Scientific Research Publishing

Open Journal of Stomatology, 2025, 15(11), 285-291
https://www.scirp.org/journal/ojst
ISSN Online: 2160-8717
ISSN Print: 2160-8709

Epstein-Barr Virus Positive Mucocutaneous Ulcer Presenting in the Oral Cavity: A Rare Entity for Maxillofacial Surgeons

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How to cite this paper: De Coninck, W. and Van Camp, P. (2025) Epstein-Barr Virus Positive Mucocutaneous Ulcer Presenting in the Oral Cavity: A Rare Entity for Maxillofacial Surgeons. *Open Journal of Stomatology*, **15**, 285-291.
https://doi.org/10.4236/ojst.2025.1511026

Received: September 18, 2025
Accepted: November 2, 2025
Published: November 5, 2025

Abstract

Epstein-Barr virus–positive mucocutaneous ulcer (EBVMCU) represents a rare, indolent B-cell lymphoproliferative disorder predominantly affecting elderly or immunocompromised patients. Its clinicopathological resemblance to aggressive lymphomas, including diffuse large B-cell lymphoma and classic Hodgkin lymphoma, necessitates meticulous diagnostic evaluation to prevent unnecessary cytotoxic therapy. We report an 80-year-old female presenting with a painful ulcer in the left retromolar trigone. Her history included bisphosphonate use for osteoporosis without documented immunosuppression. Initial suspicion favored odontogenic infection; however, incisional biopsy at tooth extraction revealed EBV-positive large B-cells, establishing EBVMCU. Imaging demonstrated localized disease. Given persistent ulceration and absence of reversible immunosuppressive factors, rituximab (anti-CD20) monotherapy was administered, achieving marked regression and complete mucosal healing within six months. This case underscores immunosenescence as a likely predisposing factor and highlights the necessity of comprehensive histopathological and immunohistochemical assessment to differentiate EBVMCU from malignant lymphoproliferative entities. While frequently self-limiting, persistent disease may warrant targeted anti-CD20 therapy.

Keywords

Case Report, Epstein-Barr Virus Positive Mucocutaneous Ulcer, Oral Surgery, Rituximab, Oncology

1. Background

Epstein-Barr Virus (EBV) positive mucocutaneous ulcers (EBVMCU) are rare benign lymphoproliferative localized lesions typically presenting in the immunosup-

pressed individual. Caused either by old age, iatrogenic immunosuppression or immune disorders [1]. They are categorized under the B-cell lymphoproliferative disorders [2]. It was first described in 2010 and classified separately by the World Health Organization in 2017 [3] [4].

Clinically, these EBV-positive mucocutaneous ulcers present as painless or mildly painful ulcers on mucosal surfaces such as gastro-intestinal tract (19%), skin (29%) and as in this case the oral cavity (52% - 69%) [2] [3] [5].

Histopathologically, this lymphoid condition can have similar histological appearances to that of diffuse large B-cell lymphoma (DLBCL) and classic Hodgkin lymphoma (CHL) [2] [5]. EBVMCU typically shows a proliferation of polymorphic CD30 positive and EBV positive B-lymphocytes, some of which mimic Hodgkin cells [6].

The prognosis for these lesions is good to excellent, as most cases regress spontaneously or regress after interruption of immunosuppressive therapy [1] [7] [8]. This makes the difficult differentiation between DLBCL and Hodgkin lymphoma extremely important, where more aggressive treatment is indicated. In rare cases, these lesions can present as persistent or recurrent, requiring additional interventions such as radiotherapy, chemotherapy, monoclonal antibodies or surgical excision [2] [3] [5] [8] [9]. Other differential diagnoses like squamous cell carcinomas, lymphomas, sarcomas, metastases or melanomas should be taken into account as clinically these can present in a very similar way [6].

2. Case Presentation

An 80-year-old woman was referred to the maxillofacial clinic by her dentist in March 2024 because of swelling in the left retromolar trigone. The lesion was noted about 7 weeks prior to presentation. It presented as a soft, red, painful lesion of 12 × 12 mm in diameter (**Figure 1**). Other symptoms included loose teeth FDI 37-38 with some purulent debris and swelling. No lymphadenopathy was noted.

The patient has a history of hypertension and bilateral breast cancer, diagnosed in 2010 and 2019. The first occurrence was treated with neoadjuvant chemotherapy, mastectomy, lymphadenectomy, postoperative radiotherapy and an aromatase inhibitor. The second occurrence was managed with surgery followed by upfront aromatase inhibitor therapy. The patient also had been receiving yearly intravenous bisphosphonate treatment (Aclasta, zoledronic acid, 5 mg) for osteoporosis. No other medical history of interest was present.

