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Mucocutaneous ulcer: a mimic of EBV + diffuse large B cell lymphoma in the immunodeficiency setting

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We read with interest the recent manuscript by McKelvie et al. [1] describing a methotrexate-related EBV + large B cell lymphoproliferation manifesting as chronic leg ulcers that the authors interpreted as diffuse large B-cell lymphoma localized to the skin. The patient was an older woman (age 76) with a history of rheumatoid arthritis who had been on methotrexate for eight years. She developed painful chronic clustered ulcers on the lower leg which on biopsy showed a dermal and subcutaneous pleomorphic infiltrate of strongly CD30 + PAX5 + CD20– EBV + B cells associated with necrosis; a Ki67 proliferation index was high and IgH gene rearrangement studies were monoclonal. Staging showed that involvement was isolated to the skin. The authors favored a diagnosis of diffuse large B-cell lymphoma over polymorphic lymphoproliferative disorder based on a lack of plasma cells, a high Ki67 proliferative index; and lack of a spectrum of neoplastic cells from small to medium to large. In our opinion, several clinical, histologic, and immunohistochemical features should also prompt consideration of the histologically alarming but usually clinically indolent entity of EBV + mucocutaneous ulcer.

EBV + mucocutaneous ulcer was initially described in 2010 [2] as localized sharply circumscribed ulcerative lesions of the skin, oropharynx, or gastrointestinal tract that occur in immunosuppressed settings, including azathioprine, methotrexate, cyclosporine A, and age-related immune senescence. The infiltrate was described as polymorphous, including a mixture of lymphocytes, immunoblasts, and cells with Hodgkin/Reed–Sternberg-like morphology; necrosis and angioinvasion were noted in some cases. The deep aspect of the lesion, when visualized, was rimmed by small reactive lymphocytes.[3] The atypical B cells were EBV + and CD30+, and some had reduced CD20 expression. Clonal Ig gene rearrangements were not infrequent, and were positive in 39% of cases studied. The clinical history and clinical photographs provided by McKelvie et al. [1] are certainly compatible with EBV + mucocutaneous ulcer, as are the large numbers of pleomorphic EBV + and CD30 + B cells with associated necrosis and the presence of a clonal IgH gene rearrangement. The provided photomicrographs do not show the deep aspect of the lesion,

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which would certainly be of interest. The presence of a high Ki67 proliferative index does not exclude the diagnosis; in our experience, when Ki67 immunohistochemistry is performed on EBV + mucocutaneous ulcer, the Ki67 proliferative index is moderate to high and can be 90% or higher.

The clinical course of EBV + mucocutaneous ulcer is indolent in the predominance of cases, with patients on iatrogenic immunosuppression generally responding to reduction of immunosuppression alone.[4,5] EBV + mucocutaneous ulcer with very similar clinicopathologic presentation and a similarly indolent clinical course has recently been described in the post-solid organ transplant [6] and the post-stem cell transplant setting.[7] Recognition of this entity in clinical settings of immunosuppression, immunodeficiency or immune senescence is quite important to avoid overdiagnosis as diffuse large B-cell lymphoma or, in cases that express CD15, classical Hodgkin lymphoma. It is crucial for the pathologist who receives a biopsy from an ulcerated lesion at a mucosal or cutaneous site to actively seek a history of immunodeficiency, and to consider this indolent diagnosis. It may not be possible to confidently distinguish EBV + mucocutaneous ulcer from more aggressive disease on small superficial or poorly oriented biopsies; in those cases we recommend providing a differential diagnosis and having an active conversation with the treating physician to guide subsequent steps such as clinical staging, rebiopsy or reduction in immunosuppression with close follow up.

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