Modern Pathology (2021) 34:2084
https://doi.org/10.1038/s41379-021-00798-7

CORRESPONDENCE

High prevalence of methotrexate use in patients with Epstein–Barr virus-positive mucocutaneous ulcer may cause confounding bias

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Received: 3 January 2021 / Revised: 22 January 2021 / Accepted: 26 February 2021 / Published online: 23 March 2021

To the Editor:

Ikeda et al. [1] described the clinicopathological features of 34 patients with Epstein–Barr virus (EBV)-positive mucocutaneous ulcer (EBVMCU). The aim of the study was to identify features which could distinguish EBVMCU from EBV-positive diffuse large B-cell lymphoma (DLBCL). The authors found that soluble IL-2 receptor (sIL-2R) levels were significantly lower in patients with EBVMCU than in patients with EBV-positive DLBCL and they conclude that this is due to the localized nature of EBVMCU. It is possible, however, that this finding results from a confounding bias. Of the 34 cases of EBVMCU studied, 30 (88.2%) arose in patients receiving methotrexate for the treatment of rheumatoid arthritis. Methotrexate therapy, particularly in the setting of rheumatoid arthritis, is known to significantly reduce sIL-2R levels [2–4]. Unfortunately, Ikeda et al. do not describe the prevalence of rheumatoid arthritis or methotrexate use in their DLBCL cohorts for comparison. As such, it is not possible to determine whether the lower sIL-2R levels seen in patients with EBVMCU, when compared to patients with DLBCL, are due to differing diseases processes or iatrogenic suppression by methotrexate. Thus, one cannot conclude that lower sIL-2R levels are a feature of EBVMCU, or that they are useful in distinguishing EBVMCU from EBV-positive DLBCL. The strong association of EBVMCU with rheumatoid arthritis and methotrexate use makes it a challenging entity to characterize. It is imperative to take this into consideration when studying EBVMCU to account for potential confounding biases and to accurately characterize EBVMCU [5].

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