EBV-associated synovial lymphoma in a chronically inflamed joint in rheumatoid arthritis receiving prolonged methotrexate treatment

A patient with longstanding rheumatoid arthritis (RA) developed swelling in a chronically inflamed knee joint while receiving prolonged methotrexate treatment. Magnetic resonance imaging and positron-emission tomography showed soft tissue swelling with intense tracer uptake. Biopsy confirmed high-grade B-cell lymphoma. He developed complete remission with rituximab plus CEOP. The role of chronic inflammation and methotrexate in the pathogenesis of lymphoma in RA was discussed.

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Case Report. A 66-year-old man suffering from seronegative rheumatoid arthritis affecting both hands, elbows and knees since 1991. His joint symptoms were not adequately controlled with non-steroidal anti-inflammatory agents (NSAID), and he had active synovitis involving small joints of the hands, wrists, elbows and knees requiring several courses of intra-muscular steroid injections and one episode of intra-articular injection into right shoulder. He received sulphasalazine 2gram daily since May 2000 in vain. The knees have been involved in each exacerbation during his clinical course apart from involvement of the small finger joints, elbows and shoulders. Radiography of both knees in 2001 showed mild degenerative change of bilateral patello-femoral space. In view of his active synovitis over his finger joints, shoulders and knees, methotrexate (10mg weekly) was started in December 2001. The dose of methotrexate was gradually stepped up to 15 mg per week since March 2003 with improvement in symptoms. His disease remained stable with normalization of C-reactive protein (CRP) and absence of arthritis at weekly methotrexate of 15mg until February 2005 when he complained of left knee pain and swelling. Due to persistent left knee pain the patient went to have acupuncture to his left knee in July 2005. One week later he developed swelling and erythema over the left knee. Peripheral white blood cell count was 10.3 x 10^9/L (normal: <11) and the CRP was 8.2 u/L (Normal<1.4). Despite intravenous antibiotics, the left knee swelling and pain persisted. A knee tap failed to yield any synovial fluid, and ultrasound scan of the left knee showed a heterogeneous soft tissue mass lesion in the left knee, predominantly in the suprapatellar bursa and the anterior joint compartment measuring 4.2 x 2.5 x 5.6cm in size. Section of the biopsy showed a piece of synovial tissue diffusely infiltrated by a monotonous population of large abnormal lymphoid cells. No acute inflammatory cells were detected to suggest an active inflammatory process, and special stains including Gram's stain for bacteria and Grocott stain for fungus were negative. Immunohistochemical staining showed that these cells were positive for B cell markers CD20, and majority showed nulear reactivity for Epstein-Barr virus-encoded early RNAs (EBER) by in-situ hybridization. Therefore, the overall features were consistent with methotrexate-associated lymphoproliferative disorder, morphologically of the diffuse large B cell lymphoma type. Serum lactate dehydrogenase was 636 unit/L (normal: <380 unit/L).

On examination the patient had no palpable lymph nodes or hepatosplenomegaly. The left knee was hot, tender and swollen. No other joints were involved. Bilateral bone marrow biopsies showed no lymphoma involvement. Magnetic resonance imaging (MRI) of the left knee showed an aggressive intra-articular lesion of the left knee with diffuse infiltration and bony erosions of the femoral condyles and the proximal tibia. Whole body positron emission and computed tomography (PET/CT) showed localized increased uptake at the left knee, distal left thigh and proximal tibia but absence of lymphadenopathy or masses elsewhere, consistent with Ann Arbor stage I non-Hodgkin's lymphoma (NHL) localized to the knee only. Methotrexate was withheld, and the patient achieved complete remission after 4 cycles of R-CEOP (rituximab plus cyclophosphamide, epirubicin, vincristine and prednisolone), followed by irradiation of the left knee, and is currently in complete remission 12 months after diagnosis.

