

CORRESPONDENCE

A case of methotrexate-related lymphoproliferative disorder resolved with discontinuation of the drug: A literature review for clinical characteristics in 105 Japanese cases

Methotrexate-associated lymphoproliferative disorder (MTX-LD) is an abnormal lymphocyte growth upon receiving MTX.¹ A long-standing immunosuppression is considered the principal cause,² although with little association with other immunosuppressants, implicating MTX-specific immunotumorigenesis. We report a case of rheumatoid arthritis (RA) who developed cutaneous diffuse large B-cell lymphoma (DLBCL) during MTX monotherapy with prompt resolution after discontinuation of the drug and summarize the clinical characteristics of Japanese cases since MTX was first approved in 1999.

A 76-year-old Japanese man presented with a 6-month history of papulo-nodules on his face. About 4 months before, indurative nodules newly appeared on the scrotum. He had more than a 10-year history of RA treated with MTX, currently taking 4 mg/week.

Examination revealed asymptomatic reddish nodules and fingertip-sized tumors scattered over the face and right scrotum (Figure 1A–D). Superficial lymph nodes were not palpable. Laboratory workup was within normal range, including WBC and lymphocyte counts (4400/ μ L and 24%, respectively), except elevated LDH (293 U/L) and sIL-2R (892 U/mL). A skin pathology showed diffuse and dense infiltrating cells with atypical nuclei throughout the dermis (Figure 1E,F), which were immunostained positive for CD20, bcl-2, and MUM1, with weakly positive for bcl-6. CD3, CD10, and EBER were negative (Figure 1G–J). Southern blotting using genomic DNA extracted from the lesional skin revealed reconstruction in the immunoglobulin JH chain gene. CT scanning showed no lymphadenopathy and organ involvement. An overall clinicopathology suggests the diagnosis of DLBCL, provisionally MTX-LD.

Continuing topical steroids and phototherapy, MTX was discontinued. His skin lesions gradually flattened with decreased serum LDH level and disappeared within 6 months of MTX discontinuation. He was disease-free during 3 months of follow-up (Figure 1K,L), and finally diagnosed as DLBCL associated with MTX-LD.

To date, 105 Japanese cases of MTX-LD, including ours, have been reported.^{3–6} Their demographics included female predominance (male-to-female ratio 1:2), reflecting that in RA, the duration of MTX treatment was 6.0 ± 5.0 years with a mean total dose of 1800 mg. Our case received a cumulative dose of 2400 mg. DLBCL was the most common phenotype (45, 40%), whereas other lymphomas were less frequent (9, 10% in each). In DLBCL, the most frequent extranodal lesion was the lungs (23, 22%), followed by the liver, mucosa, and gastrointestinal, while skin lesions were relatively low (7.6%). The overall EBER positivity was ~70%. In nine cases with skin lesions alone, including ours, four had multiple lesions, and five had solitary masses. Skin phenotypes were mostly nodules and/or tumors (8/9, 88.9%), whereas only one case showed indurative erythema; however, there seems to be no predilection for affected skin sites or ulceration status. Discontinuation of MTX spontaneously resolved the skin lesions in 69 cases (65.7%), of whom obtained a complete resolution in almost all cases. On the contrary, 6 cases (5.7%) without regression underwent surgical excision. Of 30 cases (28.5%) with lymph nodes, visceral, or multiple lesions received chemotherapy, 18% had progressive disease or recurrence, and 3% were fatal. Thus, the majority of MTX-LD more likely resolves with discontinuation of MTX,⁷ but there remain cases with treatment resistance and relapse, particularly those who are unresponsive to MTX discontinuation.

