Disclosure. *We would like to thank Mr. Hiroyuki Watanabe for his assistance in English language editing.*
Financial support: none. Conflict of interest: none.

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doi:10.1684/ejd.2015.2603

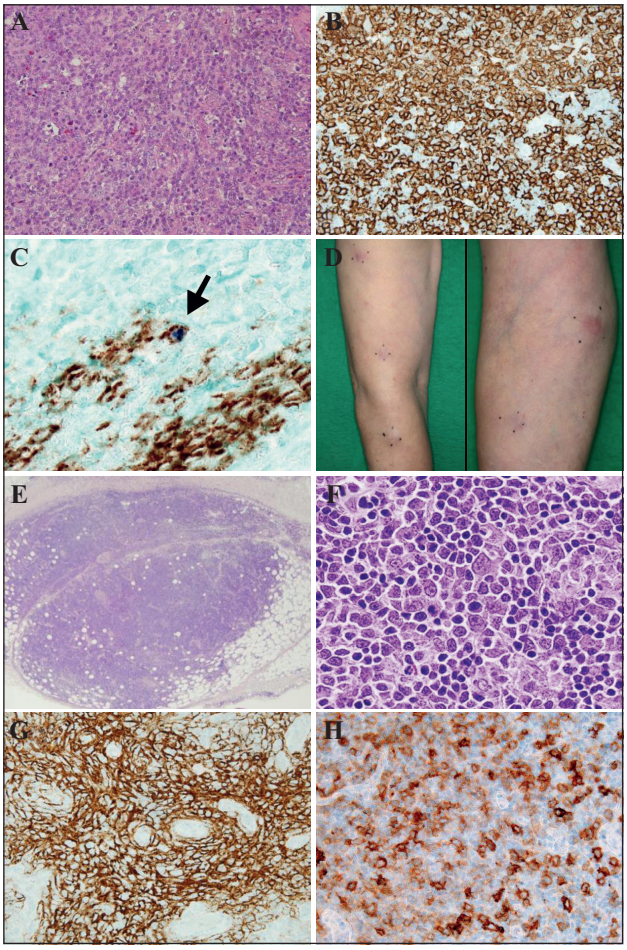

Figure 1. (A) Histological examination of lymph nodes. Numerous, medium-to-large sized, atypical, mononuclear cells with irregular nuclei (Hematoxylin–eosin, ×400). **(B)** Increasing number of $CD21^+$ follicular dendritic cells around high endothelial venules (×400). **(C)** *In situ* hybridization for Epstein-Barr virus (EBV)-encoded RNA (EBER), followed by the immunostaining of CD20. $EBER^+$ cells were positive for CD20 (indicated by arrow) (×800). **(D)** Multiple subcutaneous nodules in her bilateral upper extremities. **(E, F)** Histopathological examination of the nodule on the arm. Diffuse infiltration of medium-to-large sized, atypical lymphocytes in the subcutaneous tissues (Hematoxylin–eosin, **(E)** ×100, **(F)** ×800). **(G, H)** Atypical lymphocytes were positive for CD20 **(G)** and CD30 **(H)** (×400).

Methotrexate-associated lymphoproliferative disorder: Sequential development of angioimmunoblastic T-cell lymphoma-like lymphoproliferation in the lymph nodes and diffuse large B-cell lymphoma in the skin in the same patient

A 66-year old Japanese woman was diagnosed with polymyalgia rheumatica in October 2012 and was treated with methotrexate (MTX) at a dose of 10mg/week. Swelling of the inguinal lymph nodes appeared in February 2013. Histological examination of the lymph nodes revealed numerous, medium-to-large, atypical mononuclear cells with irregular nuclei (*figure 1A*). Increased numbers of $CD21^+$ follicular dendritic cells were observed around the high endothelial venules (*figure 1B*). The neoplastic cells stained positively for CD3 and CD5 but not for CD20 and bcl-6. Epstein-Barr virus (EBV)-encoded RNA (EBER) positive cells by *in situ* hybridization were also positive for CD20 and CD79α, but not CD3 (*figure 1C*). Quantitative polymerase chain reaction for plasma EBV DNA showed 290 copies/10^6 cells (normal: <20). The diagnosis of MTX-associated angioimmunoblastic T-cell lymphoma (AITL)-like lymphoproliferative disorders (LPD) was established and MTX was withdrawn in February 2013. Immunosuppressive agents, such as cyclosporine, tacrolimus and corticosteroids, were not used after the withdrawal of MTX. Swelling of the lymph nodes completely disappeared 6 months after the discontinuation of MTX. In April 2014, she noticed multiple 2-to-3 cm subcutaneous nodules in her bilateral upper extremities (*figure 1D*). Abnormal laboratory results included only elevated soluble interleukin 2 receptor (1291 U/ml,

