EBV-Positive Mucocutaneous Ulcer

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EBV-positive mucocutaneous ulcer (EBV-MCU) was classified as a rare new entity of the lymphoproliferative B-cell diseases by the WHO in 2017 and must be distinguished from head and neck squamous cell carcinoma by early biopsy.

Keywords: Epstein–Barr virus ; mucocutaneous ulcer ; head and neck ulcer

1. Introduction

The Epstein–Barr virus (EBV, human gammaherpesvirus 4)-positive mucocutaneous ulcer (EBV-MCU) was first described in 2010 by Dojcinov et al. and was recognised as a unique entity of the lymphoproliferative B-cell disorders by the World Health Organization (WHO) in 2017 [1][2]. Since then, about 200 cases have been described in the literature worldwide. However, so far, EBV-MCU still remains an under-recognised entity in the head and neck region to most otorhinolaryngologists and maxillofacial surgeons.

EBV-MCU clinically presents itself as a shallow and sharply circumscribed ulcer that is reported to be mostly located in the oropharyngeal mucosa (52%), on the skin (29%) or the gastrointestinal tract (19%) [3]. These ulcers generally occur as a solitary lesion but have been reported to be multifocal in 17% of all cases. Extended and painful oral and oropharyngeal mucosal defects can lead to eating disorders resulting from odynophagia and dysphagia and to severe weight loss. Roberts et al. reported a case of a 49-year-old woman with an extended oral EBV-MCU eroding the maxilla and palate, with the spontaneous loss of multiple maxillary teeth, increasing pain, the inability to tolerate food and a 36 kg unintentional weight loss, finally leading to aspiration, pneumonia and sepsis that had to be treated with radiation therapy after a failed therapy with rituximab and had a duration of response of at least 6 months [3]. Au et al. reported a case of a 72-year-old woman with a long history of Crohn’s disease presenting with a 6-month history of a base of the tongue ulcer and severe odynophagia requiring gastrostomy tube placement [4]. Alternatively, as recently published by Li et al., complete healing of a deep ulcerating EBV-MCU of the oral cavity was only achieved after bone sequestrectomy followed by closure with a local mucosal flap [5].

EBV-MCU localised in the gastrointestinal tract can also cause a variety of abdominal symptoms, from appetite and weight loss to obstruction or even abdominal emergencies, such as colon perforation [6]. Beside the painful local tissue erosion, which can be severe, systemic manifestations such as fever, lymphadenopathy, organomegaly or bone marrow involvement are normally absent [1][7][8][9].

The underlying pathomechanism of EBV-MCU evolvement is attributed to a primary infection with the EBV and a subsequent viral genome latency in B cells and certain epithelial cells. Most individuals are exposed to the virus during childhood and adolescence and undergo an asymptomatic infection or a self-limiting infective mononucleosis [10]. The oropharynx is the main access of entry for the virus and the localisation of primary infection, often within Waldeyer’s ring, which explains why EBV-MCU mainly occurs on the oropharyngeal mucosa.

After a natural infection, the circular EBV deoxyribonucleic acid (DNA) persists as an episome in the cell nucleus of the infected lymphocytes through which the EBV latency within the B cells progresses in a unique and complex latency program. EBV-produced proteins transform naïve B cells into proliferating blasts that form germinal centres and later, after the restriction of further virus gene expression, induce the B cells to differentiate into long-lived resting memory B cells. Due to the lack of major histocompatibility complex (MHC) presentation of viral antigens, the infected cells miss T-cell detection and can avoid immunosurveillance. Through the activation and differentiation of the memory B cells into plasma cells and starting the lytic life cycle, it is possible for the virus to spread and infect other B cells [11].

During immunosuppression, which, in combination with a latent EBV infection, is the main pathophysiological mechanism for EBV-MCU development, the immunosurveillance by cytotoxic T cells is reduced, and the virus can enter lytic

replication again. While the virus can be kept in a dormant state systemically, localised EBV-driven lymphoproliferations can appear.

Viral ribonucleic acid (RNA) and proteins can at least transform latently EBV-infected B cells into malignant cells by constitutional gene activation and the suppression of apoptosis [10][11].

