

CASE REPORT

Methotrexate-Associated Lymphoproliferative Disorder Presenting As Oral Ulcers in a Patient With Rheumatoid Arthritis

M.A. Pastor-Nieto,^a L.G. Kilmurray,^b A. López-Chumillas,^b F. O'Valle,^c R. García-del Moral,^c A.M. Puig,^b and P. Bautista^a

^aServicio de Dermatología, Hospital General Universitario de Guadalajara, Spain. ^bHospital Santa Bárbara, Puertollano, Ciudad Real, Spain.

^cInstituto de Biopatología y Medicina Regenerativa and Departamento de Anatomía Patológica, Facultad de Medicina, Universidad de Granada, Granada, Spain

Abstract. Methotrexate-associated lymphoproliferative disorders are a heterogeneous group of lymphoid proliferations or lymphomas that develop in patients with autoimmune diseases treated using methotrexate. These lymphoproliferative disorders are often associated with Epstein-Barr virus infection and occasionally regress after the withdrawal of methotrexate therapy. The lymphoproliferative disorder in this case was diffuse large B-cell lymphoma, unusually presenting as oral ulcers in a 79-year-old woman on treatment with methotrexate for longstanding rheumatoid arthritis. Latent membrane protein 1 positivity was detected by immunohistochemistry and Epstein-Barr-virus encoded small RNA positivity by chromogenic *in situ* hybridization. Clonality was confirmed by immunohistochemistry (K light-chain restriction), polymerase chain reaction (monoclonal immunoglobulin H gene rearrangement), and capillary electrophoresis (GeneScan). Staging procedures were negative. Withdrawal of methotrexate therapy led to complete remission within 6 weeks, and the patient is alive and disease-free 18 months after the diagnosis was made. The oral cavity is not often involved in the initial presentation of methotrexate-associated lymphoproliferative disorders, and presentation with intraoral ulcers is very rare. We have performed a review of the literature on methotrexate-associated lymphoproliferative disorders presenting as ulcers in the oral cavity.

Key words: oral ulcers, diffuse large B-cell lymphoma, methotrexate, Epstein-Barr virus, rheumatoid arthritis.

ÚLCERAS ORALES COMO MANIFESTACIÓN CLÍNICA DE PROCESO LINFOPROLIFERATIVO ASOCIADO A METOTREXATO EN UNA PACIENTE CON ARTRITIS REUMATOIDE

Abstract. Resumen. Los procesos linfoproliferativos asociados a metotrexato son un grupo heterogéneo de proliferaciones linfoides o linfomas que se desarrollan en pacientes con enfermedades autoinmunes tratados con metotrexato. Con frecuencia, se asocian a infección por el virus de Epstein-Barr (VEB) y, ocasionalmente, involucionan al suspender el metotrexato.

Se presenta un caso de proceso linfoproliferativo tipo linfoma B difuso de célula grande, con una presentación clínica inusual de úlceras orales, afectando a una paciente de 79 años, con artritis reumatoide de larga evolución en tratamiento con metotrexato. Se detectó positividad para LMP-1 (proteína latente de membrana-1) y EBER (*Epstein-Barr encoded RNA*) por inmunohistoquímica e hibridación *in situ* cromogénica, respectivamente. Se confirmó la clonalidad del infiltrado por inmunohistoquímica (restricción de cadenas ligeras κ), PCR (reordenamiento monoclonal del gen IgH) y electroforesis capilar (GeneScan). El estudio de extensión fue negativo. La suspensión del metotrexato condujo a la remisión completa en 6 semanas. Dieciocho meses después del diagnóstico la paciente continúa libre de enfermedad.

Los procesos linfoproliferativos asociados a metotrexato raramente afectan primariamente a la cavidad oral y, sólo excepcionalmente, se manifiestan en forma de úlceras. Se revisa la literatura relativa a procesos linfoproliferativos asociados a metotrexato con presentación clínica de úlceras orales.

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Palabras clave: úlceras orales, linfoma B difuso de células grandes, metotrexato, virus de Epstein-Barr, artritis reumatoide.

Correspondence:

María Antonia Pastor Nieto
Servicio de Dermatología, Hospital General
Universitario de Guadalajara
C/ Donante de Sangre s/n
19002 Guadalajara, Spain
tonales@terra.es

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Figure 1. Image showing large ulcer with irregular margins covered by a whitish-gray exudate on the ventral surface of the tongue and areas of ulceration forming a crust on the vermillion of the lower lip.

