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CASE REPORT

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Epstein–Barr virus mucocutaneous ulcer followed by Hodgkin lymphoma in multiple myeloma patient

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Abstract

Epstein–Barr virus mucocutaneous ulcers (EBV MCU) are B-cell lymphoproliferative disorders associated with immunosuppression. We report EBV MCU in a multiple myeloma patient on lenalidomide maintenance after stem cell transplant that resolved with decreased immunosuppression. Furthermore, the subsequent development of classical Hodgkin lymphoma suggests an underlying predisposition to EBV-driven lymphoproliferative disorders.

KEYWORDS

diagnostic dilemma, Epstein–Barr Virus, Hodgkin Lymphoma, immunosuppression, lenalidomide, mucocutaneous ulcer

1 | INTRODUCTION

In the last decade, generally indolent Epstein–Barr virus-associated mucocutaneous ulcers (EBV MCU) have been described.[1,2] This diagnosis was given provisional status in the 2016 World Health Organization (WHO) classification of lymphoid neoplasms but does not have clear diagnostic criteria.[2] Generally, EBV MCU are well-circumscribed, ulcerating lesions in mucosal surfaces that arise in patients with age-related[3] or iatrogenic immunosuppression.[1,4-7] The median age at presentation is 68.5 years, with a 60% female predominance.[4] Histologically, EBV MCU is characterized by a polymorphous infiltrate of EBV-transformed B cells and can include scattered abnormal lymphoid forms resembling Hodgkin/Reed-Sternberg (H/RS) cells.[1] These H/RS-like cells express CD30, which is also universally expressed in classical Hodgkin lymphoma with variable expression in other B-cell malignancies. The H/RS-like cells show faint nuclear expression of PAX5 compared with small background B cells and show variable positivity for CD20, a B-cell marker.[1] EBV MCU characteristically has an indolent course, and the lesion may resolve with a decrease in immunosuppression.[8] We report a unique case of an EBV MCU in a patient on lenalidomide maintenance therapy for multiple myeloma who had also previously had two autologous stem cell transplantations. We discuss the difficulty elucidating the precise underlying causal factor driving development of EBV MCU in such a patient. We also report the subsequent development of an EBV-associated classical Hodgkin lymphoma (CHL) in this patient and propose further research to elucidate understanding of what predisposes some patients to multiple EBV-driven lymphoproliferative disorders.

2 | CASE DESCRIPTION

A 56-year-old gentleman presented to our clinic with dysphagia. His medical history was significant only for multiple myeloma diagnosed 8 years prior to the current presentation. This had been treated with lenalidomide, bortezomib, and dexamethasone (RVD) for four cycles followed by autologous stem cell transplant. He suffered a relapse and underwent re-induction with RVD for six cycles with bortezomib stopped after four cycles due to peripheral neuropathy. He received a repeat autologous stem cell transplant and started on maintenance lenalidomide of 10 mg daily on days 1–21 of a 28-day cycle.

At the time of his presentation, 5 years after his second stem cell transplantation, he had experienced 1 month of progressive sore throat, dysphagia, and odynophagia with a 12-pound weight loss secondary to his difficulty swallowing. A tonsillar abscess was identified, the patient was started on amoxicillin/clavulanic acid, and his lenalidomide was stopped. Despite antibiotics, his symptoms persisted. A laryngoscopy showed an exophytic, ulcerating tonsillar mass. The biopsy showed a submucosal infiltrate of EBV-positive intermediate-to-large lymphoid cells and scattered H/RS-like cells, establishing a diagnosis of an EBV-positive B-cell lymphoproliferative disorder (Figure 1; left column). Plasma EBV quantitative PCR was negative. A full body positive emission tomography (PET) scan showed no sites of increased uptake. After 20 days off his lenalidomide, he reported complete resolution of his symptoms. As there was no evidence of systemic involvement with the PET scan and with clinical improvement with cessation of his iatrogenic immunosuppression, he was diagnosed with an EBV MCU. His lenalidomide was resumed at 5 mg daily and ultimately the mass fully resolved.

During follow-up, approximately a year after EBV MCU presentation, the patient developed drenching night sweats and fevers. A repeat PET scan showed diffuse lymphadenopathy in the neck, mediastinum, and abdomen, with associated splenomegaly. Biopsy of a retroperitoneal lymph node showed archetypal features of EBV-associated CHL (Figure 1; right column). Lenalidomide was again stopped, and he was started on standard CHL therapy: doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). B-cell receptor gene rearrangement studies were attempted on both biopsies, but a clonal population was not identified in either case. He completed six cycles of ABVD and is in complete remission still at 1-year post-completion of treatment.

