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CASE REPORT

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Durable remission of HIV-negative, Kaposi's sarcoma herpes virus-associated multicentric Castleman disease in patient with rheumatoid arthritis treated with methotrexate

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Abstract Multicentric Castleman disease (MCD) is a nonneoplastic lymphoproliferative disorder that has a poor prognosis. Optimal treatment is unknown. There are a few reported cases of MCD and rheumatoid arthritis. In this study, we report a patient with rheumatoid arthritis diagnosed with Kaposi's sarcoma herpesvirus-(KSHV, human herpesvirus-8) associated MCD that showed expression of viral IL-6. Treatment with methotrexate (MTX) resulted in a complete remission of her disease lasting for 54+ months. Multiple studies have suggested that MCD and rheumatoid arthritis are associated with overexpression of the growth-promoting cytokine interleukin-6 (IL-6), and that MTX downregulates the production of this cytokine in vivo. As such, we suggest that the dramatic improvement in this patient's disease is due to the immunomodulatory properties of MTX.

Keywords Castleman disease · Interleukin-6 · Methotrexate

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Introduction

Multicentric Castleman disease (MCD) is a systemic disorder characterized by generalized lymphadenopathy with fever, chills, weight loss, hepatosplenomegaly, and disordered immunologic manifestations. MCD portends a variable but often poor prognosis, with the clinical course often ending in death from infection, hematologic complications, or an aggressive non-Hodgkin lymphoma [5]. Recently, a subtype of MCD has been shown to be caused by Kaposi's sarcoma herpesvirus (KSHV) [6–9]. KSHV has been demonstrated in 40 to 50% of patients with HIV-negative MCD, and in virtually 100% of patients with HIV-positive MCD [8–10]. KSHV is known to encode a viral homologue of the growth-promoting cytokine interleukin-6 (IL-6), which is expressed in MCD and, together with human IL-6 and other cytokines, may play a role in the development of MCD [8, 11–14].

Case report

Presentation and history

A 66-year-old female retired laboratory technician presented in March 2000 with unexplained fever, lethargy, and weight loss of 1-month duration. Her past medical history included coronary artery disease, mild hypertension, and longstanding rheumatoid arthritis with joint deformity. Past treatments for the latter included Imuran and gold injections. At presentation, she had fevers up to 103°F, diffuse lymphadenopathy, and splenomegaly. Laboratory studies included a complete blood count with WBC of 7.3×10^9/l, Hb 10.6 gm/dl, and platelets 294×10^9/l with normal differential counts. She had normal liver and renal functions. Rheumatoid factor was <20 IU/ml, ESR 100 mm/h, and HIV was negative. Blood cultures were negative. Computed tomography (CT) scans of chest, abdomen, and pelvis showed splenomegaly and multiple enlarged lymph nodes in the mediastinum, axilla, and retroperitoneum.

A biopsy was performed of an axillary lymph node, which was diagnosed as showing reactive follicular hyperplasia possibly related to rheumatoid arthritis. A bone marrow biopsy demonstrated normocellulity with trilineage hematopoesis, a mild polyclonal plasmacytosis and benign lymphoid aggregates. In a retrospective review (SHS), changes suggesting the possibility of MCD were present in both specimens.

The patient was treated with nonsteroidal anti inflammatory agents and defervesced, but continued to have fatigue, night sweats, and severe asthenia. Prednisone was prescribed at 60 mg/day. Her lymphadenopathy and splenomegaly persisted. A cervical lymph node biopsy was performed.

Shortly after the biopsy, the patient was readmitted to the hospital with chest pain, hypotension, and tachycardia and was diagnosed as having an acute myocardial infarction. She underwent angioplasty and was weaned to 10 mg/day of prednisone. Before the final diagnosis of the lymphadenopathy being rendered, the decision was made to treat her with immunomodulatory therapy for rheumatoid arthritis, although the precise relationship between the arthritis and lymphadenopathy was unclear. Methotrexate (MTX) was initiated at 10 mg/week.

Two weeks after the start of MTX, the patient had improved. Her symptoms of fever, fatigue, and anorexia resolved. There was a decrease of lymphadenopathy. Over a period of 1 month, prednisone was tapered off and the MTX dose was increased to 15 mg/week. Two months posthospitalization, she had resolution of lymphadenopathy and splenomegaly as well as improvement in her hemoglobin level to the normal range. Over the past 54 months she has remained in a complete remission with MTX at 15 mg/week without any adverse effects.

