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Oral Epstein–Barr virus-positive mucocutaneous ulcer: gingival presentation of a benign lymphoproliferative lesion

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Oral EBV-positive Mucocutaneous Ulcer: Gingival presentation of a benign lymphoproliferative lesion

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Abstract

Epstein-Barr virus-positive mucocutaneous ulcer (EBVMCU) is a benign lymphoproliferative lesion related to iatrogenic or age-related immunosuppression in patients with prior Epstein-Barr virus (EBV) infection. Although the clinical presentation may resemble malignant disease, the course of EBVMCU is indolent, and regression is expected when immunosuppression is reduced. We present a case of EBVMCU in the gingiva of a 59-year-old male patient with long-standing pemphigus vulgaris. The initial presentation was suspicious for oral cavity cancer, which was ruled out with biopsy. After reduction of immunosuppression, the ulceration regressed and an area of exposed necrotic bone remained. Complete healing was achieved after sequestrectomy and primary closure with local gingival flap.

Introduction

Epstein-Barr virus-positive mucocutaneous ulcer (EBVMCU) is a recently described clinicopathologic diagnosis related to immunosuppression, either age-related or iatrogenic [1]. It was first termed by Dojcinov et. al. in 2010 when they reported 26 cases of sharply circumscribed ulcers in the skin or mucosa associated with various sources of immunosuppression [1]. In the updated version of the World Health Organization-European Organization for Research and Treatment of Cancer (WHO-EORTC) consensus classification published in 2018, EBVMCU was included as a new provisional entity [2].

Epstein-Barr virus (EBV) infection is ubiquitous, and usually occurs at an early age. After initial infection, the virus persists in the B-cells in most adults [1]. Viral latency is a characteristic of human herpesviruses (HHVs), of which EBV is referred to as HHV-4. In healthy individuals, the overall number of EBV infected B-cells is kept to a very low level by complex immunological mechanisms[3]. However, in those patients with immunosuppression, the EBV-infected cells are allowed to proliferate, resulting in various forms of EBV-induced B-cell lymphoproliferative disorders (EBV-LPDs) [4]. These include Burkitt lymphoma [5], Hodgkin lymphoma [6], post-transplant lymphoproliferative disorder [7], EBVMCU and among others.

The presentation of EBVMCU usually involves a well-circumscribed ulcer in the oral and oropharyngeal mucosa, skin, and gastrointestinal tract in patients receiving various types of immunosuppressant, or with age-related immunosenescence [1]. The ulcers can be deep, and sometimes present as through and through defects from mucosa to skin. The reported

predisposing medications include methotrexate [1], azathioprine [1, 8], cyclosporine-A [1, 8], mycophenolate [8, 9], and prednisolone in combination with other immuosuppresants [8, 9]. EBVMCU exhibits an indolent course with spontaneous regression. Treatment with radiotherapy or chemotherapy has been suggested, but the disease usually regresses spontaneously once immunosuppression is ceased or reduced [10].

Histopathologically, EBVMCU presents as ulcers with a polymorphous infiltrate at its base comprising of variable numbers of immunoblasts and large atypical large B-cells and Hodgekin's or Reed-Sternberg–like cells [1]. The immunoblasts and Reed-Sternberg–like cells are EBV-positive B-cells that are uniformly CD30 positive [8]. In this article, we present a case of EBVMCU in a patient with long-standing pemphigus vulgaris who received mycophenolic acid and prednisolone.

Case report

A 59-year-old man presented to the Department of Oral and Maxillofacial Surgery with a deep ulceration with rolled borders at the buccal gingiva in the mandibular right premolar region. The underlying bone was exposed **(Figure 1).** The lesion was present for about one month and was associated with mild pain. The patient had been diagnosed with pemphigus vulgaris for 5 years, and was managed by the dermatology department with Myfortic (Mycophenolic acid) 180 mg twice a day, and prednisolone 5 mg daily at the time of presentation of the oral lesion. Other significant medical history included type 2 diabetes mellitus and hypertension, both managed with oral medications. Upon examination, a 3 x 1 cm ulcerated area with indurated border was found at the buccal gingiva at the right mandibular first and second premolar region. The two involved teeth were mobile. Generalized desquamative gingiva was found which was consistent with pemphigus vulgaris. Computed tomography (CT) of the head and neck region did not reveal any evidence of bony involvement nor suspicious lymph nodes. Incisional biopsy was carried out under local anaesthesia.

