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SHORT COMMUNICATION

Epstein-Barr Virus-associated Methotrexate-induced Accelerated Rheumatoid Nodulosis

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Methotrexate (MTX)-induced accelerated rheumatoid nodulosis (MIARN), an adverse effect seen with MTX use, was first described in 1986 by Kremer & Lee (1) and involves the development of accelerated rheumatoid nodules (2). MIARN is diagnosed when nodules develop in a patient taking MTX without any previous history of rheumatoid nodules or in an area previously not affected by rheumatoid nodules. These nodules can develop after effective suppression of rheumatoid symptoms and disappear quite frequently when MTX is discontinued (3). Although a role for adenosine (4), HLA-DR4 (5), and 2756GG genotypes of the methionine synthase reductase gene (6) have been suggested as contributors to the underlying pathogenesis of MIARN, the mechanisms behind MIARN are still unclear. In this study, we report a case of MIARN with MTX-associated lymphoproliferative disorder (LPD) where Epstein-Barr virus (EBV) was detected in rheumatoid nodules and lymph nodes. This is the first case of EBV-associated MIARN.

CASE REPORT

A 70-year-old woman with an 8-year history of rheumatoid arthritis (RA) and dermatomyositis who had received several therapies, including MTX (5 to 15 mg per week) and prednisolone for the past 3.5 years, the cumulative dose of MTX is 1,810 mg before onset of MIARN, presented with the rapid development of several ulcerated and non-ulcerated subcutaneous nodules on the legs and arms (Fig. 1 A, B). Physical examination revealed left inguinal, egg-sized lymphadenopathy. Computed tomography of the abdomen revealed lymphadenopathy of the left inguinal region and left common iliac artery (Fig. 1D). A biopsy of a lymph node from the left inguinal region disclosed an atypical lymphoid infiltrate of small CD3⁺ T cells with Hodgkin-like cells (Fig. 2 A, B). Immunohistochemical studies showed that the Hodgkin-like cells stained positively for CD15, CD20, and CD30. EBV was detected by *in situ* hybridization using EBV-encoded small RNA (EBER). Analysis of EBV-fused termini revealed the monoclonality of EBV infection. The patient was diagnosed as having MTX-LPD. The subcutaneous nodule on the dorsum of the left foot was surgically excised. Histopathological findings showed an amorphous necrotic substance containing neutrophils at the centre of the nodule, surrounded by CD68⁺ epithelioid cells

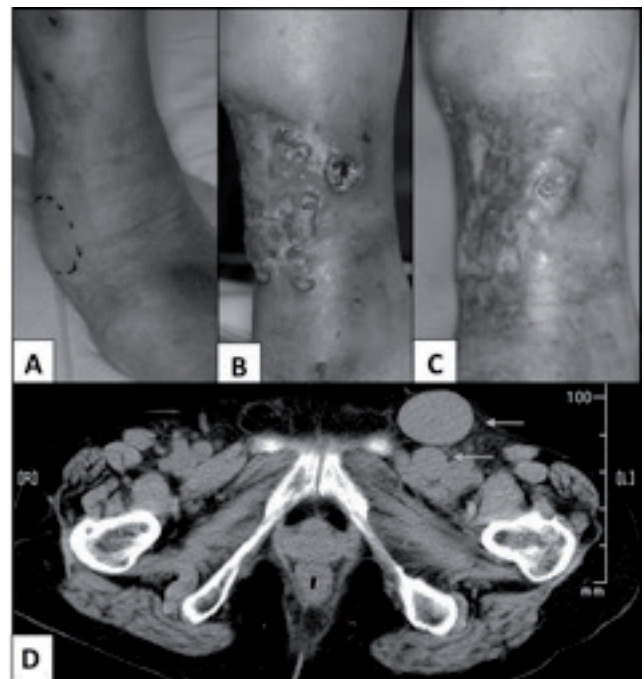


Fig. 1. Several non-ulcerated (A) and ulcerated (B) cutaneous nodules were seen on the leg during methotrexate (MTX) treatment, and were reduced approximately one month after the discontinuation of MTX (C). Computed tomography revealed lymphadenopathy at the left inguinal region and left common iliac artery (arrows) (D).

in a palisading pattern and CD20⁺ lymphocytes (Fig. 2 C, D). These pathological findings and clinical course were typical for MIARN. Remarkably, EBV was also detected in CD20⁺ lymphocytes from this subcutaneous nodule using *in situ* hybridization with EBER (Fig. 2E). Because the patient's RA had been well controlled, only MTX was discontinued. The lymphadenopathy and ulcerative nodules were reduced approximately one month after the discontinuation of MTX (Fig. 1C). Subcutaneous nodules on her legs and arms still remained after 6 months. The remaining nodule on the left lower leg was resected 3 months after MTX use was stopped. The histopathological findings showed amorphous necrotic substance surrounded by CD68⁺ epithelioid cells in a palisading pattern, but no CD20⁺ EBER⁺ cells.

