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*CORRESPONDENCE

Tatsuya Katsumi,

✉ t.katsumi1987.0401@gmail.com

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A case of EBV-positive diffuse large B-cell lymphoma arising in advanced mycosis fungoides mimicking disease progression

Shota Uchida¹, Tatsuya Katsumi^{1*}, Momo Sato¹, Yuki Saito¹, Akihiko Yuki^{1,2} and Riichiro Abe¹

¹Division of Dermatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, ²Department of Dermatology, Niigata Cancer Center Hospital, Niigata, Japan

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Dear Editors,

Although mycosis fungoides (MF) typically follows an indolent clinical course, a subset of patients progresses to advanced-stage disease and are at increased risk of developing secondary malignancies, including B-cell lymphomas [1]. The clinical manifestations of secondary lymphoma may overlap with those of progressive MF, potentially leading to diagnostic delay. This risk may be related to MF-associated immune dysregulation and cumulative effects of T-cell-directed therapies [1, 2]. EBV-positive diffuse large B-cell lymphoma (DLBCL) can arise in immunosuppressed patients, although its occurrence during MF remains poorly characterized. Here, we report a case of EBV-positive DLBCL developing during the course of advanced MF, highlighting the diagnostic challenge of distinguishing secondary lymphoma from MF progression. This case also illustrates the importance of reassessing clinically discordant lesions rather than attributing all newly developing tumors to progression of the underlying MF.

A 52-year-old female with a 24-year history of MF (initially stage IB) was referred to our department 8 years ago because of the development of cutaneous tumor lesions. Histopathological examination at diagnosis was consistent with conventional MF without evidence of large-cell transformation. She received multiple therapies, including bexarotene, interferon-gamma and brentuximab vedotin. Recently, she was treated with forodesine for 1 year, followed by mogamulizumab for 5 months, resulting in progressive disease (Supplementary Figures 1A–D). Because a prior skin biopsy had demonstrated CD30 expression in approximately 10% of atypical lymphoid cells, brentuximab vedotin was re-administered in combination with local radiation therapy for 7 months. Despite temporary stability, generalized tumors with ulceration rapidly enlarged. Contrast-enhanced CT showed deep lymphadenopathy, and serum soluble interleukin-2 receptor (sIL-2R) increased from 3,153 to 4,111 U/L within 1 month (Supplementary Figure 1E). Longitudinal changes in serum LDH, IgG, and absolute lymphocyte counts were also evaluated (Supplementary Figure 1E). The rapid clinical deterioration was considered atypical for the preceding course of her MF and prompted histopathological reassessment of lesions at different anatomical sites. Palliative resections were performed on lesions from the left waist and right forearm to relieve pain and to clarify the nature of the rapidly progressive tumors (Figures 1A,G).

Histopathology of the waist lesion showed a dense lymphoid infiltration extending from the dermis to the subcutaneous tissue, composed of small-to-medium-sized atypical cells (Figures 1B,C; Supplementary Figures 2A,B). These cells expressed CD3 and CD4