Histopathologically**(Figure 2)**, the specimen exhibited a dense atypical lymphoid infiltrate comprising of a polymorphic mixed population of lymphoid cells. These cells were of a B-cell lineage, as suggested by the diffuse CD20 immunohistochemical positivity. Moreover, in-situ hybridization showed that the specimen was positive for Epstein-Barr virus. The features were consistent with EBVMCU. Plasma EBV DNA test revealed 31 copies/mL. The patient was referred to the haematologist. The possibility of malignant lymphoma elsewhere in the body was being ruled out. Myfortic

was stopped after consultation with the dermatologist, although prednisolone was kept at that time.

The patient was reviewed two weeks after cessation of Myfortic. There was no obvious worsening of symptoms of pemphigus vulgaris, though an increase in circulating anti-intercellular substance autoantibody (anti-ICS Ab) by indirect immunofluorescence was noted (from 1/640 to 1/40 after stopping Myfortic). However, the oral lesion appeared more extensive, exposing the underlying bone. A second incisional biopsy was performed, confirming a diagnosis of EBVMCU, with no evidence of malignancy.

The lesion began to regress in size one month after stopping Myfortic, and had mostly regressed after two months. And since the symptoms of pemphigus vulgaris was under control, prednisolone was discontinued by the dermatologist as well, but gingival sloughing started soon after the cessation of prednisolone. The signs and symptoms were then managed with doxycycline and triamcinolone.

At 6 months after stopping Myfortic, the initial ulcerated lesion was no longer present, but the area of exposed bone remained. Also, pemphigus vulgaris manifested as generalized oral mucosal sloughing was noted and was becoming symptomatic. The option of restarting Myfortic was raised by the dermatologist. Cone-beam computed tomography (CBCT) showed an area of bony sequestration at the right mandibular alveolus. Sequestrectomy and primary closure with local mucoperiosteal flap was done, and the sequestrum was histologically consistent with necrotic bone. The area was well-healed at 7 weeks postoperatively **(Figure 3)**. The patient's condition of pemphigus

vulgaris was since managed with a combination of doxycycline, topical triamcinolone and protopic. No recurrence of oral EBVMCU was observed during follow-up.

Discussion

EBVMCU occurs due to the proliferation of B-cells previously infected with EBV in patients with decreased immune surveillance. Since the initial description of this entity, EBVMCU has sparked great interest within the audience of rheumatology, pathology and hematology. In the original case series reported by Dojcinov et al in 2010 comprising of 26 cases, 62% (16/26) of the patients had ulcers presented in the oropharyngeal region, while the rest were either at the skin or other parts of the gastrointestinal tract [1]. The patients consisted of mainly elderly individuals, with a median age of 77. The causes of immunosuppression included immunosenescence due to old age (17/26), and therapeutic immunosuppression due to various autoimmune diseases, such as rheumatoid arthritis, ulcerative colitis, sarcoidosis with myasthenia gravis, systemic lupus erythematosus, and allogenic stem cell bone marrow transplantation. In their cohort, all cases of EBVMCU due to therapeutic immunosuppression spontaneously regressed after reduction of immunosuppression. In those with age-related EBVMCU, half of them (5/10) had spontaneous remission after biopsy. The other half were treated with either radiotherapy, chemotherapy, or a combination of both, and the lesions also regressed after treatment.

The diagnosis of EBVMCU is based on clinical, histological, and immunohistochemical findings. Histologically, it is characterized by atypical large B-cell blasts and a polymorphous infiltrate, and Hodgkin/Reed-Sternberg (HRS) cell-like morphology is often seen [1]. These findings may resemble other hematologic diseases, such as classical Hodgkin's lymphoma (cHL) [4]. However, a few key features of EBVMCU distinguishes it from cHL, such as the presence of a mucocutaneous ulcer, the lack of lymph node involvement as well as the immunopositivity of the lesional cells for CD45 [4]. Moreover,

abundant apoptotic EBV-positive plasmacytoid cells are often seen in EBVMCU, which is not a characteristic feature in cHL [1]. In the current patient, the clinical presentation was consistent with EBVMCU: the presence of a mucocutaneous ulcer with atypical B-cell infiltrate which was positive for EBV in an immunosuppressed patient. Although a CD45 immunohistochemical staining was not performed, there was no evidence of lymph node involvement and malignant lymphoma was ruled out after consultation with the haematologist.