Discussion. Rheumatoid arthritis (RA) is associated with a higher risk of development of lymphoma with the

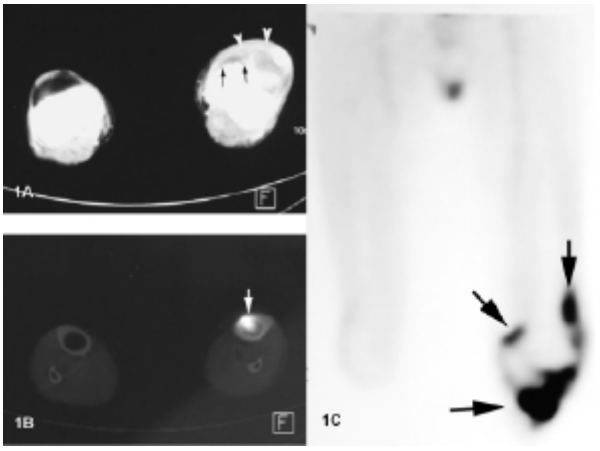

Figure 1. (A) Axial CT scan showing soft tissue synovial mass (arrowhead) arising in the left knee joint with bony destruction of the femoral condyles (arrows). (B) Axial fused PET-CT image showing abnormal uptake in the left tibia (arrows) (C) PET scan image showing multiple focal uptake around the left knee joint compatible with synovial soft tissue mass.

Figure 2. (A) Hematoxylin and Eosin staining showing atypical large lymphoid cells around a vessel. (B) Immunostain for CD20: These abnormal lymphoid cells are positive for CD20, indicative of their B-cell lineage. (c) In-Situ hybridization for EBV-associated small RNA (EBER) showed that the tumor cells are positive for EBER

majority being diffuse large B cell lymphoma.1 Moreover, some of the NHL in patients with RA were associated with EBV, thereby suggested a relationship to an underlying immunosuppression, likely related to the use of immunosuppressive treatment.[1]

There were several interesting findings in this case. First, the lymphoma masqueraded as septic arthritis with signs of acute inflammation, especially with the increasingly painful swelling after acupuncture. However, ultrasound-guided aspiration did not yield any fluid but showed soft tissue swelling instead, biopsy of which confirmed diagnosis of lymphoma. Moreover, special stains for micro-organisms were negative. The possibility of an infected joint has been further excluded by the rapid resolution of symptoms after commencement of chemotherapy as any underlying bacterial infection would have evolved into an abscess, or exacerbated with the myelosuppression induced by combination chemotherapy.

Secondly, the lymphoma localized to the synovium, and was EBV-associated. As lymphomas in immunocompromised patients are often EBV-associated, the presence of EBV in the tumor cells in this case suggested an underlying immunocompromised state, which might be contributed by the prolonged use of methotrexate. Moreover, methotrexate has been shown to result in reactivation of EBV by a significantly higher viral load in the peripheral blood of patients with RA.[2] Therefore, one might postulate that prolonged use of methotrexate in our patient might have led to EBV reactivation in the B cells inside the chronically inflamed synovium, leading to clonal B-cell proliferation and subsequent lymphomagenesis.

Thirdly, while patients with RA have been shown to have a higher risk of developing non-Hodgkin's lymphoma (NHL), synovial involvement of is rare. For instance, 18 cases of NHL have been reported in methotrexate-treated RA patients.[3] While extranodal involvement (including bone, orbit, marrow, lung and stomach) occurred in a substantial proportion of patients, none had joint involvement. Moreover, our patient had NHL arising from a RA-affected joint, thereby proposing a link to underlying inflammation. Indeed, in a review of soft tissue lymphomas, three cases (8%) were associated with a longstanding history of antecedent RA.4 Interestingly, all these 3 cases were B-cell lymphoma arising from soft tissues of the affected joints, thereby suggesting a possible role of chronic local immune stimulation in the pathogenesis.[4]

In summary, our patient developed an EBV-associated large B-cell lymphoma of the RA-affected joint 14 years after the diagnosis of RA and substantial methotrexate use, consistent with the inherent risk of lymphoma in RA, which might be further enhanced by the use of methotrexate.

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