Pathology

The second biopsy established the diagnosis of MCD. Lymph node(s) demonstrated hyperplastic and regressively transformed follicles. There was marked plasmacytosis in interfollicular regions with extension into the capsule and formation of small clusters including occasional plasmablasts within the mantle zones, highlighted on the CD138 immunostain. Paraffin section immunohistochemical stains for kappa and lambda showed that the plasma cells were not light chain class restricted. Paraffin section immunostains for KSHV latent nuclear antigen (LANA1) showed a moderate number of scattered positive cells including some larger cells in and around the mantle zones (Fig. 1a). Staining for viral IL-6 showed a moderate number of positive cells with a distribution similar to that of KSHV (Fig. 1b). Flow cytometric immunophenotypic studies demonstrated polyclonal B-cells, some surface immunoglobulin negative B-cells, and heterogeneous T-cells. Southern blot analysis for KSHV was positive.

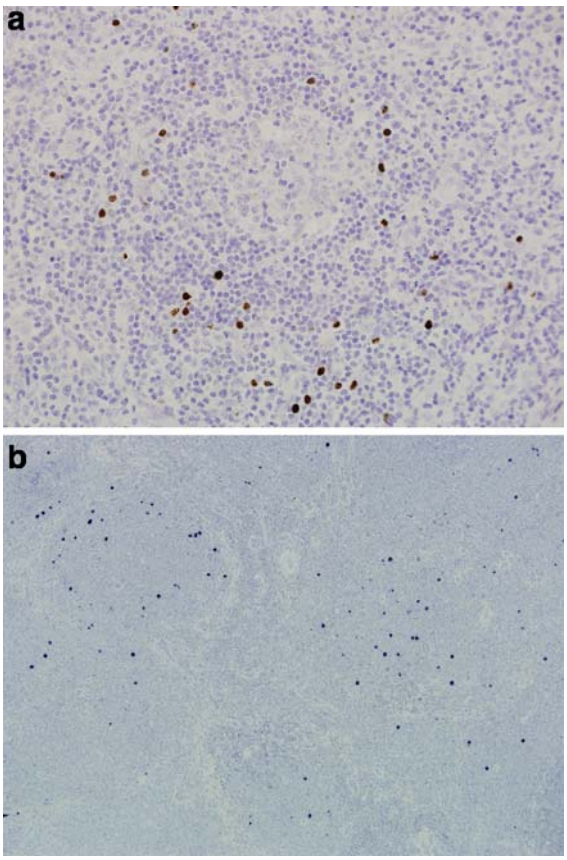

Fig. 1 **a** KSHV latent nuclear antigen (LANA1) positive nuclei are seen around a small germinal center as well as scattered elsewhere (immunostain with hematoxylin counterstain, original magnification 40×). **b** Note the viral IL-6 positive nuclei that have a similar distribution to that of the KSHV positive cells (immunostain, original magnification 10×)

Discussion

Currently there is no consensus as to the optimal therapy for MCD. MCD has been treated with corticosteroids, immunosuppressive regimens, cytotoxic drugs, and radiation [15]. The results of these therapies have not been systematically studied, but in general have been poor, with the worst response and shortest survival in the most severely symptomatic patients.

MTX was chosen in this case to treat the patient's rheumatoid arthritis. The inhibition of dihydrofolate reductase, which inhibits synthesis of pyrimidine bases, has also been shown to have immunomodulatory properties [21]. The proposed mechanism by which methotrexate has antiinflammatory activity [22] is the interference with the IL-6 pathway. IL-6 is a pleiotropic cytokine with a range of biologic activities including promotion of B-cell proliferation and stimulation of inflammatory pathways [23]. IL-6 dysregulation is also believed to play a key role in the pathophysiology of MCD [9, 11–14, 23]. Patients with MCD are known to have increased levels of IL-6 [11], and in murine studies, MCD-like lesions can be induced by promoting IL-6 dysregulation [12]. Furthermore, KSHV encodes viral IL-6 that has been shown to have similar

biologic activity to IL-6 in the signaling of downstream pathways [24]. Recently, MTX has been demonstrated to downregulate the production of viral IL-6 [25]. We therefore postulate that the patient's dramatic resolution of MCD-associated lymphadenopathy and long-lasting CR may have resulted from the downregulation of IL-6 and viral IL-6 by the MTX.

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