Consistent with the literature, the site of presentation of the current case was in the mucosal surface of the oral cavity, adjacent to two periodontally involved left mandibular premolars. It has been reported that EBVMCU of the head and neck region occurs on mucosal surfaces in close to 90% of the cases [4]. Our patient had very poor oral hygiene, attributing to the pain from the sloughing mucosa. Therefore, it was possible that, in our patient, the periodontal lesions provided a susceptible site for the development of EBVMCU, which was, in turn, related to EBV secreted in the saliva in an immunosuppressed state. More future research into this area is required in order to decipher whether the development of EBVMCU is related to periodontal disease and other chronic local infection. Similar to other reports, the reason that led to biopsy was suspicion for malignancy. The lesion began to regress one month after cessation of Mycophenolic acid. The site then presented as an area of exposed necrotic bone due to insufficient blood supply secondary to the infection and the lack of periosteum. Complete healing was achieved after sequestrectomy and primary closure with local gingival flap. Resuming systemic immunosuppression was deemed inappropriate for

this patient, and his condition of pemphigus vulgaris was being managed with doxycycline, in addition to topical triamcinolone and protopic.

In conclusion, the clinical presentation of EBVMCU can often mimic that of malignant lesions. However, correct diagnosis can be established basing on clinical, histologic and immunophenotypic grounds. Due to the indolent course of the disease, treatment strategies aim at a conservative approach. With reduction of immunosuppression, remission can be seen in most cases. Our current case of EBVMCU from iatrogenic immunosuppression due to treatment of pemphigus vulgaris highlights the importance of accurate diagnosis and that successful treatment outcomes can be reached by means of cessation of immunosuppression and conservative local surgery.

Declarations

Funding: The authors did not receive any sources of funding for this work.

Competing Interests: The authors have no competing interests to declare.

Ethical Approval: Ethical approval is exempt for case report

Patient Consent: Patient consent was obtained prior to receiving treatment at our hospital as teaching patient.

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Figure legends

Figure 1. Initial presentation of the ulcerated lesion at the right mandibular gingiva (A). Cone-beam Computed Tomography showing bone sequestrum at 6-months after cessation of Myfortic (B).

Figure 2. Low power view of the ulcer at the right mandibular vestibule reveals a highly cellular lymphoid infiltrate extending deep into the submucosa (A, H&E, x 20). The atypical lymphoid cells are medium to large-sized with ovoid to slightly elongated nuclei (B, H&E, x 400). Mitosis are frequent (arrows in B). These cells are B-cell in origin (being immunoreactive to CD20 in C, brown signals, x 400) and positive for CD30 (D, brown signals, x 400). These cells are shown to be positive for *in situ* hybridization for Epstein Barr virus encoded early RNA (E, deep blue signals, x 400, EBER stain).

Figure 3. Post-operative 7 weeks after sequestrectomy.

Figures

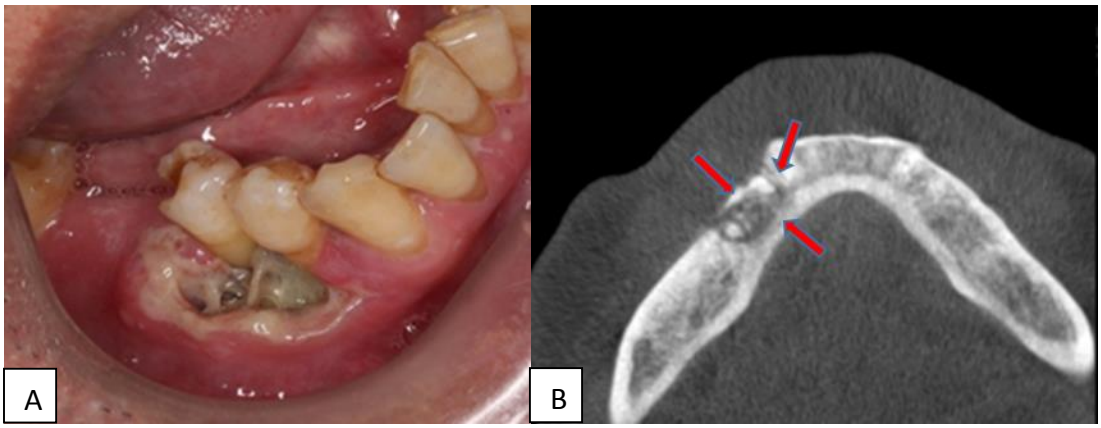

Figure 1.

