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SHORT COMMUNICATION

Cutaneous Manifestations of Methotrexate-associated Lymphoproliferative Disorders: Report of Two Cases and a Review of the Literature

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Patients receiving methotrexate (MTX) are prone to lymphomas and other lymphoproliferative disorders (LPD) including polymorphic lymphoid proliferation (1, 2). This phenomenon has been called MTX-associated lymphoproliferative disorder (MTX-LPD) and is categorised by WHO under "iatrogenic immunodeficiency-associated LPD" (3). Cessation of MTX can result in at least partial regression in 31% (3) to 60% (4) of MTX-LPD cases. Skin involvement is not a frequent feature of MTX-LPD, and there have been no reports describing its cutaneous manifestations comprehensively.

We describe 2 patients with MTX-associated Epstein-Barr virus (EBV)-positive diffuse large B-cell lymphoma (DLBCL) that spontaneously regressed after discontinuation of MTX, and we reviewed the literature of an additional 17 cases of MTX-LPD with cutaneous manifestations.

CASE REPORTS

Case 1. A 63-year-old woman with a history of dermatomyositis and Sjögren's syndrome presented with nodules on the cheeks that had begun one month previously. She had been treated with MTX (10 mg weekly) and prednisolone (8 mg/day) for 4 years. Physical examination revealed 2 cm in diameter subcutaneous nodules on both cheeks (Fig. 1a), a 1 cm in diameter crusted nodule on the lumbar area, and infiltrated erythema on the legs. An excisional biopsy of a nodule on the cheek revealed diffuse infiltrate of atypical large lymphocytes in the dermis and subcutaneous tissue (Fig. 1b). Immunohistochemistry showed lymphoid cells to be positive for CD20, MUM-1 and Bcl-2, and negative for CD10. Most of the large cells were positive for Epstein-Barr virus-encoded small RNA (EBER) *in situ* hybridization (Fig. 1c). Monoclonal IgH gene rearrangement was demonstrated by Southern blot.

A thoraco-abdominal CT scan revealed multiple nodules in the lungs, suggestive of lymphoma. The diagnosis of MTX-associated EBV-positive DLBCL was confirmed, and the MTX was discontinued. The skin lesions completely resolved in a month, and the lung lesions resolved in 4 months. No relapse of lymphoma has occurred under prednisolone therapy alone in the 8 years since.

Case 2. A 74-year-old man with rheumatoid arthritis (RA) presented with a nodule on the head that had appeared 4 weeks previously (Fig. 1d). He had been treated with MTX (8 mg weekly), bucillamine (200 mg/day) and prednisolone (5 mg/day) over a period of 9 years. Physical examination revealed a 2 cm in diameter nodule on the head. Multiple nodules on the head and ulcerated nodules on the legs appeared in the 2 weeks after the first head nodule. There was no peripheral lymphadenopathy or hepatosplenomegaly. CT scan revealed ground-glass opacity in the lungs suggestive of *Pneumocystis* pneumonia and a dissecting aneurysm of the aorta. The histopathology of a head nodule showed dense, diffuse infiltration of large lymphocytes with moderate atypia (Fig. 1e). Immunohistochemistry showed the lymphoma cells to be positive for CD20, CD79a, MUM-1 and Bcl-2. Most of the tumour cells were EBER-positive with *in situ* hybridization (Fig. 1f). Laboratory tests revealed elevated serum EBV DNA, at 19,000 copies ml^{-1} (normal limit < 100 copies ml^{-1}). The diagnosis of MTX-associated EBV-positive DLBCL was confirmed, and MTX was discontinued. The skin lesions completely resolved after a month. The pneumonia was cured with antibiotics; however, the patient died of debility caused by the inoperable dissecting aneurysm and sepsis after 2 months.

