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Clonal Epstein–Barr virus-positive mucocutaneous ulcer mimicking a mature B-cell lymphoma in a patient with mycophenolate-induced immune suppression

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A 45-year-old man with a history of systemic lupus erythematosus nephritis requiring sustained mycophenolate therapy presented with a gingival mass. The lesion was not associated with systemic B-symptoms, and the mass gradually progressed over the course of approximately 3 months. The patient was not receiving any other immunosuppressive medication and he is human immunodeficiency virus (HIV)-negative. Physical examination showed an erosive gingival ulcer, which involved the right upper alveolar ridge and surrounded the second molar. The ulcer exposed a portion of the underlying maxilla. Generalized lymphadenopathy was not detected.

Laboratory evaluation demonstrated normocytic anemia with a hemoglobin (Hb) level of 11.6 g/dL (normal range [NR], 13.4–17.2 g/dL), platelet count $428 \times 10^9/L$ (NR, $150\text{--}450 \times 10^9/L$) and white blood cell count (WBC) $7.7 \times 10^9/L$ (NR, $3.8\text{--}11.2 \times 10^9/L$). The differential was as follows: 41% neutrophils, 52% lymphocytes, 4% monocytes, 2% eosinophils and 1% basophils. Chemistry and kidney function studies demonstrated sodium 138 mmol/L (NR, 133–145 mmol/L), potassium 5.5 mmol/L (NR, 3.3–5.1 mmol/L), blood urea nitrogen 37 mg/dL (NR, 8–24 mg/dL), creatinine 2.92 mg/dL (0.50–1.20 mg/dL) and glomerular filtration rate 23 mL/min/1.73 m² (NR, > 59 mL/min/1.73 m²). An initial gingival biopsy showed an atypical lymphocytic infiltrate that was positive for a clonal immunoglobulin heavy chain rearrangement and highly suggestive of a mature B-cell lymphoma. T-cell receptor gene rearrangement studies were negative. A limited computed tomography (CT) scan was unremarkable except for chronic mucoperiosteal disease involving the right maxillary sinus. Apart from the oral cavity, positron emission tomography (PET) scan imaging detected no evidence of activity elsewhere in the body. The right gingival mass was re-biopsied for a confirmatory diagnosis.

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Sections revealed ulcerated squamous mucosa [Figure 1(A)] involved by a dense, polymorphic infiltrate including scattered large atypical lymphoid cells with scant cytoplasm, irregular nuclei, dispersed chromatin and inconspicuous nucleoli [Figure 1(B)]. The background comprised small lymphocytes, plasma cells and histiocytes. Classical Reed – Sternberg cells were not appreciated. By immunohistochemistry, the intermediate – large lymphocytes were positive for CD30 [Figure 1(C)], MUM-1, PAX-5 and EBV-LMP-1 (Epstein – Barr virus-latent membrane protein-1) [Figure 1(D)], but they were negative for CD20 and CD15. *In situ* hybridization for EBV-encoded RNA (EBER) was diffusely positive among the atypical cells. Flow cytometric analysis was negative for a monoclonal B-cell population. Overall, the clinical and pathologic findings were consistent with an EBV-positive mucocutaneous ulcer (EBVMCU).

EBVMCU is a newly described B-cell lymphoproliferative disorder with distinctive clinical features. In the initial clinicopathological series, Dojcinov *et al.* [1] described EBVMCU as a discrete lesion, which may involve a range of skin and/or mucosal surfaces, but most commonly affecting the oral cavity. Histologically, the infiltrate was polymorphous and composed of small lymphocytes, histiocytes and plasma cells. Against this background, large atypical cells were frequently distributed within the lesion, and, in some cases, these B-cell blast cells were markedly pleomorphic, resembling Hodgkin or Reed – Sternberg cells. Intermediate size lymphoid cells with angulated nuclei and pale cytoplasm were generally prominent, and several cases featured vasculitic changes. Immunohistochemically, the vast majority of cases were positive for CD30, MUM1, CD79a and EBVLMP-1. The lesional cells were also largely immunoreactive for PAX-5, OCT-2 and BOB.1, with CD15 expressed in a subset. Decreased (focal to negative) CD20 expression was reported in approximately 30% of the series. By polymerase chain reaction (PCR), a monoclonal immunoglobulin (IG) rearrangement was detected in 38.9% of cases.

EBVMCU is intimately associated with immune suppression (IS), or decreased immune surveillance due to other factors. Whereas earlier literature reported its association primarily with methotrexate [2–4], EBVMCU is known to occur in a variety of immunosuppressed states including advanced age [5,6] and iatrogenic administration of azathioprine [7,8] and cyclosporine [9]. Recently, EBVMCU was detected in up to 10% of solid organ transplant recipients with an EBV-post-transplant lymphoproliferative disorder (PTLD) [10]. In this series patients had been exposed to a variety of immunosuppressive agents including cyclosporine, mycophenolate, prednisone and tacrolimus. The patient described in the present report has an underlying retinopathy, which was exacerbated by prednisone, leading to the use of mycophenolate as the sole immunosuppressive agent for his lupus nephritis. He had no other risk factors for IS. This finding adds further support to the view that EBVMCU arises as a consequence of decreased immune surveillance from a variety of causes, and is not specific to a single agent [1].

The primary differential diagnoses are diffuse large B-cell lymphoma (DLBCL), classical Hodgkin lymphoma (cHL) and aggressive forms of EBV-PTLD. Indeed, the relatively high detection rate of an IG gene clone [1,10,11], as seen in our patient, further adds to its diagnostic confusion with a malignant B-cell lymphoma. In contrast to DLBCL, the infiltrate of EBVMCU is generally sharply defined and superficial, and features a polymorphous

background of small lymphocytes and histiocytes. While the morphologic and immunophenotypic findings may closely resemble cHL, EBVMCU 's characteristic extranodal involvement of skin or oropharyngeal – gastrointestinal mucosa is exceedingly rare in cHL [12]. Recently, the absence of serologic EBV DNA in patients with EBVMCU has been suggested as a method to distinguish it from elevated DNA copies detected in patients with more aggressive EBV-PTLDs [10].

The clinical course of EBVMCU is largely self-limited, and, in the majority of cases, withdrawal or reduction of the source of IS may lead to its resolution [1,10,13]. While rituximab has been shown to have a therapeutic effect in cases which express CD20 [14,15], to date there is no established role for the use of systemic combination chemotherapy: cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP).

In summary, we report a case of EBV-positive MCU associated with mycophenolate-induced IS for lupus nephritis. Although EBVMCU mimics DLBCL and/or cHL, aids to the diagnosis include its strong association with IS and mucocutaneous anatomic involvement. Timely recognition of this under-recognized, clinical-pathologic entity is critical to provide conservative management and avoid unnecessarily aggressive chemotherapy.

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Figure 1.

(A) Ulcerated mucosal lesion with a dense lymphocytic infiltrate ($\times 100$). (B) Polymorphous infiltrate comprising intermediate to large lymphoid cells with angulated nuclei ($\times 400$). (C) The atypical cells are positive for CD30 ($\times 200$). (D) The atypical cells are diffusely positive for EBV-LMP-1 ($\times 200$).