situ* hybridization for Epstein-Barr virus encoded RNA (EBER) (Fig. 4). They are negative for CD3, CD4, CD5, CD8, bcl-6 and CD10 immunostaining.



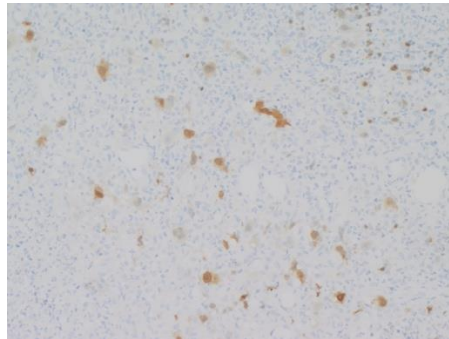
**Figure 3a** Cells expressed positive CD30



**Figure 3b** All cells are positive for CD20

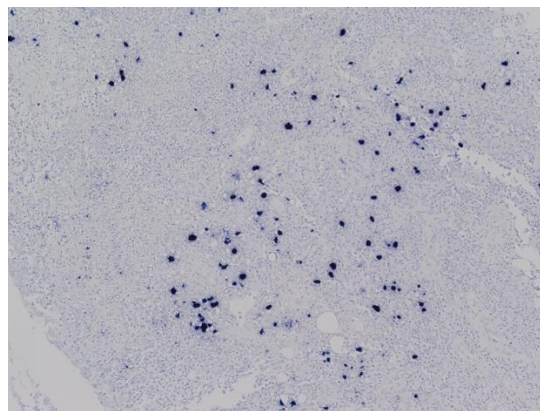


**Figure 3c** Expressed positive CD45



**Figure 3d** Cells showed positive BOB1

**Figure 3 a, b, c, d** the surface epithelium showed focal mucosal ulceration. The large neoplastic cells show positive for CD30 immunostatin. The B cell markers (CD20, CD45, PAX-5, OCT-2, and BOB1) show variable positivity.



**Figure 4** Immunohistochemically, case showed positive for EBER

### 3. DISCUSSION

Recently EBVMCU is recognized as atypical disorder that represents exceptional clinical condition, with only few cases reported with no clear management guidelines (Roberts et al., 2016). The prevalence of EBVMCU is likely underestimated since a few lesions regress without being pathologically diagnosed. The presence of specific HRS immunophenotypes and enormous sized atypical lymphocytes in other lesions, however, might lead to a misunderstanding, such as methotrexate-associated ulcers, Hodgkin lymphomas, and diffuse large B-cell lymphomas (Satou et al., 2018).

EBVMCUs occurred most frequently in the oropharynx, guts, or dermis. The oropharynx is most possible entry for EBV as well as most common site of infection (52%) and process usually takes place within lymphocytes that form Waldeyer's ring (Callan et al., 1996; Moghaddam et al., 1997). The most common instance of EBVMCU is as a self-contained lesion, but it has also occurred in another organ part (Henle et al., 1968). The gender distribution is especially striking as 62% among 52 patients with EBVMCUs are



female; 62% have EBVMCUs associated with iatrogenic immune suppression, 100% have this disorder associated with primary immunodeficiency, and 55% have this disorder associated with immunosenescence (Satou et al., 2018). Although this observation has some significance, it has not been clear on the significance of it seeing as how there a clear gender bias among has not been other EBV-associated lymphoproliferative disorders except for Burkitt lymphoma and mixed cellularity Hodgkin lymphoma (Morton et al., 2006).

Sometimes lesions may lead to cause localized self-limited welt and occasionally it may locally quite destructive, particularly in instances where iatrogenic immunosuppression is maintained or increased. Within eight weeks after the removal of immunosuppression, full remission is achieved almost without exception. A therapeutic intervention may be necessary if persistent and symptomatic cases in elderly patients do not result from those related to the ulcer, the patients are otherwise without systemic symptoms, lymphadenopathy, and furthermore are immunocompromised. Rituximab is considered as a single agent accomplishes excellent results. Usually, different forms of immunosuppression associated with EBVMCU. There are several immunosuppressive agents that can be used to treat idiopathic inflammatory and autoimmune conditions, including cyclosporin-A (CyA), azathioprine (AZA), and methotrexate (MTX). Patients who undergo solid organ transplants are frequently given the immunosuppressive drugs AZA and CyA, although for this population the immune effects may be more noticeable than for patients with autoimmune diseases. Many previous studies showed lymphoproliferative disorder associated with these suggested agents (Tanner and Alfieri, 2001; Chen et al., 2009).

In a previous report, cHLs (or Hodgkin-like lesions) were associated with EBV in patients with inflammatory bowel disease and shared many of the same characteristics as in our case. It was noted previously that lesions that closely resembled EBV-positive mucocutaneous ulcer were most often associated with MTX, and these symptoms were usually regressed after drug withdrawal or stopped, and they were believed to be the result of toxic or metabolic effects, rather than an EBV-related cause (Au et al., 2006). Several reported cases showed non-specific ulcerations microscopically, but there was no histological confirmation for the majority (Callan et al., 1996; Deeming et al., 2005). Post-transplantation, CyA has also caused similar lesions, which affect mainly oropharyngeal mucosa (Nalesnik et al., 1998). The following has been reported 13% and 8% of cases of age-associated EBV-LPD present with extranodal manifestations involving skin and tonsils, respectively (Dojcinov et al., 2010).

Our study suggests that EBVMCU is a rare lesion that can occur in many different clinical settings, especially in those with an impaired immune response to EBV, such as in progressed age in extensive ranges of cases.

#### 4. CONCLUSION

EBVMCU is a recent rare pathology with a variety of etiologies, associated with immune suppression and with a common mechanism of pathogenesis. Clinically, this disorder is often characterized by apathetic and self-limited clinical course characterized by manifestations on the skin and mucosa that are circumscribed and isolated. The lapse in immunosurveillance is minimal and local, resulting from the EBV infection. Based on the high regression rate after immune suppression withdrawal along with deflating course observed in age-related cases, conservative management of this condition is encouraged. Morphologically and immunophenotypically, we observe some similarities to cHL, particularly the high percentages of CD30 positivity. As EBVMCU is histopathologically similar to other lymphoproliferative disorders, misdiagnosis for this condition may occur, leading to mismanagement of its treatment and management. Several features of the clinical, morphological, and immunophenotypic presentations are needed to make the diagnosis. A precise diagnosis can still be made based on the patient history, findings and the appearance of the EBV-positive cells. At the present time, further studies are needed to help guide physicians in choosing the correct treatment as well as understanding the prognosis of EBVMCU.

#### Declaration of patient consent

Not required. The study is based on observation only, as patient is not at risk in this study. This submission does not contain any personal details that might identify the patient; therefore, consent was not obtained from the patient.

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## Conflicts of interest

The authors declare that there are no conflicts of interests.

## Data and materials availability

All data associated with this study are present in the paper.

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