MUM1 immunostain for quantification of plasma cells in myeloma patients as it mitigates the degree of overestimation.

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EBV positive mucocutaneous ulcer with plasmacytic/plasmablastic differentiation and *MYC* rearrangement: a diagnostic challenge and a mimic of plasmablastic lymphoma

Sir,

Epstein–Barr virus positive mucocutaneous ulcer (EBVMCU) is a provisional entity in the 2017 World Health Organization (WHO) classification of lymphoid neoplasms. It is defined as a localised, indolent lesion occurring in cutaneous or mucosal sites in patients with immunosuppression including age-related, human immunodeficiency virus (HIV)-related, or iatrogenic such as those receiving immunosuppressants for transplantation and autoimmune diseases, or cancer patients receiving chemotherapy.[1–3] Histologically, there is a dense polymorphic infiltrate comprising a substantial number of large transformed B-cells, often with Hodgkin/Reed–Sternberg-like features that are EBV positive and mostly CD20 positive, usually accompanied by a band-like infiltrate of reactive T-cells. Plasmablastic lymphoma (PBL) is an aggressive lymphoma comprising a diffuse proliferation of large cells resembling B immunoblasts or plasmablasts that are negative for CD20/PAX5 and positive for CD138/MUM-1 with a plasmacytic immunophenotype. PBL occurs most commonly in the oral cavity of HIV patients or in those with other causes of immunodeficiency. EBV infection is positive in about 60–75% of PBL cases. Furthermore, *MYC* rearrangement occurs in around half of the cases with PBL, and this genetic alteration is more common in EBV positive than EBV negative cases.[4] EBV is rarely positive in plasmacytoma, either in immunocompromised or immunocompetent patients. Herein we present a case with rheumatoid arthritis and long-term use of methotrexate and prednisolone who developed a EBVMCU in the oral cavity. Interestingly, the EBV positive large cells were CD20 negative, *MYC* rearranged with monoclonal plasmacytic/plasmablastic cells. Although our case resembled PBL or plasmacytoma, the lesion was localised and completely regressed after reduction of the doses of immunosuppressants without chemotherapy or radiation therapy, supporting the diagnosis of EBVMCU. This case illustrated that EBVMCU may be of plasmablastic morphology/immunophenotype and there is a grey-zone area between EBVMCU and PBL. Nevertheless, clinical and pathological correlation is essential as highlighted in the current case report.

A 72-year-old woman had a history of rheumatoid arthritis for at least 8 years and was under treatment with methotrexate (10 mg per week), prednisolone (10 mg per day) and hydroxychloroquine since January 2010. She developed a 2×1 cm, well-demarcated ulcer with peripheral elevation in her right lower lingual gingiva near the mouth floor (Fig. 1A). The incisional biopsy in May 2018 showed mucosal ulceration and a dense polymorphic infiltrate composed of medium-sized lymphoid cells admixed with many plasma cells (ranging from mature, atypical plasma cells to occasional plasmablasts), some neutrophils, and histiocytes (Fig. 1B). Some large atypical cells with vesicular nuclei and irregular nuclear membrane were noted (Fig. 1C,D). Mitotic figures were occasionally seen. Immunohistochemically, the large lymphoid cells expressed CD19, with a partial expression of CD30 and bcl-2, but not CD10, CD20, CD56, bcl-6, cyclin D1, or HHV-8 (Fig. 2). The proliferation index by Ki-67 was 80% (Fig. 2F). Around 30% of cells were marked by MYC (clone EP121, also known as Y69; Epitomics, USA) and this result was considered negative using the current cut-off criterion of 40% as used in diffuse large B-cell lymphoma. There was a moderate amount of CD3 positive reactive T-cells in the background and many plasmacytic cells highlighted by CD138 and IRF4/MUM-1 (Fig. 2D,E). These plasmacytic cells were monotypic for lambda light chain expression (Fig. 2G). *In situ* hybridisation for EBV-encoded small RNA was positive, mainly in the larger cells (Fig. 2H). Polymerase chain reaction-based clonality study showed a clonal *IGH* rearrangement. Fluorescence *in situ* hybridisation using paraffin section with Vysis break-apart probes revealed *MYC* rearrangement which was positive in 19% of cells (Fig. 2I),

