**Abstract**

Epstein-Barr virus (EBV)-positive mucocutaneous ulcer (EBVMCU) is a unifocal mucosal or cutaneous ulcer that is histologically characterized by proliferating EBV-positive atypical B cells. While EBVMCU demonstrates a histology similar to that of EBV-positive diffuse large B-cell lymphoma (DLBCL), their clinical behavior differs. Thus, characterizing distinguishing features of EBVMCU and EBV-positive DLBCL is critical. To identify unique characteristics between EBVMCU and lymphoma, we analyzed the clinicopathological and genetic features of 34 Japanese patients with EBVMCU and compared them to those of 24 EBV-positive DLBCL patients and 25 EBV-negative DLBCL patients. All patients with EBVMCU had localized ulcerative lesions, and 31 patients (91%) were using immunosuppressants, such as methotrexate (MTX) or hydroxycarbamide. All patients that were followed up with exhibited good prognosis following immunosuppressant reduction or chemotherapy. Additionally, 17 EBV-positive DLBCL patients, and 15 EBV-negative DLBCL patients, received chemotherapy ($P < 0.001$, $P < 0.001$, respectively). Our data showed that EBVMCU did not increase indicators associated with lymphoma prognosis, such as soluble interleukin 2 receptor (sIL-2R) and lactate dehydrogenase (LDH) compared to those in the EBV-positive DLBCL or EBV-negative DLBCL groups (sIL-2R, $P < 0.001$, $P =$

0.025; LDH, *P* = 0.018, P = 0.038, respectively). However, histologically, EBVMCU exhibited EBV-positive, variable-sized, atypical B-cell proliferation. Thus, EBVMCU was histologically classified as: (1) polymorphous; (2) large cell-rich; (3) classic Hodgkin lymphoma-like; and (4) mucosa-associated lymphoid tissue lymphoma-like. Moreover, genetic analysis showed that immunoglobin heavy chain (IGH) gene rearrangement did not differ significantly between EBVMCU and EBV-positive DLBCL (44% vs. 32%; *P* = 0.377), or between EBVMCU and EBV-negative DLBCL (44% vs. 58%; *P* = 0.280). Therefore, it is difficult to distinguish EBVMCU from EBV-positive DLBCL using only pathological and genetic findings, suggesting that clinical information is important in accurately distinguishing between EBVMCU and EBV-positive DLBCL.