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Epstein–Barr virus positive mucocutaneous ulcer of vulva

Sir,

Epstein–Barr virus positive mucocutaneous ulcer (EBV-MCU) is a recently recognised B cell lymphoproliferative disorder that is driven by latent EBV infection. The ulcer is described to occur in patients with age-related or iatrogenic immunosuppression, often with a Hodgkin-like pattern and an indolent course, including spontaneous regression.[1] In humans, EBV is the most common persistent virus infection, where it elicits the B-cell proliferation and transformation. The World Health Organization (WHO) 2017 discusses two lymphoproliferative diseases that are associated with EBV: EBV positive diffuse large B cell lymphoma and EBV-MCU. EBV-MCU is a rare provisional entity which is likely under-reported secondary to its recent recognition and morphological and immunophenotypical similarities to Hodgkin lymphoma. EBV-MCU occurs most commonly in the oropharynx, gastrointestinal tract and skin.[2] To the best of our knowledge there is no report in the English published literature of EBV-MCU presenting as a vulval introital ulcer.

Here we present a case of an EBV-MCU in a 78-year-old female, who presented with a vulval introital ulcer. She was a known case of rheumatoid arthritis on methotrexate (MTX) for 3 years, 20 mg per week. There was no history of trauma, or tobacco consumption. The clinical examination revealed a 4×4 cm introital ulcer in the midline. An excisional biopsy of the ulcer was performed. The histological examination revealed squamous mucosa with extensive ulceration (Fig. 1A). The underlying granulation tissue showed a moderate infiltrate of lymphoid cells admixed with a few scattered eosinophils (Fig. 1B). Many of the lymphoid cells showed atypia with enlarged 'blastic' appearing nuclei and clear cytoplasm. However, the infiltrate appeared polymorphous with zonation of the less mature appearing lymphoid cells in the superficial stroma. The atypical lymphoid cells were positive for CD20 (Fig. 1C), EBER (Fig. 1D), Bcl2, CD30, CD43, and CD15 and negative for CD3, CD10, bcl6, CD5, CD23, CD5 and CD4. In view of the history of MTX induced immunosuppression, histology, and supporting immunohistochemistry, a diagnosis consistent with EBV-MCU was made by two general surgical pathologists (SA, CSL) and a haematopathologist (CCCC).

Polymerase chain reaction (PCR) amplification for gene rearrangements of the IgH, Ig-kappa (IgK), TCR-beta (TCRB) and TCR-gamma (TCRG) (courtesy of Dr Benhur Amanuel, PathWest) showed monoclonal IgK rearrangement. Positron emission tomography (PET) scan and CT-scan performed 2 months following surgery showed no evidence of nodal or extranodal involvement by the lymphoproliferative disease. The patient was managed by reducing her immunosuppressant therapy for her rheumatoid arthritis and she remained free of the disease at follow-up 5 months following the initial diagnosis.

In 2010, Dojcinov *et al.*[3] first reported the entity EBV-MCU in 26 patients, nine associated with immunosuppression caused by MTX, azathioprine, and cyclosporine-A given for autoimmune diseases and 17 with ulceration of the skin or mucosa with no systemic involvement as evident in this case. In 2014, Hart *et al.*[4] reported seven patients of EBV-MCU in 70 solid organ transplant recipients with EBV positive post-transplant lymphoproliferative disorder (PTLD). In 2015, Bunn *et al.*[5] described two cases of AIDS-related EBV-MCU. Most EBV-MCU cases are self-limited, however a few reported cases have progressed or even transformed into classical Hodgkin lymphoma (CHL).[6] In the latter cases, it is unclear whether EBV-MCU might be a precursor of CHL or the initial diagnosis was actually EBV positive CHL with overlapping features with EBV-MCU. The spectrum of age-related, EBV positive lymphoproliferative disorders (aEBVLPD) was first described by Oyama and co-workers and distinctively occurs in elderly patients without any history of immunosuppression.[7]

