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Methotrexate-related lymphoproliferative disorder of the oral region in patients with rheumatoid arthritis

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ABSTRACT

Objective: The purpose of this study was to verify the characteristics of methotrexate (MTX)-related oral lymphoproliferative disorders (LPDs) in rheumatoid arthritis (RA) patients.
Methods: Twenty-eight cases of MTX-related oral LPDs with RA, which included 14 cases from English articles and 14 cases from Japanese literature, were collected. Data on demographic characteristics, clinical features, pathological diagnosis, weekly and total amount of MTX, concomitant drugs for RA, treatment, and follow-up period and outcomes were analyzed.
Results: Gingiva was the most frequent site (19, 67.9%), followed by tongue (4, 14.3%). Histopathologically, 15 cases (78.9%) were diffuse large B-cell lymphoma. All oral cases except for one case were Epstein–Barr virus (EBV)-positive. As an initial treatment, MTX was withdrawn for all cases including two cases of firstly decreasing the dose of MTX. Recurrence was reported in one case (4.8%). In gingival 19 cases, ulceration was found in 16 cases (84.2%), pain in 13 cases (68.4%) and alveolar bone exposure in 11 cases (57.9%).
Conclusions: The occurrence of MTX-related oral LPDs showed a predilection for gingiva with frequent characteristics of ulceration, pain and bone exposure. Almost all cases were EBV-positive.

Contents

1. Introduction

Methotrexate (MTX), an antimetabolite of folic acid, is an immunosuppressive agent that has been commonly used in patients with autoimmune diseases, including rheumatoid arthritis (RA), over the last two decades [1]. MTX is still recommended for use as an anchor drug of RA. Low-dose and long-term pulsed MTX therapy of less than 25 mg/week has been commonly used in patients with RA in western countries [2]. It is well known that patients with immunodeficiency have a higher risk of lymphoproliferative disorders (LPDs) and the occurrence of iatrogenic immunodeficiency-associated LPDs caused by MTX as an adverse effect has been described in the World Health Organization among the "Immunodeficiency associated LPDs" [3]. In addition, an association between LPDs and the appearance of Epstein–Barr virus (EBV) has been suggested. EBV is known to be associated with a variety of LPDs and several malignancies, including Burkitt's lymphoma,

☆ Asian AOMS: Asian Association of Oral and Maxillofacial Surgeons; ASOMP: Asian Society of Oral and Maxillofacial Pathology; JSOP: Japanese Society of Oral Pathology; JSOMS: Japanese Society of Oral and Maxillofacial Surgeons; JSOM: Japanese Society of Oral Medicine; JAMI: Japanese Academy of Maxillofacial Implants.

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undifferentiated nasopharyngeal carcinoma, Hodgkin's lymphoma, nasal natural killer/T-cell lymphoma, gastric carcinoma, and B-cell lymphoma in immunocompetent patients, and infection with or reactivation of EBV by immunosuppression is suspected to cause these diseases [4,5]. Clinically MTX-related LPDs arise as solitary or multiple masses in the whole body, and approximately 40–50% of cases occur in extranodal sites which include the gastrointestinal tract, skin, liver, lung, and kidney [6,7]. Though stomatitis caused by MTX cytotoxicity may occur, the occurrence of LPDs in the oral region is extremely rare and only 14 cases, including our recent case, have been reported in the English-language literature [8–19]. Of these, nine were Japanese patients. Fourteen cases of MTX-related LPDs arising in the oral region have been reported in the Japanese-language literature; all of them were Japanese patients [20–27]. It was observed that most of the MTX-related oral LPDs cases were Japanese patients. But it is unclear why reported cases of oral MTX-related LPD are frequent in Japan yet.

Despite the advent of new effective biologic agents, MTX is still recommended for use worldwide as the most effective drug and as an anchor drug to enhance or maintain the efficacy of biologic agents [1]. There is a possibility that patients with MTX-related oral LPDs will increase in number from now on. In this paper, we present the characteristics of MTX-related LPDs of oral region precisely reviewing both English and Japanese articles.

2. Patients and methods

A systematic literature review was performed using electronic databases (PubMed for English language literature and website of Japan Medical Abstracts Society for Japanese language literature) to identify relevant publications between 1960 and April 2015 that included cases of MTX-related oral LPD. Additionally, a manual search was conducted by cross-referencing from the retrieved manuscripts. Data on demographic characteristics, local findings, systemic occurrence, pathological diagnosis, EBV detection, total and/or weekly dose of MTX, administration period of MTX, concomitant drugs for RA, treatment, and outcomes and follow-up period were collected for each study. Cases presented by only abstract and reporting inconsistent data regarding histological diagnosis were excluded.