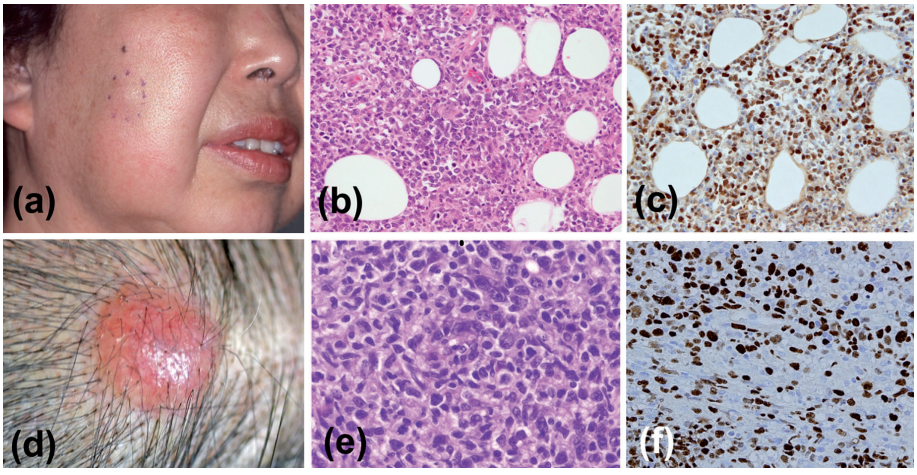

Fig. 1. (a) Case 1. A subcutaneous nodule on the cheek. (b) Nodular infiltrate of atypical lymphoid cells in the subcutaneous tissue. (H&E, original magnification × 200). (c) A majority of the large cells express EBV-encoded small RNA (EBER) by *in situ* hybridization. (EBER-ISH, original magnification × 200), (d) Case 2. A nodule on the head. (e) Dense infiltrate consisting of large neoplastic lymphocytes with large nuclei in the dermis. (H&E, original magnification × 200). (f) A majority of the large cells express EBER by in situ hybridization (EBER-ISH, original magnification × 200).

DISCUSSION

An English-language PubMed search for MTX-LPD with skin lesions found 17 cases, which we analysed as well as the present 2 cases (Table SI[1]). Of the 19 cases, 13 involved skin

alone and 6 presented skin lesions as the initial manifestation. The mean age was 68 years with a male:female ratio of 5:14. Underlying diseases included rheumatoid arthritis in 11 cases (of which 1 accompanied Sjögren's syndrome), dermatomyositis in 5 cases (of which 1 accompanied Sjögren's syndrome), mycosis fungoides in 2 cases, and non-rheumatoid peripheral arthritis in 1 case. Concomitant drugs included PSL in 11 cases, azathioprine in 1 case (5), and infliximab in 1 case (6). Most of the cutaneous manifestations were nodules, however, erythema, ulcers and a solitary plaque were also seen. Histologically, 12 cases (63%) were B-cell lymphoma, of which 8 cases were DLBCL. In addition, there was 1 case of T-cell lymphoma (7), 1 of composite lymphoma (8), and 5 whose diagnosis was "LPD". Expression of EBV in tumour cells was confirmed in 13 of 18 cases (72%) by immunohistochemistry and/or EBER *in situ* hybridization. MTX was discontinued in 15 cases, and infliximab was also discontinued in the case on both drugs (6). The lesions spontaneously resolved in 12 (80%) of the cases that were observed without any additional treatment after withdrawal of MTX. Three patients recovered after chemotherapy with cessation of MTX.

These results show a similar tendency to reports that predominantly described MTX-LPD without skin lesions (4, 9). They have shown that the frequency of DLBCL and positive rate of EBV was higher in nodal and extranodal MTX-LPD than in LPD without association with MTX. In terms of the response after withdrawal of MTX, Ichikawa et al. (4) reported that the lesions regressed completely in 17 out of 47 cases (36%) of nodal and extranodal MTX-LPD, regressed partially in 11 cases and exacerbated after regressing once in 5 cases. Gaulard et al. (3) showed that 28/90 cases (31%) regressed at least partially after discontinuation of MTX, a rate that is lower than in the present study with cutaneous lesions. The response to discontinuation of MTX may be better in cutaneous-oriented MTX-LPD, however, this could be biased by the limited number of patients and shorter observation periods.

Although patients with rheumatoid disease have an innate immune dysfunction that makes them susceptible to lymphoma it is believed that MTX and other immunosuppressants contribute to the development of LPD to various degrees (3). It is hypothesised that chronic iatrogenic immune suppression causes lymphoma by leading to the loss of immune surveillance (10). In addition, EBV plays a positive role in lymphomagenesis, as previously described (1, 9). Recently, independent case reports of lymphomas associated with infliximab and other biologics have been reported (6, 11, 12). Most of these had a history of MTX use, and the independent potential and frequency of biologics to cause LPD has not been clarified.

In light of the present study, we believe it is important to consider iatrogenic immunodeficiency-associated LPD as a differential diagnosis when a patient under potent immunosuppressants develops lymphoma. Initial observation accompanied by the discontinuation of the immunosuppressant is recommended before radiation or chemotherapy, which might otherwise be associated with increased morbidity.

The authors declare no conflict of interest.

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