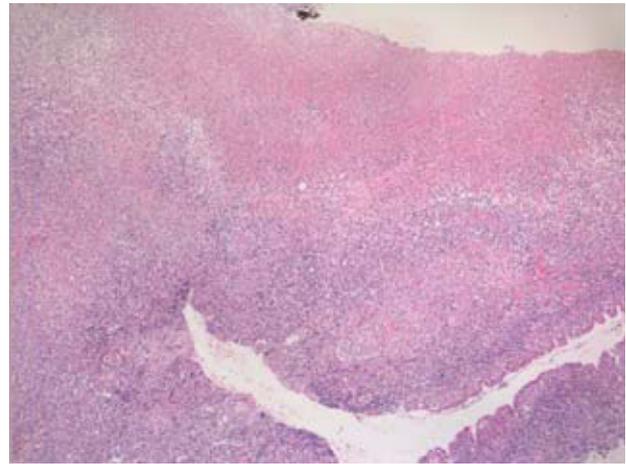


Figure 2. Histopathology showing a fibrinous necrotic slough beneath which is a lymphoid proliferation with diffuse involvement of the entire thickness of the mucous membrane. Hematoxylin-eosin, original magnification $\times 10$.

Introduction

The 2001 World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues recognizes 4 categories of lymphomas and lymphoproliferative disorders associated with immunodeficiency or immunosuppression: a) lymphoproliferative disorders associated with primary immunodeficiency, b) lymphomas associated with human immunodeficiency virus (HIV) infection, c) posttransplant lymphoproliferative disorders, and d) lymphoproliferative disorders associated with methotrexate therapy.¹

This last category comprises lymphoid proliferations or lymphomas that affect immunocompromised patients treated with methotrexate for various autoimmune diseases (rheumatoid arthritis, psoriasis, dermatomyositis),^{1,2} and that can resemble large B-cell lymphoma, Hodgkin lymphoma, or a polymorphic posttransplant lymphoproliferative disorder. They are usually associated with Epstein-Barr virus infection and occasionally regress after withdrawal of methotrexate therapy.¹

We describe a case of a lymphoproliferative disorder with the morphology of diffuse large B-cell lymphoma, positive for Epstein-Barr virus, in a patient with long-standing rheumatoid arthritis treated with methotrexate. The primary site was confined to the oral mucosa and the disorder presented as oral ulcers.

Case Description

The patient was a 79-year-old woman with a 20-year history of rheumatoid arthritis who had been receiving treatment with methotrexate for 17 years at a variable dose

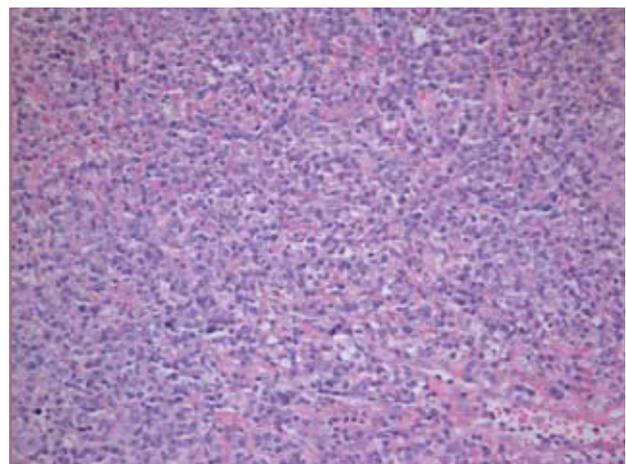


Figure 3. The neoplasm is composed of lymphoid cells with large pleomorphic and hyperchromatic nuclei, with mitotic figures. Hematoxylin-eosin, original magnification $\times 20$.

of between 5 and 12.5 mg/wk and who consulted for painful lesions in the oral cavity that had appeared 2 months earlier.

The lesions consisted of large ulcers covered with a grayish exudate, indurated on palpation, and located on the ventral surface of the tongue, the cheek mucosa, the floor of the mouth, and the lower lip (Figure 1). Histopathology identified a dense infiltrate composed of large lymphoid cells with irregular margins occupying the full thickness of the mucous membrane. The cells were arranged in sheets, with numerous mitotic figures (Figures 2 and 3). Immunohistochemistry showed the neoplastic cells to be positive for CD45, CD20, and CD79a, with numerous activated CD30+ cells (Figure 4), and negative for CD15, CD21, and CD23. The Ki-67 proliferation