EBV-associated malignant B-cell lymphoproliferations include diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), plasmablastic lymphoma (PBL) or lymphomatoid granulomatosis (LG). Some conventional histopathologic criteria overlap with those of an EBV-MCU and may lead to diagnostic challenges or even misdiagnosis [2][10][11][12][13][14][15][16][17].

There are various forms of immunosuppression that are attributed to the development of EBV-MCU. In most cases, EBV-MCU is iatrogenic (56%) and is caused by immunosuppressive drug therapy. Several cases related to azathioprine, cyclosporin A, cyclophosphamide, tacrolimus, mycophenolate, tumour necrosis factor-alpha (TNFα) inhibitors and, above all, methotrexate (MTX) as a treatment for rheumatoid arthritis have been described [3][14][15][16][17][18][19][20]. Interestingly, methotrexate and cyclosporin A seem to be able to directly activate EBV lymphocyte proliferation [3][19]. EBV-MCU has also been described in immunosuppressed recipients after solid organ or bone marrow transplantation [7][21][22].

The other great risk factor is immunosenescence (40%) due to advanced age caused by a natural depressed T-cell function [1]. Therefore, age-associated immunosenescence seems to be a significant predisposing factor, especially for patients on immunosuppressive drug therapy [1][7][20][23][24][25][26].

EBV-MCU has been also attributed to primary immunodeficiencies and to human immunodeficiency virus (HIV) infections, but there are only few cases reported in the literature so far [17][27][28][29][30].

Histopathologically, EBV-MCU is a sharply circumscribed ulcer that is characterised by a polymorphous infiltrate of EBV-positive atypical immunoblasts, which range in size, and other inflammatory cells, such as lymphocytes, plasma cells, eosinophils and histocytes [1]. The atypical immunoblasts show a Hodgkin and Reed–Sternberg (HRS) cell-like morphology, which is difficult to distinguish from those present in classical Hodgkin lymphoma. Presenting a B-cell immunophenotype, these HRS-like cells express CD20, CD30, MUM1, PAX5, OCT-2, CD79a, BOB1 and, in about half of the cases, CD15. A clonal rearrangement of the immunoglobulin genes might be observed, indicating clonal out growths of the EBV-positive B cells. A small rim of surrounding T-lymphocytes can be commonly found. These T cells are mainly CD8-positive and often show a monoclonal or clonal restriction of T-cell receptor (TCR) gene rearrangements, leading to a limited repertoire against EBV epitopes [1]. Furthermore, apoptotic cells and necrosis can be detected as well.

Epstein–Barr virus-encoded small RNA (EBER) in situ hybridization shows an EBV presence in small B cells, plasmacytoid apoptotic cells and immunoblasts [1][13][18].

Especially in aged patients with a natural reduced response of the immune system to new antigens and without any further cause for immunosuppression, EBV-MCU was described as a nearly asymptomatic disease that can regress spontaneously without any treatment [1][13][31][32][33]. In patients on immunosuppressive drug therapy, complete remission could be successfully observed after a dose reduction of their immunosuppressive medication [8][12][18][19][23][24][25][26][34]. However, in some severe and persistent cases, EBV-MCU had to be treated with the monoclonal CD20 antibody rituximab or even with more extended chemotherapy, local radiation therapy, surgical interventions or a combination of these options to receive an adequate response [1][3][4][5][6][7][16][17][18][35].

2. EBV-MCU and Haematologic Malignancies

EBV-MCU usually appears because of a medically induced immunosuppression or because of advanced-age-associated immunosenescence. Beside the age, which is seen as a co-factor, immunodeficiency in patient was mainly caused by a relapsing chronic lymphatic leukaemia. CLL was mentioned to be one of the most common haematologic malignancies known to produce immune defects independent of therapy [36]. The histopathologic and immunohistochemical features of the ulcers of the pharynx and the lower lip showed the characteristic pattern of an EBV-MCU with a B-cell polymorphous infiltrate, including HRS-like cells and an expression for CD20 and CD30, and also showed areas consistent with simultaneous CLL/SLL infiltration. Thus, the manifestation of the CLL/SLL, clearly presented in the lymph node biopsy, was also detectable in both ulcers. The simultaneous manifestation of an EBV-MCU and another malignant disorder within the same lesion had not been described in the literature before.

