Epstein-Barr virus-positive CD30+ B-cell lymphoproliferative disease with histologic features resembling grade III lymphomatoid granulomatosis induced by methotrexate

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Abstract

Methotrexate (MTX) is a first-line systemic medication used to treat rheumatoid arthritis because of its immunomodulatory effects. However, MTX has also been linked to the development of lymphoproliferative disorders (LPD) in patients with rheumatoid arthritis. We describe a patient with long-standing rheumatoid arthritis treated with MTX who developed cutaneous Epstein-Barr virus (EBV)-positive B cell lymphoproliferative disease resembling grade III lymphomatoid granulomatosis localized to the right leg. The lymphomatoid process resolved with withdrawal of the MTX. The pathogenesis of iatrogenic lymphoproliferative disorder was most likely triggered by the rheumatoid inflammation and the immunosuppressing effects of MTX, which led to EBV reactivation. We recommend a trial of MTX discontinuation prior to considering chemotherapy in patients with rheumatoid arthritis treated with MTX who develop EBV-positive B cell lymphoproliferative disease resembling a high grade B-cell lymphoma.

Keywords: B cell, Epstein-Barr, grade III, lymphoma, lymphomatoid granulomatosis, lymphoproliferative disease, methotrexate, rheumatoid arthritis, spontaneous regression, virus

Introduction

Methotrexate (MTX) is a first-line systemic medication used to treat rheumatoid arthritis (RA). However, the use of MTX is also associated with the development of lymphoproliferative disorder (LPD), which is well reported in the literature. Its etiologic basis has been attributed to immunosuppressing effects of MTX combined with the hyperinflammatory state associated with RA [1]. Herein, we describe a patient with long-standing RA treated with MTX who developed cutaneous Epstein-Barr virus-positive (EBV^+) CD30+ atypical B cell infiltrate that morphologically and phenotypically resembled grade III lymphomatoid granulomatosis. The lymphoma resolved after the MTX treatment was withdrawn.

Case Synopsis

An 80-year-old man with a 20-year history of RA treated with oral MTX presented with a 4-month history of an asymptomatic but worsening rash confined to his lower right leg. He had no systemic symptoms such as weight loss, fever, or chills. He was previously treated with multiple courses of antibiotics for presumed cellulitis with no improvement. Physical examination of his right leg revealed multiple punched-out hemorrhagic ulcerations and flat pink-purple blanching patches with areas of confluence extending from the knee to the ankle (**Figure 1**).

Two punch biopsies were performed to render a diagnosis. The pathology of both biopsies demonstrated similar histologic features, including an angiocentric mixed lymphocytic infiltrate

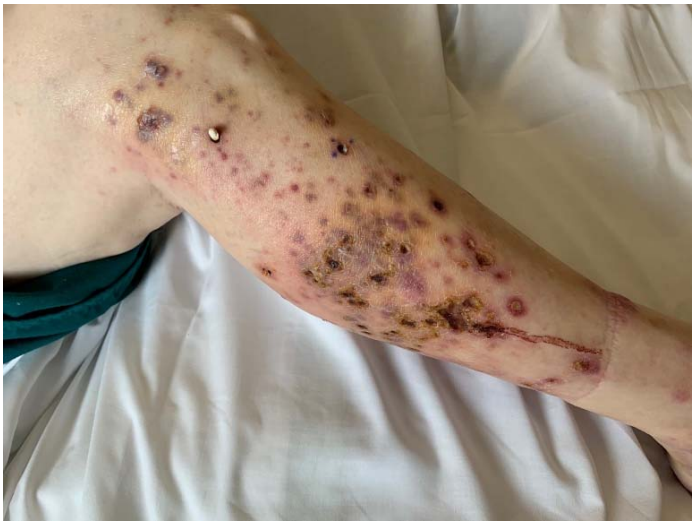

Figure 1. *Right lower leg with multiple punched-out hemorrhagic ulcerations and flat pink-purple blanching patches with areas of confluence extending from the knee to the ankle.*

containing markedly atypical transformed immunoblastic-appearing cells with associated vascular injury characterized by mural and luminal fibrin deposition (**Figure 2**). The atypical blastic-appearing cells were CD45^{+} CD79a^{+} CD20+, BCL2+ CD30+ EBV+ and exhibited weak BCL6 staining. There was a very high proliferation index in excess of 90% revealed by the extent of nuclear staining for Ki67. The atypical lymphocytes did not show immunoreactivity for CD43, EMA, MUM1, CD138, CD10, CD56, P63, ALK, and CD3 [2]. The findings were