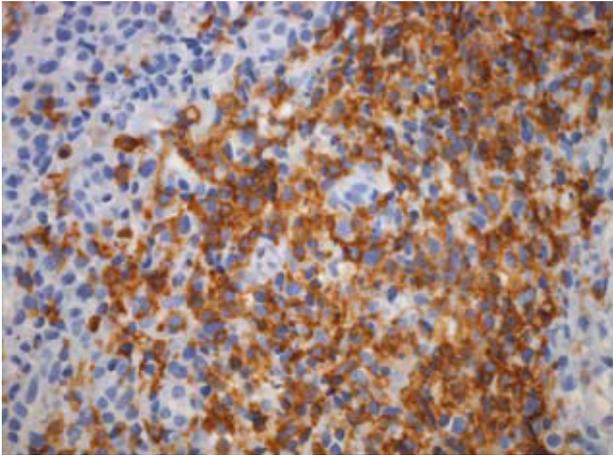


Figure 4. The majority of neoplastic cells are intensely positive for CD20 (immunohistochemical marker for B cells). Original magnification $\times 40$.

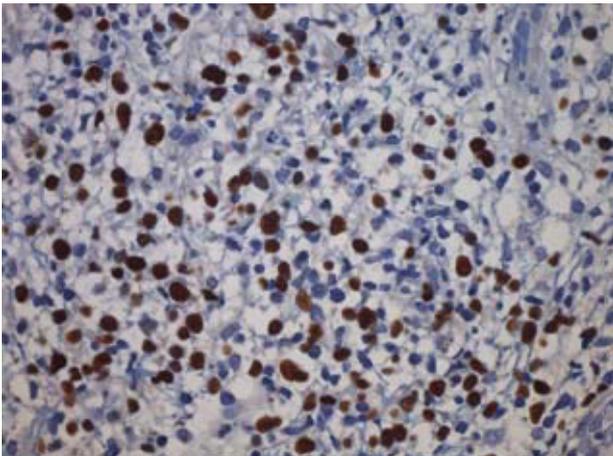


Figure 5. Epstein-Barr encoded small RNA of the Epstein-Barr virus was detected in most of the cells composing the lymphoid proliferation by chromogenic in situ hybridization. Original magnification $\times 40$.

index of the neoplasm was more than 70%. A minority population of small T cells (CD3+ and CD43+), macrophages (CD68+), and natural killer cells (CD56+) was identified. Latent membrane protein 1 positivity was detected by immunohistochemistry and Epstein-Barr-virus encoded small RNA positivity by chromogenic in situ hybridization (Figure 5). Immunohistochemistry detected κ light chain restriction. Clonality of the infiltrate was confirmed by polymerase chain reaction of immunoglobulin H gene rearrangement and by capillary electrophoresis (GeneScan). Direct immunofluorescence was negative. Complete blood count and biochemistry were normal, except for elevated levels of lactate dehydrogenase (210 U/L; reference values, 98-192 U/L) and $\beta 2$ -microglobulin (3.68 mg/L; reference values, < 2.4

mg/L). No changes in folic acid levels were observed. No other pathological findings or enlarged lymph nodes were detected on examination of the skin and mucosa, and analysis of tumor extension (computed tomography of the head and neck, thorax, abdomen, and pelvis) was negative. A diagnosis of methotrexate-associated lymphoproliferative disorder (Epstein-Barr-virus positive diffuse large B-cell lymphoma) was made and the drug withdrawn. Within 6 weeks complete epithelialization of the ulcers was observed. Remission of the lesions was confirmed histologically. Eighteen months after the diagnosis was made, the patient is in complete remission.

Discussion

Lymphoproliferative disorders affecting patients with autoimmune diseases treated with methotrexate can present varied histopathological patterns. Diffuse large B-cell lymphoma accounts for 35% of such cases. Less frequently, cases of Hodgkin lymphoma (25%), Hodgkin-like lesions (8%), follicular lymphoma (10%), Burkitt lymphoma (4%), and peripheral T-cell lymphoma (4%) have been reported. In 14% of patients polymorphous lymphocytic or lymphoplasmacytic infiltrates have been described.¹ Approximately half of the patients are positive for Epstein-Barr virus. The rate of Epstein-Barr virus infection depends on histological type. Positivity for Epstein-Barr virus was detected in 50% of the cases of diffuse large B-cell lymphoma, in 75% of Hodgkin lymphomas and Hodgkin-like lesions, in 50% of lymphoplasmacytic infiltrates, and in 40% of follicular lymphomas.¹

The proportion of cases that resolve following withdrawal of methotrexate is dependent on the presence of Epstein-Barr virus infection and on histological type. The majority of patients who respond to this measure are positive for Epstein-Barr virus. Forty percent of the cases of diffuse large B-cell lymphoma and 30% of the cases of Hodgkin lymphoma resolve following withdrawal of methotrexate. Patients who do not experience remission require chemotherapy. Overall survival is 50% in patients with diffuse large B-cell lymphoma and 75% in patients with Hodgkin lymphoma.¹