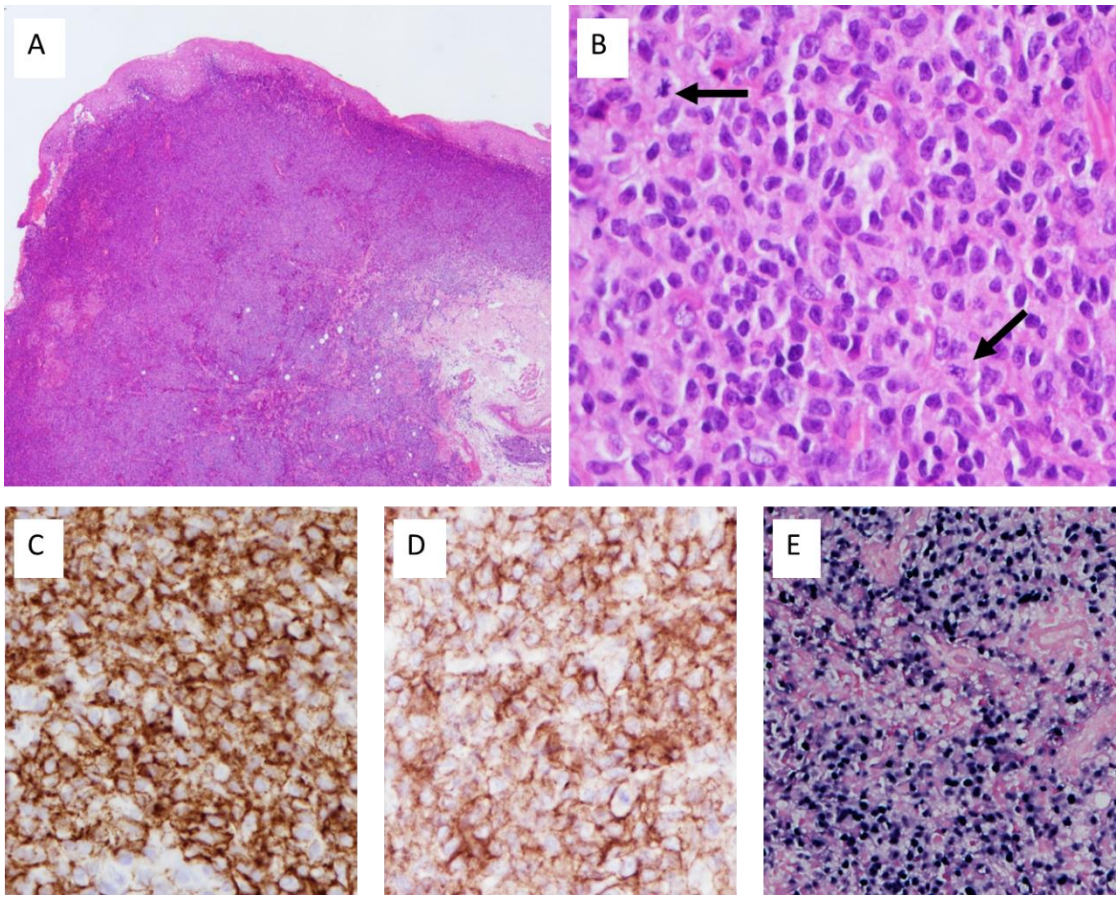

Figure 2.

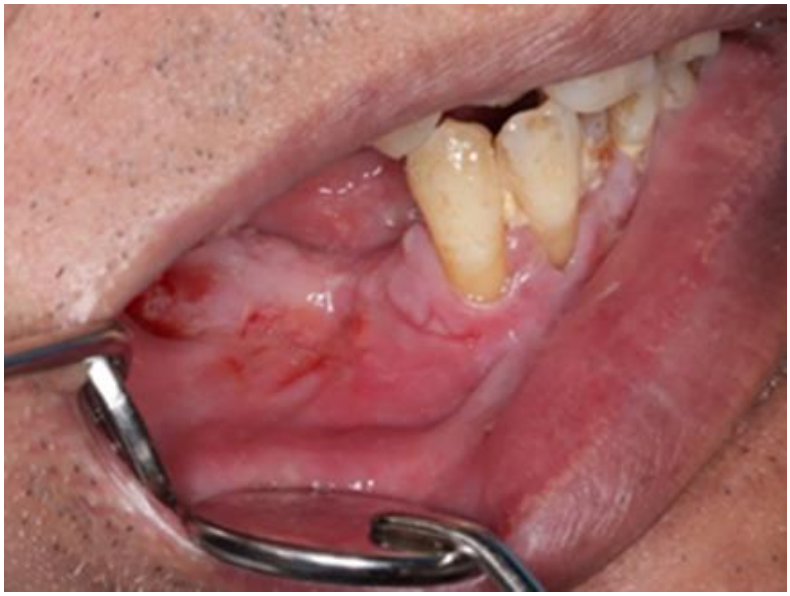

Figure 3.