A panoramic tomography (**Figure 2**) showed peri-radicular osteolysis around teeth FDI 37 and 38. At the moment of presentation, the lesion presented itself as an infection from dental origin, albeit somewhat atypical. These two mobile teeth in the centre of the lesion were removed at the same time as two separate incisional biopsies were taken. This biopsy showed abnormal large B-cells that were positive for EBV, which after extensive immunologic testing (positive for EBV, CD20, CD3, CD15, CD30, PAX-5, MUM-1 (**Figure 3**)), confirmed the diagnosis of Epstein-Barr virus–positive mucocutaneous ulcer. Given the absence of EBV-posi-

tive cell-sheets and the localization the diagnosis of DLBCL was less fitting nor did the histology fit with classic Hodgkin-lymphoma.

A positron emission tomography - computed tomography (PET/CT) (**Figure 4**) showed localized disease.

After short consultation with the patient the following treatment options were presented: Radiotherapy or treatment with rituximab, an anti-CD20 agent. The preference was expressed for rituximab. Treatment with 8 doses of rituximab over a period of 3 months (June-August) showed good healing and regression of the lesion. Follow-up radiologic examination by cone beam computed tomography (CBCT) of the jaw as well as a PET/CT 6 months after treatment (**Figure 5**) showed slow but steady healing and involution after tooth extraction.

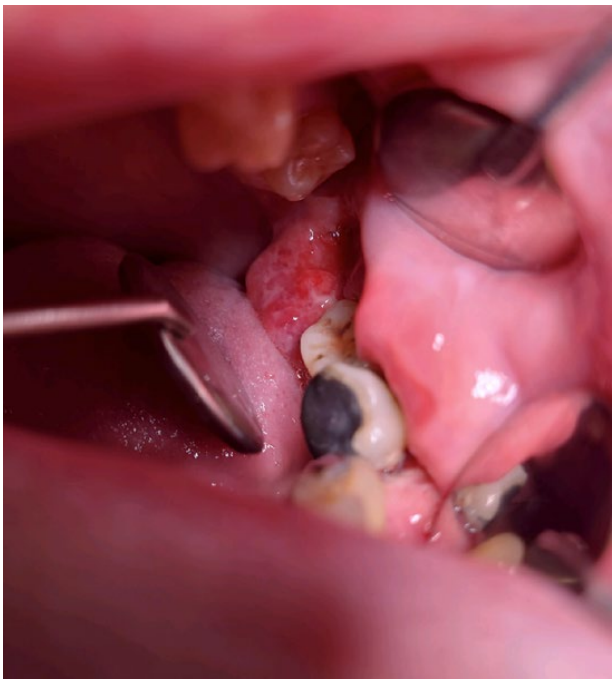

Figure 1. Clinical image.

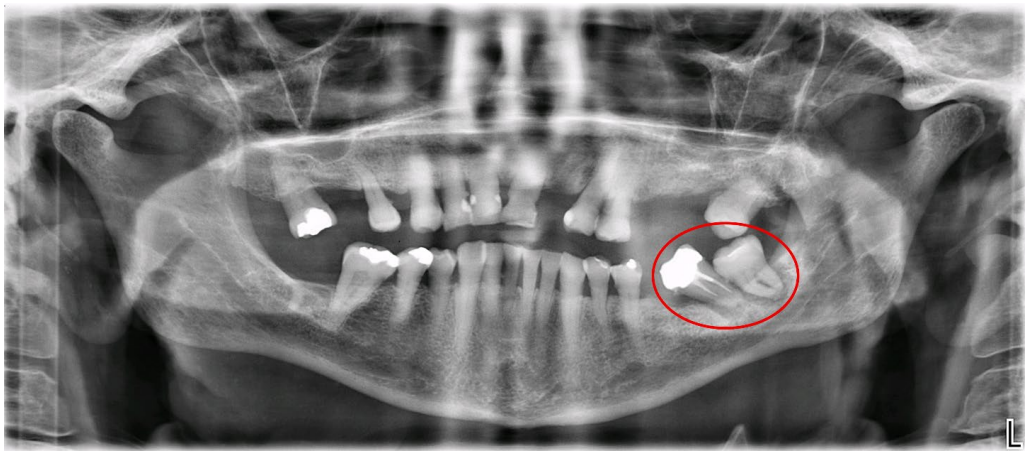

Figure 2. Panoramic tomography.

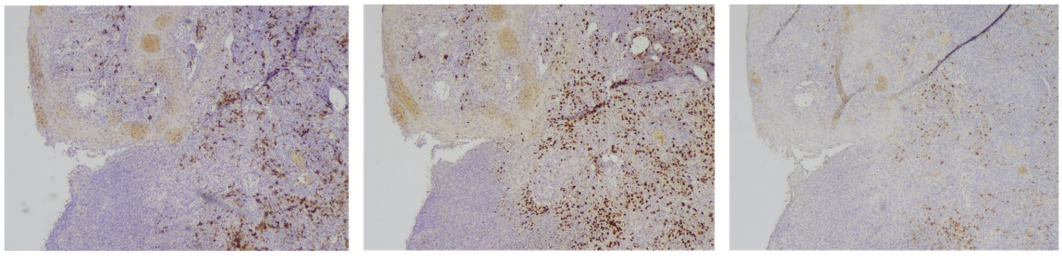

Figure 3. From left to right: CD20-, MUM1-, EBV-colouring.