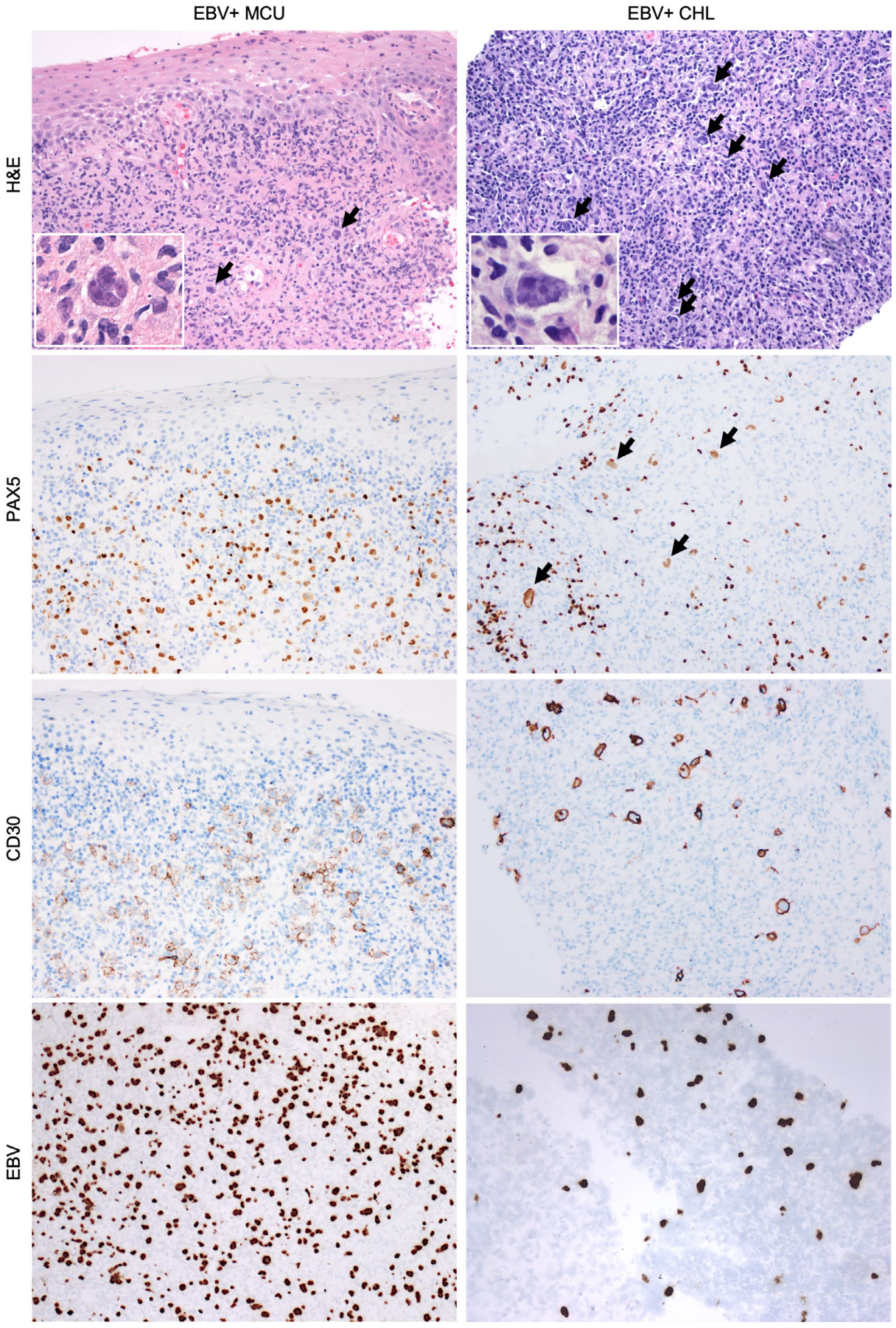
3 | DISCUSSION

It was difficult to elucidate the exact etiology driving the formation of an EBV MCU in our patient. Certainly, his iatrogenic immunosuppression from lenalidomide seemed a clear culprit, especially as his EBV MCU resolved with a decrease in dose. However, he also had an autologous stem cell transplant 8 years and then again 5 years prior to the development of the EBV MCU, which also could have played a role. While EBV MCU arising in the setting of post-stem cell transplant has been reported,[1,9,10] to our knowledge, this case is the first of an EBV MCU arising in the setting of lenalidomide therapy for multiple myeloma maintenance treatment. This case shows the difficulty in fully understanding the driving factor behind EBV MCU, but the importance of the recognition of this condition is due to the indolent course and need for only reduction of immunosuppression for resolution.