DISCUSSION

Nodules in patients with RA consist of various types: (i) rheumatoid neutrophilic dermatitis which is an infre-

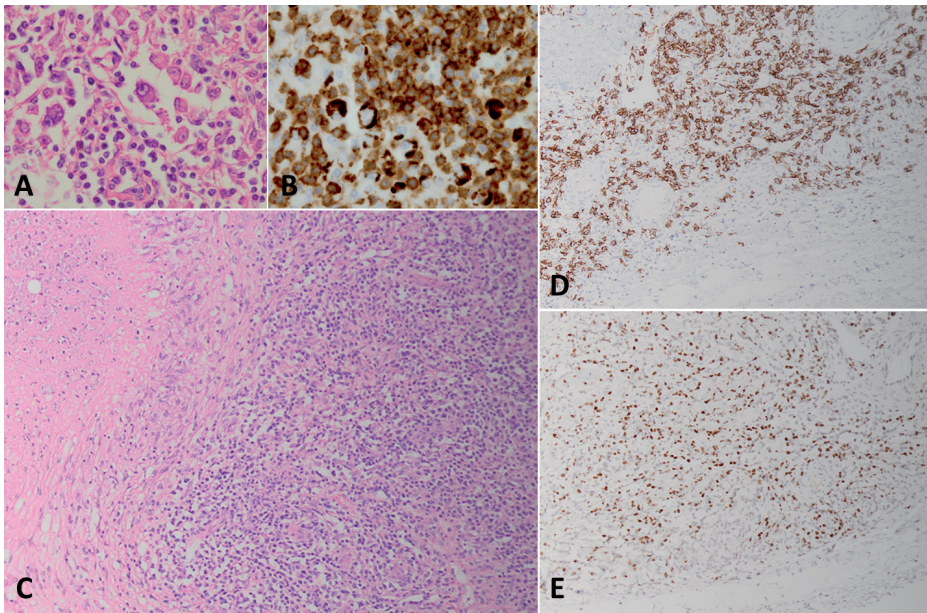


Fig. 2. Histopathologic features obtained from the resected inguinal lymph node. Histological appearance of the inguinal lymph node (A) (HE stain: $\times 400$) revealed Hodgkin-like cells. These cells were positive for CD3 (B) (immunostaining: $\times 400$). The histological appearance of the cutaneous leg nodule revealed an amorphous necrotic mass containing neutrophils (C) (HE stain: $\times 100$). Many cells in these nodules were positive for CD20 (D) (immunostaining: $\times 100$), and some CD20 positive cells were positive for EBV-encoded small RNA (E) (immunostaining: $\times 100$).

quent cutaneous manifestation of RA and characterised by a heavy dermal infiltrate of neutrophils with variable degrees of leukocytoclasia but no vasculitis (7), (ii) rheumatoid nodules which are the most common extra-articular manifestation of RA and histologically have granulomas with areas of central necrosis surrounded by activated macrophages and T lymphocytes infiltrating in a perivascular distribution (8), and (iii) MIARN (2–5). Furthermore, the cases of lymphomatoid granulomatosis associated with MTX therapy (9) and MTX-LPDs (10) are reported as EBV-associated nodules in patients with RA.

In this case, only the cessation of MTX improved the ulcerative nodules and lymphadenopathy, with disappearance of EBV-infected cells in the remaining subcutaneous nodule. This improvement suggests that MTX-associated immunosuppression can impair immune surveillance of EBV-infected cells, leading to the development of EBV-associated MIARN, as well as MTX-LPDs. It is presumed that the pathogenesis of MTX-LPDs includes the impairment of cell-mediated immune reactions to EBV-infected B cells. In addition, it is most likely that the reactivation of latent EBV infection induced by MTX is associated with the development of MIARN.

The authors declare no conflicts of interest.

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