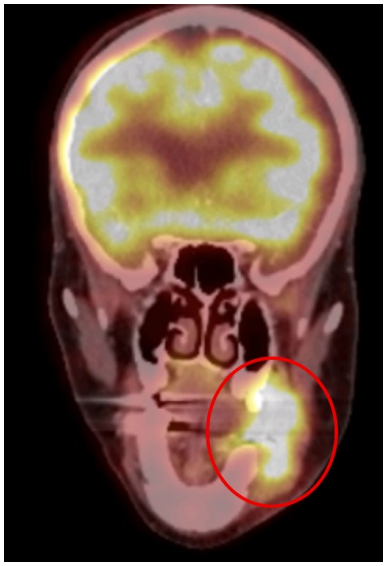

Figure 4. PET/CT before treatment.

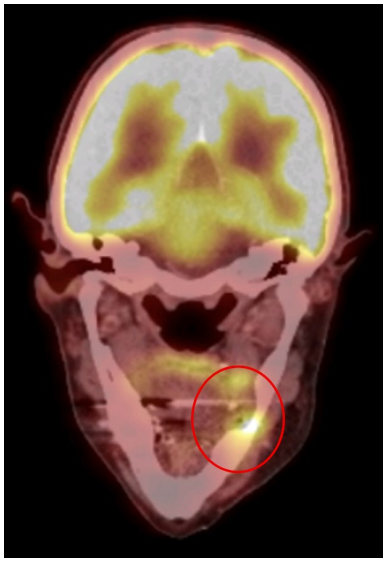

Figure 5. PET/CT 6 months after treatment.

3. Discussion

EBVMCU usually presents as an unifocal, ulcerative lesion associated with various types of immunosuppressive diseases or -states. It can present as a mucosal as well

as a cutaneous lesion. The possible causes for immunosuppression are either pharmacologically induced (e.g. methotrexate, azathioprine, mycophenolate, cyclosporine, tumour necrosis factor inhibitor), age-related factors or various immunodeficiency diseases e.g. HIV [6] [9]. Usually, no lymphadenopathy or involvement in any other organ is noted [3].

This pathology has a good prognosis with a 93% 5-year survival rate [10]. Nearly all cases reported were self-limited. However, a few cases with progression to disseminated disease have been described [10] [11].

During initial clinical investigation the differential diagnosis included infectious disorders, autoimmune diseases and malignancies. The most notorious malignancy being squamous cell carcinoma [12]. Warranting the clinician to proceed with biopsy prelevation.

Our article presents a case of EBVMCU with bisphosphonates as the only remarkable medication. Our case was ultimately treated with rituximab. Given no other case with bisphosphonates has ever been described nor any pathophysiologic pathway points to zoledronic acid as a causative agent for B-cell immunomodulation, the most probable etiologic factor in this case was age-related decline in immune system function called "immunosenescence". A recent study by Lafuente-Ibañez de Mendoza I *et al.* reviewed all currently published cases of immunosenescence, providing a demographic table with ages between 64 and 89 years [6]. They described a peri-implant lesion with which our case shows multiple similarities: chronic inflammation around periodontally doubtful teeth, 80+ years of age, no causative pharmacological agent nor immunosuppressive disease. Finally, leading to proliferation of EBVMCU [6]. Given the capability of EBV to evade immune surveillance, combined with the weakening immune system, more specific the T-cells of the elderly patient, suggests that EBV proliferation is less inhibited contributing to increased EBV load.

Most of the cases described in literature interrupted immunosuppressive treatment resulting in resolution of the disease. In our case, due to the lesion being persistent and the absence of immunosuppressive treatment, therapy was initiated with rituximab (monoclonal anti-CD20 antibody) to control disease proliferation. Other options include surgery, radiotherapy or chemotherapy. One being more aggressive than the other [3] [5] [6]. In our case, only incisional biopsy, extraction of affected tooth and improvement of oral environment alone did not result in complete remission [5].

4. Learning Points/Take Home Messages

1) EBVMCU is a rare lymphoproliferative disorder, often occurring in elderly or immunocompromised individuals and can mimic aggressive lymphomas such as DLBCL or classic Hodgkin lymphoma.

2) EBVMCU poses great difficulties in differential diagnosis requiring an extensive clinicopathological and immunohistochemical investigation.

3) EBVMCU shows a very good prognosis with almost no reported cases of

malignant degeneration.

4) EBVMCU should be considered by clinicians when encountering persistent oral ulcers in the elderly. Especially when odontogenic infections are ruled out.

Disclosure of Artificial Intelligence Use

During the preparation of this work the author used GEMINI and ChatGPT in order to check for grammatical errors. After using this tool/service, the author reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

Funding

The authors did not receive any sources of funding.

Conflicts of Interest

No competing interests to declare.

Ethical Approval

No ethical approval was required for this case report

Patient Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request

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