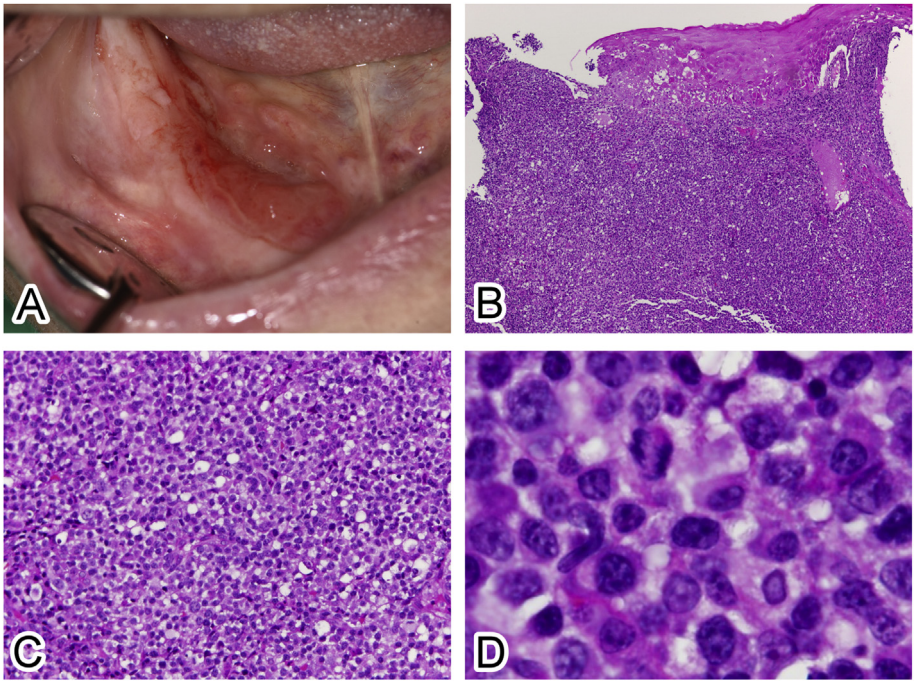

Fig. 1 (A) Circumscribed ulcerative lesion in the oral cavity. (B) Dense infiltrate beneath the squamous mucosa (H&E). (C,D) Higher-power views show plasmacytic cells and plasmablasts.