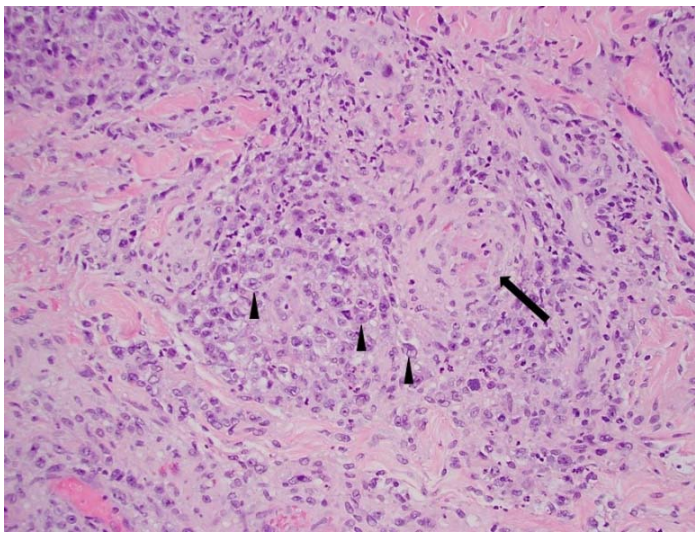

Figure 2. *Medium-power photomicrograph of H&E-stained biopsy punch showing collections of cells with large irregular vesicular nuclei and prominent nucleoli (arrowheads) surrounding a blood vessel containing a fibrin thrombus (arrow), 20×.*

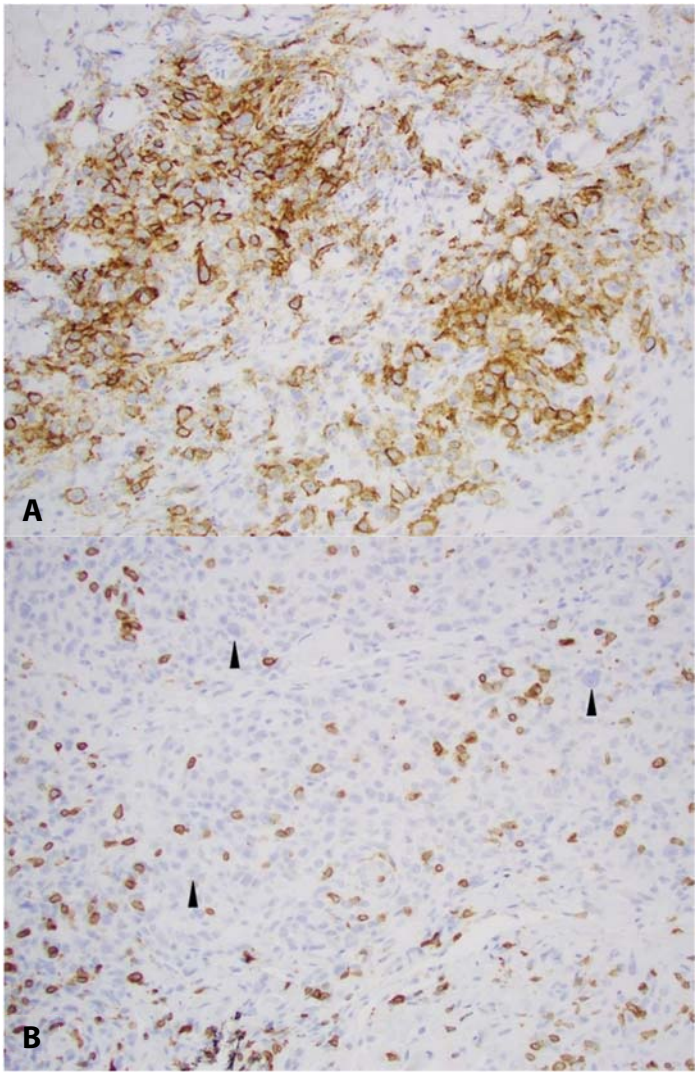

Figure 3. ***A)*** *Immunohistochemical stain for CD20 highlights the atypical cells, 20×.* ***B)*** *The large atypical cells (arrowheads) were immunonegative for CD3, whereas the smaller T lymphocytes within the infiltrate were positive, 20×.*

consistent with an EBV^{+} large B-cell LPD resembling grade III lymphomatoid granulomatosis as a variant of diffuse large B-cell lymphoma (**Figures 3, 4**).

The oncology department was consulted and further work-up advised. Blood work showed no evidence of tumor lysis syndrome or progressive cytopenia. Positron emission tomography revealed extensive uptake of contrast agent only in the skin of the right leg, with no lymphadenopathy or splenomegaly. The patient was subsequently diagnosed with MTX-associated B cell LPD. Given the stability of the rash and the lack of systemic involvement, the sole treatment was withdrawal of MTX and close clinical follow-up.