There are few described cases of a synchronous or metachronous appearance of EBV-MCU and different lymphoproliferative diseases [13][16][22][36], with only three cases occurring in association with a present haematologic

malignancy [36][37][38].

Khazal et al. reported on a 75-year-old male patient with a medical history of CLL many years earlier that had been treated with rituximab, fludarabine and cyclophosphamide as well as recurrent left arm Merkel cell carcinoma that was treated by radiation therapy, surgery and pembrolizumab [37]. He presented with a painful gingival ulcer with progress to mandibular infiltration that fit the histological characteristics of an EBV-MCU. A bone marrow evaluation showed 60–70% CLL infiltration. Although the large HRS-like cells within the ulcer biopsy raised the possibility of a Hodgkin-type Richter transformation of the CLL, the diagnosis was finally based on clinical presentation and course.

The second case described a 29-year-old adult with intermediate-risk acute T-cell lymphoblastic leukaemia (T-ALL) who was treated with Children's Oncology Group protocol AALL0434 chemotherapy, including methotrexate and mercaptopurine, at the time of left-sided throat pain caused by an exudative left palatine tonsillar ulcer [38]. The biopsy of the ulcer showed a polymorphous infiltrate of lymphocytes, neutrophils, plasma cells and histiocytes as well as HRS-like cells. These cells were positive for CD20, CD30, CD45 and EBER and were negative for CD5, CD10 and CD15, which was, all in all, consistent with the diagnosis of an EBV-MCU. As in the previous case, there were no simultaneous histological signs of the T-ALL within the ulcer. After the EBV-MCU did not regress despite a reduction of the immunosuppressive drug therapy, a single dose of rituximab (375 mg/m^2) was administered and the ulcer resolved within two weeks.

Pina-Oviedo et al. analysed the clinical and pathological features of patients who developed a lymphoproliferative disorder after a therapy for a haematologic malignancy [32]. One of these patients, an 82-year-old woman with CLL under treatment with fludarabine, cyclophosphamide and rituximab, developed an EBV-MCU at the base of the tongue. Histopathology and immunohistochemistry were typical for EBV-MCU, with cells positive for CD20, CD30, CD45/LCA, CD79a, PAX5, OCT2 and EBER and negative for CD3, CD15 and BOB1. Thus, no infiltration by the CLL was noted. Three months later, she developed cervical lymph nodes that were infiltrated by an EBV-positive diffuse large B-cell lymphoma (DLBCL) and died. While DLBCL was the most common type of LPD after cancer therapy, the primary haematologic malignancy among this study group was predominantly CLL, assuming a certain predisposition for developing an EBV-positive lymphoproliferative disorder (EBV + LPD).

3. EBV-MCU and Other LPDs, a Challenge of Differentiation

EBV-MCU shares morphologic and phenotypic characteristics with more aggressive forms of lymphoproliferative disorders, such as EBV-positive diffuse large B-cell lymphoma (DLBCL), classic Hodgkin lymphoma (cHL), post-transplant lymphoproliferative disorder (PTLD), plasmablastic lymphoma (PBL), anaplastic large cell lymphoma (ALCL) or lymphomatoid granulomatosis (LyG), which sometimes makes it extremely difficult to distinguish.

4. EBV-Positive Diffuse Large B-Cell Lymphoma (DLBCL)

EBV-positive diffuse large B-cell lymphoma (DLBCL) is a high-grade lymphoma with a poor outcome. It presents a wide range of morphological features, from polymorphous infiltrates of HRS-like cells, immunoblasts and plasma cells in an inflammatory background of histiocytes and lymphocytes with areas of prominent necrosis and angioinvasion to a T-cell-like or more monomorphic pattern [39]. The cells are positive for CD20, CD19, CD79a, PAX5, OCT2, BOB1, MUM1 and CD30, with variable co-expression of CD15. CD10 is mostly negative and CD45 and BCL6 show a variable expression. There is a widespread positivity for EBER. These almost indistinguishable similarities to EBV-MCU, cHL may be misleading and all clinical, histologic, and immunohistochemical features must be considered to avoid misdiagnosis [14]. Both diseases predominantly occur in elderly people with presumed immunosenescence, but while EBV-MCU shows a localised nature and often a self-limiting course, DLBCL occurs as a generalised, extranodal progressive disease. The sharply circumscribed EBV-MCU with a small rim of T cells at the base can be differentiated from the more infiltrative pattern in DLBCL. Considering the findings of Ohata et al., a mutational panel and the absence of CD10 and BCL6 expression in EBV-MCU can be supportive [40].