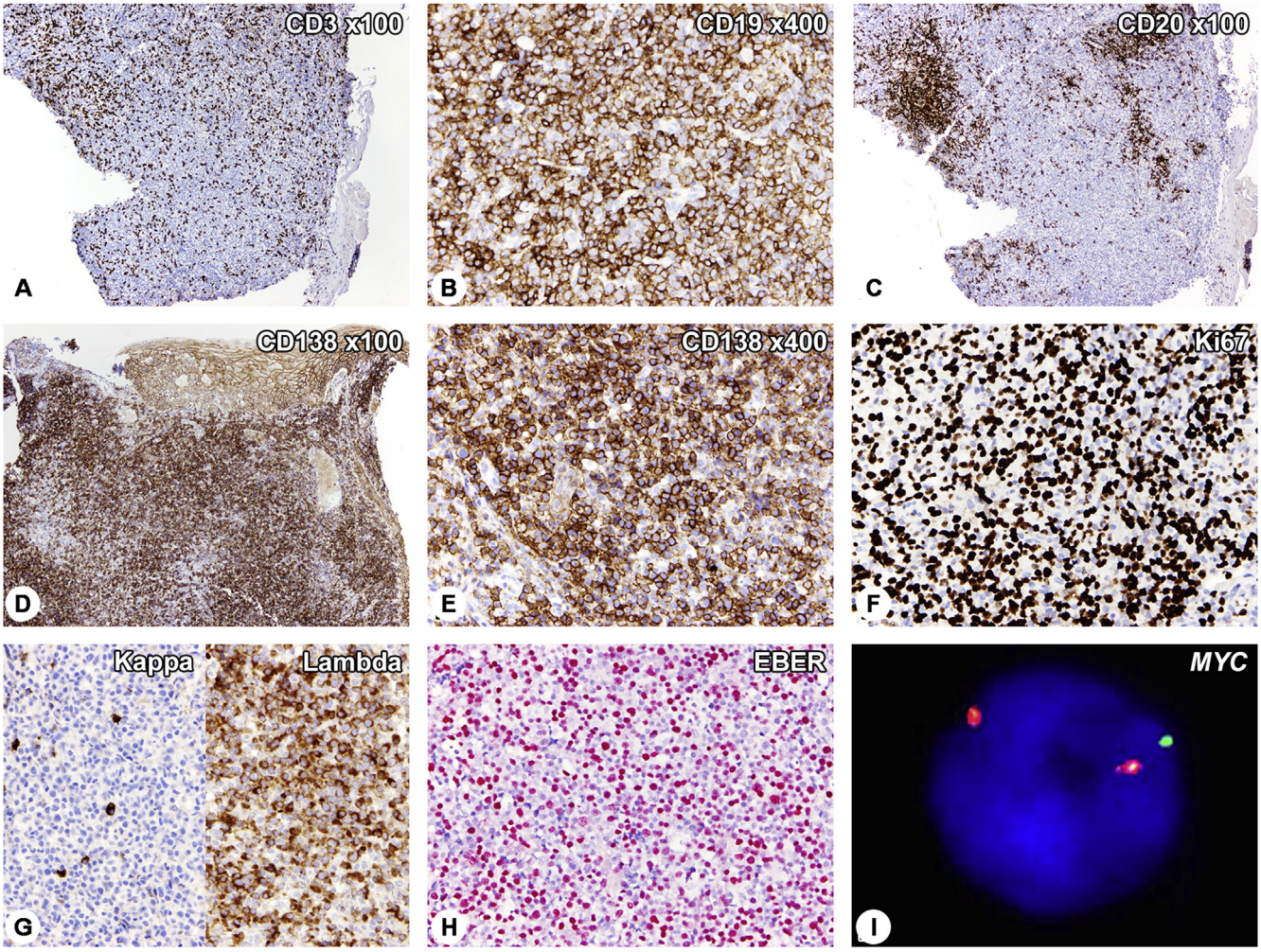

Fig. 2 Immunohistochemically, most of the infiltrating plasmacytic/plasmablastic cells are negative for (A) CD3, CD10 (not shown), or (C) CD20, but positive for (B) CD19 and (D,E) CD138, (F) with a high labelling index by Ki-67. (G) They are monotypic for lambda light chain expression, (H) positive for EBV by *in situ* hybridisation, and (I) *MYC* rearranged by fluorescence *in situ* hybridisation.

but not the *BCL2* or *BCL6* loci. There was no *MYC/IGH* reciprocal translocation by dual colour dual fusion probe.

Her serum levels of albumin, globulin, total protein, creatinine, calcium, immunoglobulin (Ig)A, IgG, and IgM were all within normal ranges. Serum protein electrophoresis was negative for any paraprotein. Magnetic resonance imaging (MRI) scans of the lower back 9 months prior to the oral biopsy showed lumbar radiculopathy, without evidence of any osteolytic bone lesions. Furthermore, the tumour cells expressed CD19, which is mostly negative in plasmacytoma. All these findings excluded the differential diagnosis of plasma cell myeloma or plasmablastic myeloma. The patient achieved complete remission after reduction of the immunosuppressants to half of the dosages (methotrexate to 5 mg per week and prednisolone to 5 mg per day) in June 2018, without chemotherapy or radiation therapy. She remained free of disease or recurrence for 13 months as of June 2019 with the reduced dosages.

EBVMCU was first described by Dojcinov *et al.* in 2010, and so far there have been less than 100 reported cases in the literature.[4] In a recent review, Prieto-Torres *et al.* broadened the spectrum of EBVMCU and described some unusual features, such as cases presenting as multiple lesions in a single anatomical location, monomorphic large cell morphology, angioinvasive pattern, PDL1 expression in large B-cells, and EBER expression in the adjacent epithelial cells.[5] In our case, we found many CD20 negative, lambda light chain-restricted plasmacytic/plasmablastic cells with clonal immunoglobulin receptor gene rearrangement and *MYC* rearrangement, which has not been described in EBVMCU yet. This finding has broadened the histopathological spectrum of EBVMCU and raised a challenging differential diagnosis with PBL. There are two morphological patterns of PBL, one with monomorphic plasmablastic cells and the other with more mature plasma cells. Nevertheless, a polymorphic infiltrate with large lymphocytes, eosinophils, plasma cells, and histiocytes is characteristic for EBVMCU as in our case, but not in PBL. The large cells in EBVMCU usually express B-cell markers (CD20, CD79A, PAX5, BOB1, and OCT2), CD30, IRF4/MUM-1, and LMP1. In contrast, the tumour cells of PBL are negative for CD20 and PAX5, and rarely positive for LMP1. About one-third of EBVMCU cases are clonal for immunoglobulin receptor gene or T-cell receptor gene rearrangement, which may lead to a misdiagnosis of B- or T-cell lymphoma.[6]

In conclusion, the current case broadens the histological spectrum of EBVMCU, as rare cases like ours can show plasmacytic/plasmablastic immunophenotype with clonal B-cell receptor gene rearrangement and *MYC* rearrangement. Clinical and pathological correlation is essential as these cases need to be differentiated from PBL or plasmablastic myeloma or EBV positive plasmacytoma.

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Phenytoin-associated necrotising lymphadenitis mimicking Kikuchi disease

Sir,

Histiocytic necrotising lymphadenitis, also known as Kikuchi disease, usually affects young adults of Asian descent who present typically with fever and painless, unilateral cervical lymphadenopathy.[1] Most cases follow a benign, self-limited course with spontaneous remission within a few months. The aetiology remains unclear. Both autoimmune and infectious aetiologies, especially viral infection, have been suggested,[1] but an association with phenytoin administration has not been reported. Pathologically, Kikuchi disease is characterised by a mixed population of plasmacytoid dendritic cells, histiocytes, T cells and immunoblasts with many cells undergoing apoptosis.[2] Three morphological patterns have been described, and a temporal relationship has been suggested from proliferative phase to necrotic and then xanthomatous phase.[2] However, the full morphological spectrum of Kikuchi disease is found only rarely in a single biopsy specimen. Thus, the well-known differential diagnosis may include lymphadenopathy in systemic lupus erythematosus (SLE) and infectious lymphadenitis.[3] Here, we report a case of phenytoin (Dilantin)-induced necrotising lymphadenitis which mimicked Kikuchi disease.

A 23-year-old Taiwanese man presented with convulsive status epilepticus characterised by episodic focal seizures with intermittent secondary generalisation in the past 12 months. He carried the HLA-B*1502 allele and took