Extranodal sites (gastrointestinal tract, skin, lung, kidney, soft tissues) have been reported in 40% of cases, although this figure depends on histological type. Thus extranodal involvement is observed in 50% of diffuse large B-cell lymphomas, 20% of Hodgkin lymphomas and Hodgkin-like lesions, 100% of lymphoplasmacytic lymphomas and atypical lymphoplasmacytic infiltrates, and 40% of follicular lymphomas.¹ Methotrexate-associated diffuse large B-cell lymphomas presenting initially in the skin are extremely rare, and only a few cases of this disease have been reported.³⁻⁶

Table 1. Published Cases of Methotrexate-Associated Lymphoproliferative Disorders With Primary Involvement of the Oral Cavity Manifesting as Ulcers

Case	Sex/Age, y	Underlying Disease	Clinical Manifestation	Histological Type	Epstein-Barr Virus Infection/ Diagnostic Technique	Course/Follow-Up Period
Kalantzis et al ¹⁰ (2005)	Woman/ 72	NS	Ulcer in mucosa of anterior maxilla, exposed bone, tooth loss	Polyclonal B-cell lymphoproliferative disorder	+/NS	Resolution following withdrawal of methotrexate/ NS
Acero et al ¹¹ (2006)	Woman/ 79	Rheumatoid arthritis	Maxillary ulcer affecting the gums and vestibule Alveolar bone resorption of the maxilla and hard palate	Diffuse large B-cell lymphoma with numerous plasmablasts and atypical plasma cells	+/serology	Resolution following withdrawal of methotrexate and MACOP-B/ 1 year
Present study (2008)	Woman/ 79	Rheumatoid arthritis	Oral ulcers on the tongue, floor of the mouth, and lower lip	Diffuse large B-cell lymphoma	+/LMP 1 (immunohistochemistry and EBER (in situ hybridization))	Resolution following withdrawal of methotrexate/18 months

Abbreviations: EBER, Epstein-Barr encoded small RNA; LMP 1, latent membrane protein 1; MACOP-B, mitoxantrone, adriamycin, cyclophosphamide, vincristine, prednisone, and bleomycin; NS, not specified.

Only 2% of lymphomas present initially in the oral cavity, and rarely manifest as ulcers. In the majority of cases, swelling is the predominant manifestation. In a series of 58 patients with lymphomas of the oral cavity, only 2 presented with ulceration.⁷ Primary involvement of the oral cavity manifesting as ulcers is very uncommon in immunodeficiency-associated lymphoproliferative disorders. In an article published in 2008, Elad et al⁸ reviewed the 10 published cases of posttransplantation lymphoproliferative disorders with primary involvement of the oral cavity. Of these 10 cases, only 3 had manifested as ulcerations. This review did not cite a previous article by Bruce et al⁹ describing a case of Epstein-Barr virus-associated diffuse large B-cell lymphoma presenting as a tongue ulcer in a pancreatic transplant patient. Only 2 cases of methotrexate-associated lymphoproliferative disorder with a clinical presentation of oral ulcers and bone destruction have been reported in the literature (Table).^{10,11} The case we describe is exceptional because of the exclusive involvement of the oral mucosa and the clinical presentation of oral ulcers without bone involvement.

The differential diagnosis of methotrexate-associated lymphoproliferative disorders includes other Epstein-Barr virus-associated cutaneous lymphomas such as plasmablastic lymphoma, Burkitt lymphoma, and nasal-type natural killer-cell/T-cell lymphoma. Plasmablastic lymphoma is a rare variant of diffuse large B-cell lymphoma with an immunophenotype (CD20- or +/-,

CD138+, BCL-6-) that corresponds to the terminal phases of B-cell differentiation. It is usually found in the oral cavity of HIV-positive patients, although it has been reported in transplanted HIV-negative patients as well, and is usually associated with a poor prognosis.^{4,12,13} Burkitt lymphoma is a highly aggressive B-cell lymphoma that can develop in the maxillofacial region and spread to the oral cavity with ulceration. It is characterized by a relatively uniform proliferation of medium-sized B-cells with the immunophenotype CD5-, CD10+, CD20+, Bcl-2- and translocation of the c-myc gene.^{14,15} Nasal-type natural killer-cell/T-cell lymphoma of the oral cavity is usually located on the palate or gums and is characterized by aggressive behavior and a diffuse angiocentric and angioinvasive infiltration of medium or large cells positive for CD3, CD43, CD45RO, CD56, and TIA-1.¹⁶

Conflicts of Interest

The authors declare no conflicts of interest.

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