Epstein–Barr virus mucocutaneous ulcers usually manifests as ulcers in the oropharynx, skin, and gastrointestinal tract.[11] EBV MCU is most frequently reported as localized to the oral cavity (41% to >70% of cases),[4,12-14] followed by colon (19%–40% of cases), esophagus (30%), rectum (20%), and terminal ilium (10%).[12,15] Most of the initial reports showed that EBV MCU were isolated lesions,[1] but more recently patients have been reported to have multifocal disease, typically confined to a single anatomic region.[12,16] Uniformly, and likely definitionally, there is no evidence of systemic involvement.[1,7,16]

In isolation, the histologic features of EBV MCU can be difficult to differentiate from other EBV-associated B-lineage neoplasms.[16] The lesions are composed of intermediate-to-large B cells with scattered H/RS-like

FIGURE 1 Histology of EBV+Mucocutaneous Ulcer (EBV MCU; left column) and EBV+Classic Hodgkin Lymphoma (CHL; right column). The EBV MCU (left column) is characterized by a proliferation of variably sized lymphoid cells in the submucosa, including large Reed-Sternberg-like cells that can be seen from low-power (arrows, H&E, objective magnification ×4) and higher magnification (inset; objective magnification ×40). The EBV MCU was diffusely positive for CD20 (not shown), with the nuclear B-cell-specific marker PAX5 highlighting the cytologic pleomorphism of the infiltrate (objective magnification ×4). CD30 stained a significant subset of cells (objective magnification ×4), and EBV-EBER expression was abundant (objective magnification ×10). In contrast, the CHL showed scattered Hodgkin and Reed-Sternberg cells (arrows, H&E, objective magnification ×4; inset, objective magnification ×40) in a background of predominantly small lymphocytes, histocytes, and plasma cells. The neoplastic cells show typical faint expression of PAX5 (arrows) and CD30 (original objective magnification ×4) compared with small non-neoplastic B-cell aggregates in the background and were negative for CD20 (not shown). The large neoplastic cells were positive for EBV-EBER (objective magnification ×10)


EBV+ MCU
EBV+ CHL
H&E
PAX5
CD30
EBV

cells, the majority expressing EBV-encoded small RNAs (EBER), certainly on the morphologic spectrum of EBV-associated diffuse large B-cell lymphoma (DLBCL).[14] The H/RS-like cells seen in EBV MCU can show morphologic and immunophenotypic features of CHL.[12] In fact, prior to EBV MCU being recognized as a clinicopathologic entity in 2016 by the WHO, many of these ulcerations may have been classified as EBV DLBCL or CHL,[12] leading to patients receiving more aggressive and toxic treatment with multi-agent chemotherapy than may be necessary.

Epstein–Barr virus mucocutaneous ulcers can arise in the setting of age-related immunosuppression (median age 80 years old),[1,3] iatrogenic immunosuppression,[4-7] and rarely with an underlying immunodeficiency syndrome including human immunodeficiency virus (HIV).[4,7,12,16,17] Iatrogenic immunosuppression can be associated with inflammatory bowel disease therapy,[11,16,18] in the post-solid organ transplant setting,[19] for treatment of hematologic malignancies,[4,20] and in the post-stem cell transplant setting.[1,9,10] The review by Sinit et al[4] characterized the immunosuppressants used in cases of EBV MCU as follows: methotrexate (46%), azathioprine (11%), mycophenolate (11%), prednisone (11%), rituximab (8%), and cyclosporine A (8%). Across the literature, methotrexate is the most commonly cited immunosuppressant associated with EBV MCU.[5-7,21,22] An association with maintenance lenalidomide has not previously been documented. This is an area where further study is needed.