3. Results

Fourteen cases of oral MTX-related LPDs in the English-language literature and 14 cases in the Japanese-language literature were gathered [8–33]. Except for 5 cases, all 23 cases (23/28, 82.1%) were Japanese patients. The main characteristics of oral MTX-related LPDs are shown in Table 1, and the summary of the oral MTX-related LPDs and the gingival MTX-related LPDs is given in Table 2 and Table 3, respectively. The patients had a mean age of 69.2 years (ranging from 40 to 87 years), with a sex distribution of 19 females and 9 males (2.1:1). Eighteen patients (18/28, 64.3%) had oral LPD alone and six (6/28, 21.4%) developed multiple systemic occurrences of LPDs. In oral sites, the gingiva was affected in 19 cases (19/28, 67.8%): upper gingiva in 14 cases (14/19, 73.4%), lower gingiva in 2 cases (2/19, 10.5%), and gingiva of both sides of jaw in 3 cases (3/19, 15.8%). Tongue was affected in four cases (4/28, 14.3%), and floor of the mouth, lip, oral multiple sites, oral cavity, and hard palate were affected in one patient each. Most frequent local findings were ulceration (24/28, 85.7%) and pain (18/28, 64.3%). In gingival LPDs, ulceration, pain and alveolar bone exposure were found in 84.2% (16/19), 68.4% (13/19), and 57.9% (11/19) of cases, respectively. As for treatment of RA, 12 patients (12/28, 42.9%) were treated with steroids and 3 cases (3/28, 10.7%) were treated with steroids and infliximab. The duration of MTX treatment ranged from 5 months to 17 years (mean 8 years 5 month) (22/28). Weekly dose of MTX was 2–16 mg (mean 8 mg) (14/28) and total dose of MTX was 260–3722 mg (mean 1954 mg) (6/28). Regarding the histological subtypes of LPDs, there was a predominance of a diffuse large B-cell lymphoma (DLBCL) (19/28, 67.9%). The other nine cases were three polyclonal B-cell lesions (3/28, 10.7%), two B-cell type LPDs (2/28, 7.1%), a polymorphous small lymphocytic lymphoplasmacytic infiltrate (PSLLPI) (1/28), a Hodgkin-like lymphoma (1/28), a polymorphic LPD (1/28) and a T-cell dominant polymorphic LPD (1/28). All cases except for one case of T-cell dominant polymorphic LPD were EBV-positive. As the treatment of LPDs, MTX was discontinued in all cases, including two cases in which MXT was discontinued after a temporal decrease. Additionally, four cases (4/28, 14.3%) received chemotherapy, one case received local excision, and one case received chemotherapy and local excision. Recurrence was found in one case (1/28, 3.6%) that developed multiple occurrences of LPDs. Four cases (4/28, 14.3%) were given bisphosphonate (alendronate sodium hydrate) for the treatment of osteoporosis. The length of follow-up ranged from 1 to 72 months (mean 23 months) (22/28).

4. Discussion

The occurrence of MTX-related LPDs has been described to be 0.0004% to 0.009% in worldwide reports [3]. The basic administration amounts of MTX in Japan are less than in Western countries because of the body structure, susceptibility, effect, and side effect of Japanese subjects, but the ratio of MTX-related LPDs in Japan was not different from other countries [34]. As to the occurrence of MTX-related LPDs, various factors such as the age of onset of RA, duration of MTX treatment, total dose of MTX administration, RA disease activity, EBV infection, and Sjögren syndrome complications have been described in the literature [16,35–38], but the association between these factors and the occurrence of MTX-related LPDs remains controversial.

It is interesting to note that all of the Japanese MTX-related oral LPDs cases were published during the past 10 years and 16 cases (70%) were published from 2011 to 2015. In fact, from 2011, the given maximum weekly dose of MTX in Japan has been increased from 8 mg to 16 mg. Recently, Kameda et al. [34] described the characteristics of MTX-related LPDs in Japanese; only the mean weekly MTX dose was in close association with the occurrence of MTX-related LPDs in Japanese. The mean weekly dose of MTX they reported was 8.4 mg, which was similar to that of ours (8 mg). Though the sample size of this study was small, there may be association between the occurrence of MTX-related oral LPDs and the weekly dose of MTX.

An association between LPDs and the appearance of Epstein–Barr virus (EBV) has been suggested. Approximately 30–50% of cases of LPDs have been shown to be EBV-positive [6,7]. In this study, all cases, except for one case, of MTX-related oral LPDs were positive for EBV and almost all cases were histologically DLBCL. Age may be a confounding feature in the patients whom EBV positive mucocutaneous LPD was linked to iatrogenic immunodeficiency [14]. But there is a significant difference in patient age and prognosis between age-related EBV positive mucocutaneous LPDs and iatrogenic immunodeficiency-related LPDs, including those due to MTX. Age-related EBV positive mucocutaneous LPDs show no evidence of immunosuppression and tend to occur in patients older than 60 years, many of whom relapse and die in spite of chemo-radiation therapy [14,15].

Waldeyer's ring is a common reservoir for EBV and EBV is frequently found in the gingival crevicular fluid, saliva, salivary glands, and gingival tissues [39–42]. EBV plays a crucial role in the transformation of B-lymphocytes into immortalized human primary