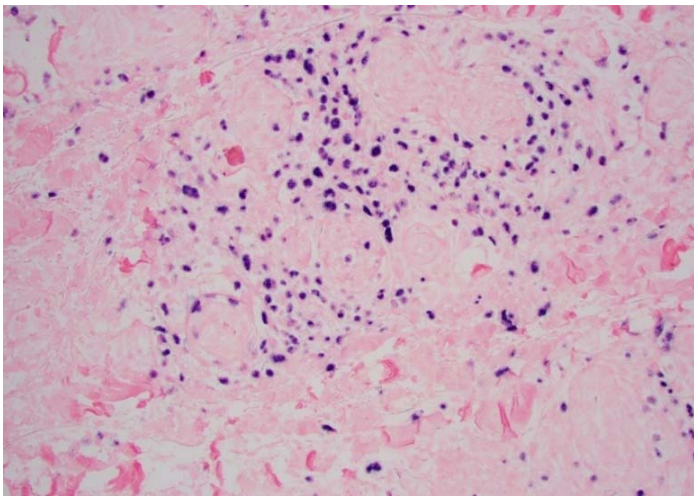

Figure 4. *In situ hybridization for Epstein-Barr virus demonstrating positivity (dark blue/purple; counterstained with eosin). 20×.*

At one month, the leg was significantly improved and at 6 months all ulcerated areas on the patient's right lower extremity had completely healed, with only pink scaling patches and hyperpigmented macules remaining (**Figure 5**). The patient has had no recurrence after 1.5 years.

Case Discussion

The patient in this case presented with an angiocentric and angiodestructive atypical large B cell infiltrate in the setting of iatrogenic and endogenous immune dysregulation. The overall presentation was diagnostic of MTX-associated B cell LPD. The three main considerations from a morphologic perspective are EBV-positive mucocutaneous ulcer, grade III lymphomatoid granulomatosis, and EBV-positive diffuse large cell lymphoma, [3]. Given the regression following MTX withdrawal and degree of angiocentricity of the neoplastic B cell infiltrate this process was categorized as MTX-associated LPD resembling grade III lymphomatoid granulomatosis. Although EBV-positive mucocutaneous ulcer is an important consideration this diagnosis was ultimately not favored because of the extent of neoplastic large B cell infiltration. Typically in the EBV-positive mucocutaneous ulcer there is an admixture of smaller B cells and a polymorphous inflammatory cell infiltrate.

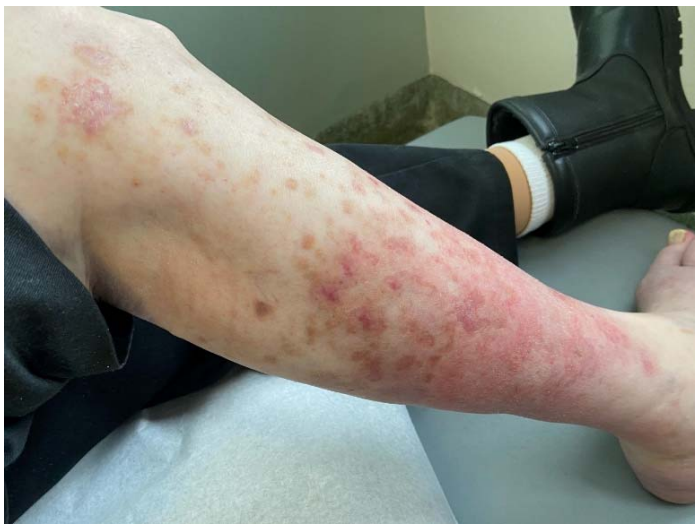

Figure 5. *All ulcerated areas on the right lower extremity healed completely, with only pink scaling patches and hyperpigmented macules remaining.*

An important question to address is how the variables of RA, MTX, and EBV in the patient's case are connected. The risk of lymphoma in patients with RA increases as the inflammatory activity increases: the odds that patients with high levels of inflammatory activity will develop lymphoma are 25 times higher than for patients with low inflammatory activity [4].

The mechanism by which methotrexate treatment causes B cell LPD in patients with RA is not fully elucidated. Methotrexate increases the likelihood of EBV reactivation by activating certain immediate early viral promoters that will lead to the release of infectious virus from latently infected cells, a key event in the development of certain LPDs such as lymphomatoid granulomatosis [7]. Methotrexate is lympholytic and has been associated with a reduction in the absolute lymphocyte count. Very likely tumor evasion due to a reduced tumor-specific T cell response is a key pathogenetic event in the evolution of MTX associated B cell LPD. In any patient with RA who develops B cell LPD including cases resembling grade III lymphomatoid granulomatosis and other forms of EBV positive large B-cell lymphoma in the setting of MTX therapy the first line of therapy should be drug withdrawal regardless of the extent of atypia. Forty to seventy percent of cases respond to withdrawal of MTX therapy [9].

As in this described case, the response time to MTX withdrawal is quick, with patients responding within

a few weeks [8,10]. However, close clinical follow-up is needed because of the risk of recurrence, for which chemotherapy is recommended [11].

Conclusion

We outline a unique case involving a patient treated for 20 years with MTX for RA who suddenly developed a cutaneous EBV+ angiocentric CD30 positive large B cell infiltrate resembling grade III lymphomatoid granulomatosis but with an indolent course given the complete regression following MTX withdrawal. It is highly probable that the lymphocytic effects of MTX enable EBV reactivation and facilitate tumor evasion. We strongly recommend considering MTX withdrawal in cases of EBV+ LPD in patients with RA prior to starting systemic chemotherapy.

Potential conflicts of interest

The authors declare no conflicts of interest.

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