Furthermore, Satou et al. observed that, in contrast to DLBCL and cHL, immune evasion via the programmed cell death protein 1/programmed cell death 1 ligand 1 (PD1/PD-L1) pathway is usually absent in EBV-MCU [18]. However, Daroontum et al. reported a case of a PD-L1-positive EBV-MCU in a patient with multiple EBV-driven lymphoproliferative B-cell disorders [41]. All lesions had PD-L1 expression in the EBV-positive large B cells and HRS-like cells, but there was evidence for a clonal relationship among these lesions by PCR analysis for IGH. The majority of DLBCL show clonal IGH and restricted or oligoclonal TCR rearrangements because of a reduced T-cell repertoire [1]. EBV DNA serum levels often correlate with the burden of disease [39].

The clinical presentation of EBV-MCU, with its strictly localised occurrence and the absence of mass lesions, is crucial in distinguishing these two entities [10][14][16]. There are some reports of lesions that were initially diagnosed as DLBCL before being reclassified as EBV-MCU [9], and, therefore, special attention should be drawn to their similarity.

5. Classic Hodgkin Lymphoma (cHL)

Classic Hodgkin lymphoma (cHL) is one of the most common lymphoma types worldwide. It is associated with a non-obligatory presence of EBV infection and most commonly leads to an impressive cervical and mediastinal lymphadenopathy. Patients are often presenting B symptoms. cHL shares some (immune)histological characteristics with EBV-MCU, especially the presence of CD30-positive HRS cells co-expressing CD15 in a strong inflammatory background. These cells are also positive for MUM1. The tumour cells show a downregulation of B-cell markers and transcription factors such as OCT2 and BOB1, with a remaining slight expression of PAX5, whereas EBV MCU more often expresses CD 20 [10][14].

In EBV-associated cHL, typically only the HRS cells are positive in EBER in situ hybridization, which is an important fact regarding the differentiation to EBV-MCU in which EBER positivity can be detected in several different cell types. In addition, EBV MCU displays an EBV latency type III with expression of the Epstein–Barr virus nuclear antigen 2 (EBNA 2), whereas cHL presents latency type 0/I or II and is negative for EBNA 2. At least HRS cells express PD-L1 ligands and consistently express LMP1 that starts the NF-kappa B and JAK/STAT signalling pathway, leading to proliferation [10][14]. Applying to this entity as well as for the DLBCL, the clinical presentation of the EBV MCU with strict localised and superficial occurrence is crucial in differentiating these two entities [10].

6. Plasmablastic Lymphoma (PBL)

Another important EBV-associated LPD that also mainly occurs in the oral cavity is the plasmablastic lymphoma (PBL), a highly aggressive form of non-Hodgkin lymphoma (NHL) with an immunophenotype of terminally differentiated B cells and a loss of typical B-cell antigen expression. The large plasmablasts lack CD20, CD19, CD45 and PAX5 and show an expression of plasma cell markers that are positive for CD79a, MUM1, CD38 and CD138 [12][14]. The cells show an overall expression of MYC protein, and the proliferation rate is high (Ki-67). Most cases are EBV-positive in the EBER in situ hybridization. The PBL is associated with immunosuppression, mainly due to HIV infections, and its localisation in the head and neck region makes it important as a potential differential diagnosis of EBV-MCU. Beside the immunohistochemical differences, PBL shows a monomorphous pattern with sheets of plasmablasts, whereas the EBV-MCU is characterised by a typical polymorphous pattern [9][12]. In contrast to the benign course of EBV-MCU, the prognosis of PBL is poor, with high observed mortality rates.