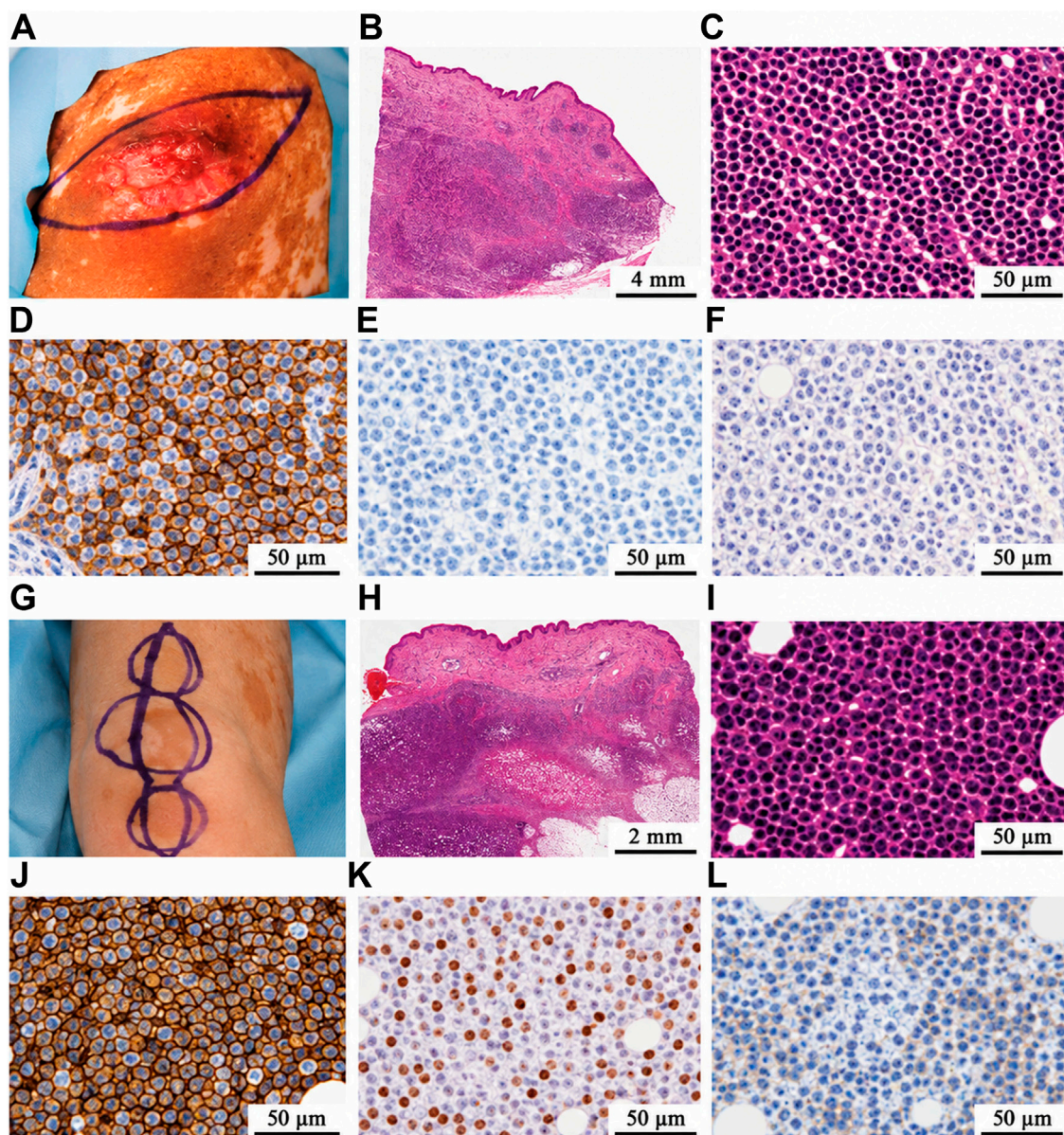


FIGURE 1
Clinical and histopathological findings. Clinical presentation of MF, erythematous nodule on the left waist (A). The pathological findings showed dermal to subcutaneous lymphoid infiltration (B) and small to medium atypical cells (C). Immunohistochemical staining: the majority of the cells are positive for CD4 (D), and negative for CD20 (E), EBER-ISH (F). Clinical findings of DLBCL. Three nodules on the right arm (G). The pathological findings showed subcutaneous lymphoid infiltration (H) and large, atypical cells (I). Immunohistochemical staining: the large cells are positive for CD20 (J), EBER-ISH (K). CD4 is expressed only in a few small-sized cells (L).