EBV has long been associated with B-cell lymphoproliferative disorders. After primary infection at an early age EBV persistently infects B cells of most adults. The virus elicits B-cell transformation and proliferation through complex mechanisms. The viral genes upregulate a variety of cellular antigens and expression of genes in B cells. Key molecular pathways controlling the cell cycle, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), are activated and virus-induced cytokines exert paracrine proliferative effects.[8] The pathological features are identical regardless of the anatomical site or cause of immunosuppression. Histologically, EBV-MCU is characterised by a polymorphous infiltrate and atypical large B cells with Hodgkin/Reed Sternberg (HRS) cell-like morphology and admixed abundant T cells. Angioinvasion and necrosis can be present in addition to surface ulceration. The large B cells are consistently positive for EBV by latent membrane protein (LMP) and *in situ* hybridisation. About one-third of cases are clonal for immunoglobulin receptor gene or T-cell receptor gene rearrangement. These pathological, immunophenotypical, and molecular features might overlap with lymphoma.[9]

In summary, EBV-MCU must be distinguished from the more aggressive systemic PTLD and lymphomas, especially CHL, EBV positive diffuse large B-cell lymphoma, plasmablastic lymphoma, and anaplastic large cell lymphoma. A

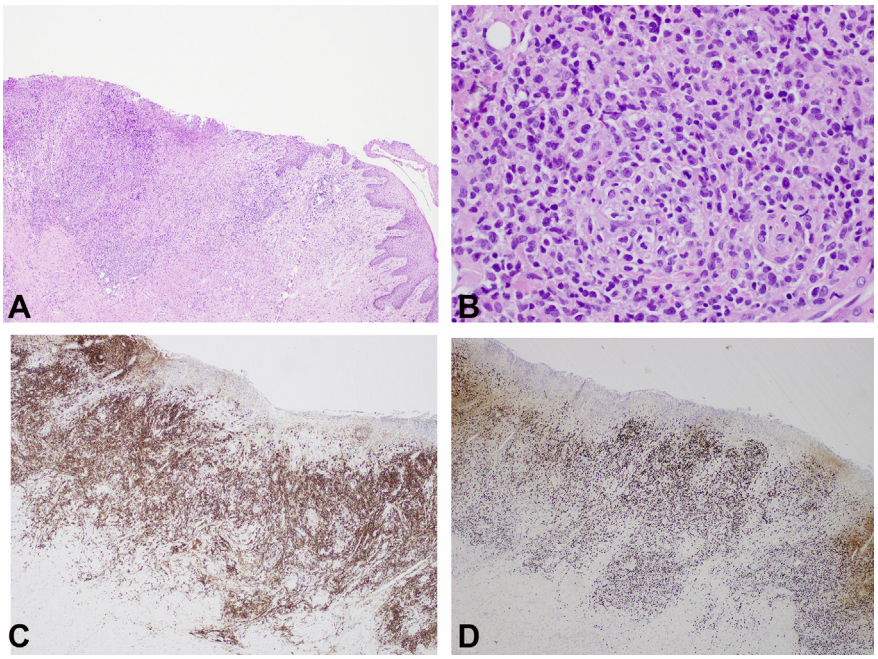

Fig. 1 Microscopy. (A) Low power of the lesion showing squamous mucosa with extensive ulceration. (B) High power image showing moderate infiltrate of atypical lymphoid cells. (C) The atypical lymphoid cells are strongly CD20 positive. (D) The atypical cells are strongly EBER positive.

medical history should always be taken to determine if the patient is on immunosuppressive medications. The current understanding of EBV-MCU is classically a self-limited condition. While no guidelines exist, management is conservative and includes withdrawal or decrease of immunosuppressant dose. Hence, pathologists must have knowledge of these diseases and a thorough clinicopathological investigation of this rare entity is important to avoid erroneous diagnosis and overtreatment.

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Mammary-type myofibroblastoma in the head and neck region

Sir,

Mammary-type myofibroblastoma (MTMF) is a mesenchymal tumour composed of cells with myofibroblastic differentiation initially described in the breast. It has been classified as benign by the World Health Organization (WHO) as it neither recurs locally nor metastasises.[1] Cytogenetic analysis of MTMF has identified consistent deletions at 13q resulting in the loss of tumour suppressor gene *Retinoblastoma* (*RB1*) at 13q14 chromosomal region, a genetic