7. Post-Transplant Lymphoproliferative Disorder (PTLD)

Post-transplant lymphoproliferative disorder (PTLD) is an immunodeficiency-related proliferation of B cells that are latently infected with EBV after solid organ transplantation and is another important disease to consider in the differential diagnosis of EBV-MCU [7]. The symptoms are nonspecific and can be like those in infectious mononucleosis. PTLD can form tumour masses that may obstruct organs or spread further, leading to organ dysfunctions. The monoclonal form has an especially aggressive course. The histological features contain the full range of B-cell maturation, from immunoblasts to plasma cells and variable-sized lymphocytes. The HRS-like cells are positive for CD20 and CD30, while CD15 has been reported to be negative. There is an expression of LMP1, inducing an uncontrolled cell proliferation. EBER is mainly positive for EBV. Blood levels of EBV DNA measured by PCR have been shown to predict the development of PTLD [31]. Hart et al. detected EBV DNA in the blood of patients with solid organ transplantation in about 80% of all cases, presenting a quantifiable EBV viremia [7][31]. This viremia usually does not present in patients with EBV-MCU and, therefore, can be a further distinguishing feature [17][21][42]. Nevertheless, the presence of EBV DNA in the blood does not automatically exclude the diagnosis of EBV-MCU [9]. EBV DNA and antibody levels in the blood of patients with EBV-MCU has not been regularly measured and should be further investigated. EBV MCU can arise with typical clinical presentation and corresponding histomorphology in the background of immunodeficiency caused within the post-transplant setting. In those cases, no formal differential diagnosis is necessary, but the lesion should be reported as polymorphous PTLD with features of an EBV-MCU [10].

8. Anaplastic Large Cell Lymphoma (ALCL)

Anaplastic large cell lymphoma (ALCL) is a type of NHL with the presence of large pleomorphic cells that are positive for CD30 and is another differential diagnosis of EBV-MCU due to histological similarities. It typically presents at a late stage

with systemic symptoms as a general lymphadenopathy, extranodal disease or as a cutaneous ulcer. A rare subtype can occur after breast implant reconstruction. The cells are negative for CD3 and for EBV in the EBER in situ hybridization [17][43].

9. Lymphomatoid Granulomatosis (LyG)

Lymphomatoid granulomatosis (LyG) is an EBV-driven B-cell LPD that is associated with immunosuppression with angiodestructive features and is characterised by a cell infiltrate of small T cells and variable numbers of large atypical immunoblasts and HRS-like cells that are positive for CD20, CD30, LMP1 and EBER but not usually for CD15. The differentiation to EBV-MCU merely relies in the clinical presentation with lung lesions or affliction of the central nervous system [33].

10. Head and Neck EBV-MCU Management

Beside all these histological similarities to other lymphoproliferative disorders, EBV-MCU predominantly occurs in the mucosa of the oral cavity and the oropharynx and, therefore, mimics squamous cell carcinomas at first sight. As these two entities can clinically present in a similar morphology and the treatment of each is completely different, it is very important to take an early biopsy to exclude an oral or oropharyngeal squamous cell carcinoma. Of course, this also applies to ulcerative lesions of the skin in the head and neck region, as with the ulcer of the lower lip in patient.

As EBV-MCU is still a rare entity of lymphoproliferative disorders, it is important to mind it as a potential disease in elderly and immunocompromised patients with persistent cutaneous or mucosal ulcerative lesions. An early biopsy must be taken to distinguish it from other malignant disorders. Imaging, a blood examination, including EBV serology, and, in some uncertain cases, a bone marrow biopsy can be helpful to exclude a systemic lymphoproliferative disorder.

Since the awareness for EBV-MCU is currently still low and ulcerative lesions can be easily misdiagnosed, there might be cases of unnecessary patient overtreatment [8]. Due to the limited experiences, no consensus or formal guideline for EBV-MCU treatment exist, and therapeutic strategies are only based on case reports and literature reviews.

If possible, immunosuppressive drug therapy should be reduced or discontinued as a first step. Conservative treatment is possible if the ulcer remains localised. In persistent or progressive cases, rituximab monotherapy (375 mg/m^3, four weekly doses) or as a part of a chemotherapy (R-CHOP) should be considered. Local radiation had a beneficial effect in destructive courses. The selection of the appropriate therapy should be made in regard to clinical and individual aspects. However, in accordance with Hujoel et al., a lack of response within three months should always lead to another biopsy to re-evaluate the diagnosis of EBV-MCU [44].

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