(Figure 1D) but lacked CD20 (Figure 1E) and CD30 (Supplementary Figure 1C). They were also negative for EBV-encoded RNA *in situ* hybridization (EBER-ISH) (Figure 1F), consistent with her known MF. In contrast, the forearm lesion showed large atypical cells in the subcutaneous tissue (Figures 1H,I) that expressed CD20 (Figure 1J; Supplementary Figure 2D) and CD30 (Supplementary Figure 2F). EBER-ISH was positive in the forearm lesion (Figure 1K). These cells were negative for T-cell markers (Figure 1L; Supplementary Figure 2E). Ki-67 showed a high proliferative index in both the superficial and deep components (Supplementary Figures 2G,H). The predominantly monomorphic proliferation of large atypical B cells, together with EBER positivity and a high proliferative index,

supported the diagnosis of EBV-positive DLBCL rather than a polymorphic EBV-associated B-cell lymphoproliferative disorder. Thus, simultaneous examination of two clinically distinct lesions demonstrated persistent MF in the waist lesion and EBV-positive DLBCL in the forearm lesion. This clinicopathological discordance was critical for recognizing that the rapidly progressive lesions could not be explained solely by progression of the pre-existing MF. Quantitative polymerase chain reaction (PCR) for EBV-DNA using whole blood showed a viral load of 5×10^2 copies/mL. The EBV latency pattern could not be determined because immunohistochemical staining for LMP1 and EBNA2 was not performed. Following the diagnosis of EBV-positive DLBCL, the

patient's disease progressed rapidly. Systemic chemotherapy, including R-CHOP, was not administered because of her poor performance status. Lymph node biopsy was not performed because of poor condition and patient preference. The patient passed away 3 months later because of progressive lymphoma. No autopsy was undertaken.

B-cell lymphomas arising in patients with MF/SS are uncommon but may mimic progression of the underlying disease [1, 3, 4]. EBV-associated B-cell lymphoproliferative disorders have been reported in patients with T-cell lymphomas in the setting of impaired immune surveillance [2, 5]. Patients with MF/SS are at increased risk of secondary hematologic malignancies, including in early-stage disease [1, 4]. This association may involve disease-related immune dysfunction as well as treatment-associated impairment of immune surveillance. In our patient, longstanding advanced MF and exposure to multiple systemic therapies may have contributed to impaired immune surveillance. However, a direct causal relationship between any individual therapy and the development of EBV-positive DLBCL cannot be established. Clinically, rapidly progressive lesions could have been interpreted as progression of tumor-stage MF or large-cell transformation. Notably, the two lesions were clinically similar but represented different lymphoid neoplasms histopathologically. This underscores the value of sampling multiple lesions when the clinical course becomes atypical or unexpectedly aggressive, as a single biopsy may not adequately represent clinically heterogeneous lesions. Careful comparison of newly developing lesions with the patient's previous clinical and histopathological findings may provide clues to an alternative diagnosis. Changes in lesion morphology or behavior should prompt renewed histopathological assessment rather than assumption of uniform disease progression. Although progression of MF alone could not be completely excluded given MF heterogeneity, the forearm lesion showed a distinct immunophenotype, including CD20 and EBER positivity, supporting the diagnosis of EBV-positive DLBCL. Moreover, our case indicates that circulating EBV-DNA levels may remain low despite substantial local tumor activity; thus, low PCR titers do not exclude EBV-associated malignancies. Tissue-based evaluation therefore remains important when clinical or histopathological findings raise suspicion for an EBV-associated lymphoproliferative disorder. Repeated multisite biopsies, including nodal biopsy when feasible, should be considered in patients with atypical or discordant progression. A limitation of our case is that lymph node biopsy and autopsy were not performed; therefore, the systemic distribution of B-cell lymphoma could not be histologically established. This case highlights the importance of considering EBV-associated B-cell lymphoma when patients with MF develop atypical or rapidly progressive lesions. In particular, evaluation for EBV using EBER-ISH should be considered when DLBCL is suspected during the course of MF.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical approval was not required for the studies involving humans because Ethical approval was not required for this single case report in accordance with the applicable institutional guidelines. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements because Written informed consent to participate was not required because this was a single case report and did not constitute human subjects research under the applicable institutional guidelines. Written informed consent for publication was obtained from the patient. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was used in the creation of this manuscript. During the preparation of this work, the authors used ChatGPT (GPT-5.6 Sol, OpenAI) for language editing and improvement of readability. The authors reviewed and edited the output and take full responsibility for the content of the publication.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontierspartnerships.org/articles/10.3389/jcia.2026.17789/full#supplementary-material>

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