Epstein–Barr virus mucocutaneous ulcers typically shows an indolent clinical course.[1,13] One series showed 96.6% of cases had a complete remission.[8] Most ulcers regress after cessation or reduction of the inciting immunosuppression.[12] It has thus been suggested that patients with EBV MCU secondary to iatrogenic immunosuppression require only immunosuppression reduction.[12] Alternatively, therapy is usually required in patients with a primary immunodeficiency and patients with gastric EBV MCU.[4,12,14,16,23-25] In fact, EBV MCU presents earlier and with a more aggressive clinical course in patients with a primary immunodeficiency.[12] When necessary, patients have been managed with systemic chemotherapy including rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); rituximab and bendamustine; and radiotherapy.[16] Given our patient's relatively young age and response to lenalidomide reduction, iatrogenic immunosuppression was a presumed risk factor for EBV MCU, though as mentioned, his stem cell transplant history could have also affected this development. This case highlights the broad array of factors that can predispose a patient to the development of EBV MCU.

Another important clinical finding in our case was that our patient developed EBV-positive CHL approximately 1-year post-EBV MCU diagnosis. Development of a subsequent EBV-driven malignancy after regression of an EBV MCU has been previously documented.[10,26] Daroontum et al[26] described a patient with resolved EBV MCU who, 18 months later, developed an EBV-positive nodal polymorphous B-lymphoproliferative disorder and subsequently EBV-positive DLBCL. It was unclear to the authors whether this represented stepwise progression of a single event or three independent processes, though there was no evidence of clonal relationship between these three diseases on biopsy.[26] Satou et al[10] presented a patient with EBV MCU after autologous stem cell transplant that regressed who later developed EBV-positive polymorphic post-transplant lymphoproliferative disorder. Both reports describe patients who may, for different reasons, be prone to EBV-driven lymphoproliferative disorders, with the first case having an unclear etiology except for age and the second patient being immunosuppressed after autologous stem cell transplant. Our patient also developed two histologically distinct and likely clonally independent EBV lymphoproliferative disorders and may also have an underlying predisposition to these proliferations in addition to his immunosuppression from myeloma therapy. It has been shown at least in the solid organ transplant setting that genetic changes in anti-inflammatory cytokines increase susceptibility to EBV-associated post-transplant lymphoproliferative disorders.[27] There are also hereditary associations leading to this susceptibility as well.[28] However, in the absence of these settings, there is a paucity of literature on acquired predispositions to EBV-driven lymphoproliferations. Further study is needed on patients with multiple EBV-positive lymphoproliferative disorders and predisposing factors to these malignancies.

In our patient, clinical response to withdrawal of immunosuppression and histologic differences between the tissue biopsies suggest the EBV MCU and the CHL are unlikely to be clonally related. PCR-based B-cell receptor gene rearrangement studies were attempted but a clonal population was not identified in either the EBV MCU or CHL. This may reflect known assay sensitivity limitations, particularly common in CHL and similar proliferations. Unfortunately, we cannot definitively prove or disprove clonal association between the EBV MCU and the CHL.

Interestingly, a patient with suspected EBV MCU that apparently progressed to CHL has been described.[11,14] This patient had Crohn's disease on methotrexate and infliximab and subsequently developed suspected EBV MCU in the splenic flexure, sigmoid colon, and rectum. The ulcers persisted despite immunosuppression reduction. Subsequent colectomy showed pathology features consistent with CHL, as well as HRS-like cell involvement in the liver and nodes.[11] Likely under strict WHO criteria, the initial diagnosis of an EBV MCU would not

be supported as EBV MCU is not typically multifocal and the reported proliferation did not resolve with decreased immunosuppression. While this brings up the question if EBV MCU can progress to CHL, it also points out the difficulty in accurately diagnosing with the entire clinical spectrum of pathology not yet elucidated.[10]

4 | CONCLUSION

Epstein–Barr virus mucocutaneous ulcers is an important entity to have on the differential diagnosis for patients who are immunosuppressed and/or have a history of a stem cell transplant presenting with ulcerating lesions.[9,19,29] Our case shows lenalidomide as a possible driving factor for the development of EBV MCU which has not yet been reported. We show the challenge of making the diagnosis of EBV MCU when patients have a history of multiple exposures to immunosuppressants. Further study is needed into the array of immunosuppressants that can predispose patients to EBV MCU. Our patient developing a second, unrelated EBV-driven malignancy, CHL, also highlights the need for further understanding of the etiology behind some patients being more prone to EBV-driven malignancies.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Moriah Forster, MD, Yuri Fedoriw, MD, and Natalie Grover, MD, involved in conception or design of the work, drafted the article, critically revised the article, and published the final approval of the version. Sascha Tuchman, MD, MHS critically revised the article and published the final approval of the version.

CONSENT

Published with the written consent of the patient.

DATA AVAILABILITY STATEMENT

None.

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