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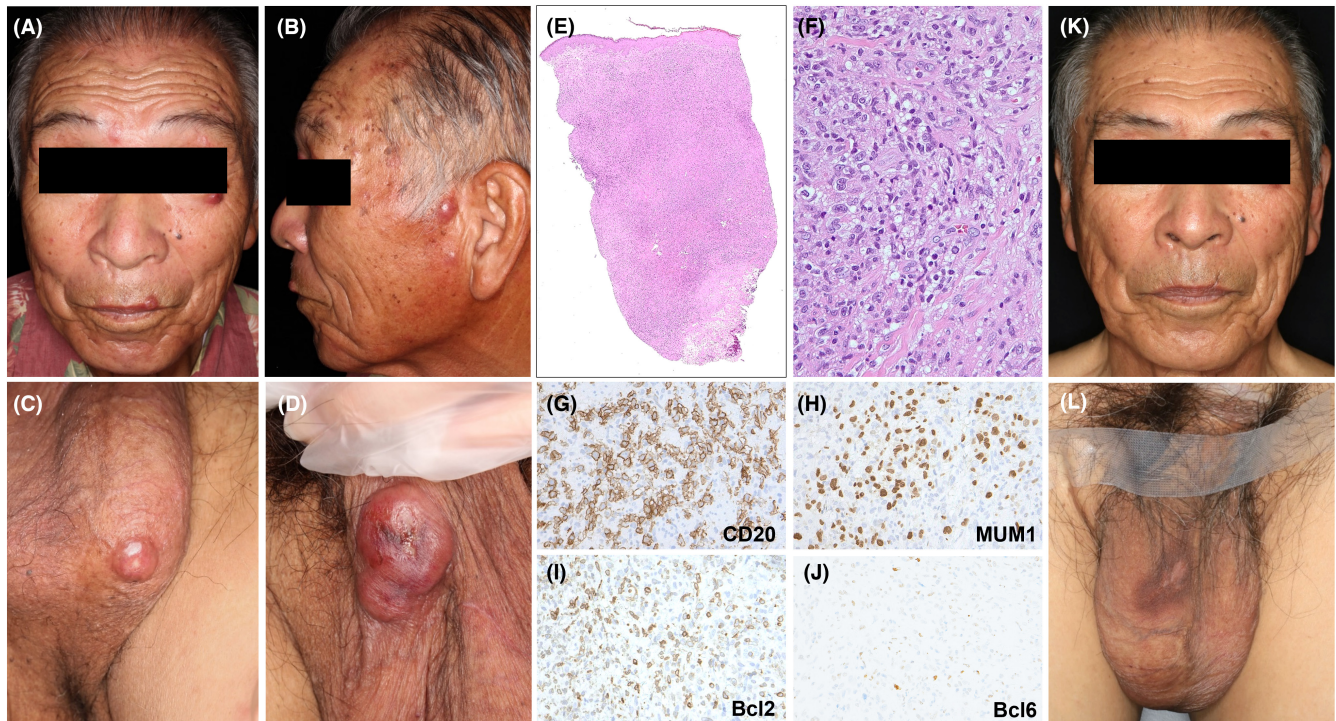


FIGURE 1 Clinicopathological findings. Clinical pictures show various-sized, indurative papulo-nodules scattered on the face (A, B) and tumors on the right scrotum (C, D). Skin pathology shows dense cellular infiltration throughout the entire dermis (E), which consists of lymphocyte-like cells with large and multiple atypical nuclei, small lymphocytes with prominent nucleoli, and Reed-Sternberg cell-like mirror-imaged cells (F). Immunohistochemistry demonstrated positive for CD20, MUM1, and bcl2 and partially weakly positive for bcl6 (G, H, I, and J, respectively). After 3 months of MTX discontinuation, all the skin lesions in the face and scrotum became flattened with pigmentation (K and L, respectively).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

Approval of the research protocol: No human participant was involved in this study.

Informed Consent: N/A.

Registry and the Registration No.: N/A.

Animal Studies: N/A.

Correspondence

Noritaka Oyama, Department of Dermatology, Faculty of Medical Sciences, University of Fukui, 23-3 Matsuoka-Shimoaizuki, Eiheiji, Fukui 910-1193, Japan.

Email: norider@wine.plala.or.jp

ORCID

Noritaka Oyama  <https://orcid.org/0000-0003-4934-5205>

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Shintaro Higashida MD¹

Erina Kodaka MD¹

Hikomichi Iwasaki MD, PhD²

Hideaki Sakai MD³

Noritaka Oyama MD, PhD¹ 

Minoru Hasegawa MD, PhD¹

¹Department of Dermatology, Faculty of Medical Sciences, University of Fukui, Fukui, Japan

²Department of Infection Control and Prevention, Faculty of Medical Sciences, University of Fukui, Fukui, Japan

³Sakai Dermatology Clinic, Tsuruga-Fukui, Japan

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