normal: 135-483). Histopathological examination of the nodule revealed diffuse infiltration of medium-to-large polymorphic atypical lymphocytes in the subcutaneous tissues (*figures 1E,F*). There were no Reed–Sternberg cells. The atypical lymphocytes were positive for CD20 (*figure 1G*), CD30 (*figure 1H*), CD10 and bcl-6 but not CD3 and CD5. Fifty percent of atypical cells were positive for MIB-1. EBER positive lymphocytes were detected by *in situ* hybridization. The diagnosis of MTX-LPD in the skin, comprised of a diffuse large B-cell lymphoma (DLBCL), was established. During a four-month follow-up period, the cutaneous nodules spontaneously regressed.

MTX has an immunosuppressive effect and is thought to be associated with the development of LPD. MTX-associated LPD is classified as "other iatrogenic immunodeficiency-associated LPD" in the World Health Organization classification of tumors of hematopietic and lymphoid tissues [1]. 48 MTX-LPD patients treated with MTX until the diagnosis of LPD for periods of 2 to 131 (median 54) months have been reported [2]. The spontaneous regression of LPD following the withdrawal of MTX strongly suggests the potential pathogenetic role of MTX in LPD. However, the pathogenesis of the development of LPD by MTX has not been clearly established. Patients with RA develop LPD at a frequency 2 to 5.5 times higher than the general population [3], suggesting that the abnormal immune state of RA might also contribute to the development of LPD. In our case, it is possible that a polymyalgia rheumatica-induced abnormal immune state might also have been associated with the pathogenesis of LPD. Further studies are required to clarify the association of MTX with the development of LPD.

Histologically, DLBCL (60.4%) and Hodgkin lymphoma (12.5%) are common in MTX-LPD [2]. Approximately half of all MTX-LPD develop in extranodal sites, such as the lung, kidney, gastrointestinal tract and bone marrow [2]. However, reports of cases of MTX-LPD developing in the skin are limited [4]. The present case is rare in that the BCL in the skin developed after the cessation of MTX and two types of LPD, i.e., AITL-like and BCL, developed sequentially. Kikuchi *et al.* also reported a patient with TCL followed by BCL and suggested that long-term chemotherapy and EBV infection might be associated with the development of multiple lymphomas [5].

EBV is detected at high frequency in MTX-LPD (27.1%; 13/48) [2]. Spontaneous remissions of EBV-LPD are common, especially when there is ulceration [6]. The five-year survival rate of EBV-positive MTX-LPD (76.3%) is better than that of EBV-negative (54%) [2]. Rizzi *et al.* reported that MTX-LPD patients who achieved complete remission (CR) exhibited increased frequencies of DLBCL (24%), extranodal involvement (32%) and EBV infection (56%), and that near CR occurred within four weeks after the discontinuation of MTX [7]. Our case fulfilled all these favorable conditions for CR, suggesting that our patient required a period of a careful wait-and-see approach, rather than more aggressive cytotoxic therapies. Widespread use of immunosuppressive agents will lead to an increase in the frequency of LPDs. It is important for dermatologists to recognize the diagnosis and appropriate treatment of MTX-LPD. ■

Disclosure. *Financial support: none. Conflict of interest: none.*

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doi:10.1684/ejd.2015.2582

Dermoscopic findings of piloleiomyoma with hypertrichosis

Cutaneous leiomyomas are benign tumors arising from smooth muscle cells. Herein, we describe a rare case of piloleiomyoma with hypertrichosis, in which the dermoscopic examination revealed features similar to those of dermatofibroma.

A 51-year-old man presented to our hospital with a nodule on his shoulder, which he had noticed 1.5 months earlier. Physical examination revealed a firm, brownish, painful nodule, 12 mm in diameter, with hypertrichosis on the left shoulder (*figure 1A*). The dermoscopic findings showed a central white patch, a delicate pigment network, several dotted vessels and hypertrichosis (*figure 1B*). His family history and medical history were unremarkable. Histopathological examination revealed a slightly thickened epidermis with parakeratosis and basal pigmentation, and a poorly demarcated eosinophilic tumor located within the dermis. The tumor consisted of interlacing bundles of spindle cells with no sign of atypism, intermingled with various amounts of collagen bundles; a hair follicle was