Letters to the Editor

A case of rheumatoid arthritis complicated by two different types of lymphoproliferative disorder

Sirs,

Several studies have shown that patients with rheumatoid arthritis (RA) have a two- to three-fold increased risk of developing lymphoproliferative disorders (LPDs) compared with the general population (1, 2). The high disease activity of RA or treatment drugs for RA have been implicated in its pathogenesis (3, 4). Herein, we describe a patient with RA complicated by two different types of LPD: methotrexate (MTX)-associated LPD and subcutaneous panniculitis-like T-cell lymphoma (SPTCL).

A 76-year-old woman was diagnosed as having RA because of positive rheumatoid factor test, erosive changes in the carpal bones, and symmetrical polyarthritis in hand, finger, and knee joints. She had a smoking history for 50 years. During treatment with 8 mg/day of prednisolone, 8 mg/week of MTX, and 250 mg/day of bucillamine for two years, bilateral axillary lymph node swelling and infiltration in the right lung developed abruptly. The biopsy of the lymph nodes revealed polymorphic lymphoid proliferation and necrosis. In situ hybridization showed the expression of Epstein-Barr virus (EBV)-encoded RNA (EBER) in the $CD20^+$ cells. The patient was diagnosed as having EBV-positive MTX-associated LPD (group II, polymorphic) (5). After discontinuation of MTX and bucillamine and treatment with methylprednisolone pulse therapy, the lymph node swelling and the lung infiltration disappeared. Thereafter, her active arthritis persisted.

After three years, the patient noticed skin indurations with itching on her right buttock. X-ray of the hands revealed ankylosis in the carpal bones, and chest X-ray revealed adenocarcinoma in the right lung S6 lobe. The skin biopsy showed a diffuse panniculitis-like infiltration of atypical lymphocytes in the subcutaneous tissues (Figure 1), negative EBER, and monoclonal rearrangement of T-cell receptor β gene, leading to the diagnosis of SPTCL (6). The helper T-cell subset was not analyzed. The patient underwent a radical lobectomy for lung adenocarcinoma, followed by 62 gray of local radiotherapy and eight courses of chemotherapy for SPTCL. At present, the patient has no evidence of recurrence.

In this case, MTX-associated immunosuppression appeared to be the cause of first LPD because the reactivation of latent EBV reactivation was found. Until today, more than 100 cases of LPDs in RA patients treated with MTX have been reported (5). EBV infection has been found in 41% of such LPDs (3). This disease entity is described as MTX-associated LPD in immunodeficiency-associated LPD of the World Health Organization (WHO) classification (5). Histopathological features of MTX-associated LPD are similar to those of non-Hodgkin lymphoma or Hodgkin lymphoma (5). MTX withdrawal occasionally leads to a spontaneous LPD remission (7), strongly indicating a causal link between MTX treatment and LPD development, but no increase in lymphoma associated with MTX was established (8, 9).

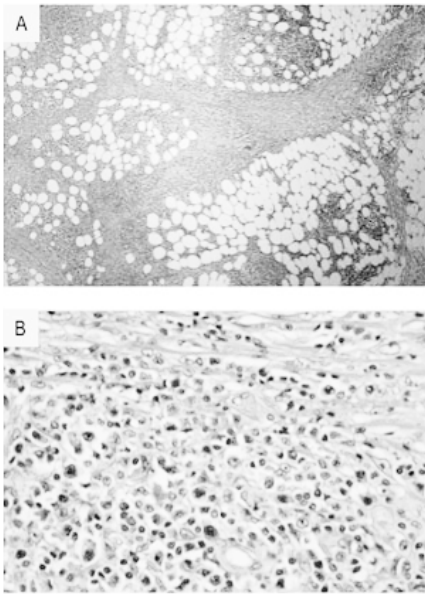

Fig. 1. Histopathology of skin showing diffuse panniculitis-like infiltration of lymphocytes in the subcutaneous tissue (A) (hematoxylin and eosin, original magnification x 40). The infiltrating cells are small to large atypical lymphoid cells (B) (hematoxylin and eosin, original magnification x 400).

In contrast, Baecklund *et al*. (3) reported a strong casual association between high inflammatory activity and LPDs. At the development of second LPD, the present case had long-standing active joint inflammation and progressive joint destructions, indicating that RA disease activity was associated with its development. SPTCL is a rare form of T-cell lymphoma, representing less than 1% of non-Hodgkin lymphomas. It is a cytotoxic T-cell lymphoma positive for CD8 with the expressions of cytotoxic molecules including granzyme B and perforin, mimicking lobular panniculitis. Lymphoma subtype that develops in patients with RA is mostly B-cell lymphoma, but Levy *et al*. (10) also reported a case of subcutaneous T-cell lymphoma in RA patient. At present, the pathogenesis of T-cell lymphoma in RA is unclear. Prolonged antigenic stimulation to T-cells may have a role in its lymphomatogenesis.

The patient had lung adenocarcinoma as a third neoplasm. In addition to RA disease activity or immunosuppression, certain environmental or genetic factors might contribute to the development of these neoplasms.

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