Massive hemorrhage and osteonecrosis of the jaw in the patient with methotrexate-associated lymphoproliferative disorder: Report of a case and review of literature

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ABSTRACT

Introduction: Methotrexate-associated lymphoproliferative disorder (MTX-LPD) is one of the adverse effects of methotrexate (MTX). We report a case of MTX-LPD that caused osteonecrosis and massive bleeding without regression following MTX withdrawal.

Case Report: A 61-year-old woman was referred to our hospital because of delayed socket healing after dental extraction. She had been diagnosed with rheumatoid arthritis (RA) and received MTX treatment for six years. At the first visit, a 15 mm × 15 mm bone exposure and swelling of the surrounding gingiva in the right upper molar region were observed. We performed an incisional biopsy of the necrotic bone and surrounding mucosal tissue. The histopathological diagnosis was diffuse large B-cell lymphoma (DLBCL). Therefore, we referred the patient to the Department of Hematology in our hospital. She was diagnosed with MTX-LPD based on the history of MTX therapy for RA, and MTX was discontinued immediately. However, the lesion progressed and caused bleeding that required blood transfusion and hemostasis by microfibrous collagen and tie-over even after the withdrawal of MTX. Subsequently, rituximab, cyclophosphamide, vincristine, and prednisolone (R-COP) chemotherapy was initiated. After 3 courses of chemotherapy, sequestrectomy was performed under local anesthesia. She achieved complete remission after 8 courses of chemotherapy, and there was no recurrence of necrotic bone exposure or gingival swelling.

Conclusion: Approximately 80% of MTX-LPD cases occurring in the oral region show regression after MTX discontinuation, but we experienced a case in which bleeding occurred with progression of the lesion after discontinuation. Careful follow-up is required during the MTX discontinuation period.

Keywords: Diffuse large B-cell lymphoma, Massive hemorrhage, Methotrexate-associated lymphoproliferative disorder, Osteonecrosis of the jaw

INTRODUCTION

Methotrexate (MTX) is currently the most widely used first-line conventional synthetic disease-modifying
anti-rheumatic drug (csDMARD) in the treatment of rheumatoid arthritis (RA) [1]. It has been associated with a range of adverse effects, including cytopenia, serious infections, liver damage, synovitis, myelopathy, interstitial pneumonia, mucocutaneous ulcer, and MTX-associated lymphoproliferative disorder (MTX-LPD). Methotrexate-associated lymphoproliferative disorder, which is classified as other iatrogenic immunodeficiency-associated LPD in the WHO classification 2017, rarely occurs in the oral and maxillofacial region [2]. Medication-related osteonecrosis of the jaw (MRONJ), which is associated with bisphosphonates, anti-receptor activator of nuclear factor κB ligand (anti-RANKL) (denosumab), and antiangiogenic medications, has been widely recognized [3]. Recently, it has been reported that several cases of MTX-LPD in the gingiva accompany osteonecrosis of the jaw (ONJ) without antiresorptive and antiangiogenic medications [4–6]. Besides, to our knowledge, half of the MTX-LPD cases show regression by MTX withdrawal [2, 7], and no case that caused massive bleeding because of progression of the lesion has been reported in the oral region. Here, we report a case of MTX-LPD with jaw osteonecrosis and massive hemorrhage as a result of progression of the lesion after MTX withdrawal. In addition, we performed a systematic literature review to investigate cases of MTX-LPD in the oral region.

CASE REPORT

A 61-year-old woman was treated with extraction of the maxillary right first and second molars at dental clinic in August 2017. One month later, the patient was referred to Department of Dentistry and Oral Surgery, because of delayed socket healing after dental extraction. Her past medical history was significant for RA and myocardial infarction. The RA had been treated with MTX 12 mg once weekly since 2011. She had been taking cilostazol medications. At the first visit, oral examination revealed a 15 mm × 15 mm area of exposed bone with necrotic soft tissue in the right posterior maxilla (Figure 1). A reddish swelling of the gingiva was found in the surrounding exposed bone, but there was no bleeding or pain. A dental panoramic radiograph revealed absence of healing of the extraction sockets and osteosclerosis around the right upper molar. Computed tomography (CT) showed thickening of the maxillary sinus mucosa, while there was no obvious separation of the sequestrum (Figure 2A and B). Abnormal fluorodeoxyglucose uptake (maximum standardized uptake value, 13.8) in the right posterior maxilla area was observed on positron emission tomography/CT (PET/CT) (Figure 2C). Furthermore, uptake by other organs, including the adrenal gland, multiple intrapulmonary nodules, muscles, bones, and lymph nodes was observed (Figure 2D). Blood tests revealed elevated levels of C-reactive protein (CRP, 2.01 mg/dL), soluble interleukin-2 receptor (sIL-2R, 1980 U/μL), and lactate dehydrogenase (LDH, 431 U/L), respectively. We considered the possibility of MTX-LPD and other malignant tumors, and performed an incisional biopsy in the exposed bone and surrounding mucosal tissue. Histopathological findings of the bone confirmed a sequestrum with empty osteocytic lacunae and bacterial infection, including colonies of Actinomyces spp. in the marrow space. It did not reveal tumor cells, including atypical lymphocytes, usually found in MTX-LPD. Pathological analysis of the mucosal tissue showed infiltration of numerous lymphocytes and diffuse proliferation of large-sized atypical lymphoid cells under the epithelium surrounding the gingiva (Figure 3A). Immunohistochemical analysis showed CD20+, CD3–, CD5–, and CD10– cells. Ki67+ was detected in 80% of these cells. Additionally, Epstein–Barr encoding region (EBER) was detected in almost all atypical cells by in situ hybridization (Figure 3B). Based on these findings, the histopathological diagnosis was diffuse large B-cell lymphoma (DLBCL) with jaw osteonecrosis. Therefore, we referred the patient to the Department of Hematology in our hospital. She was diagnosed with MTX-LPD based on the history of MTX therapy for RA, and MTX was discontinued immediately.

However, the lesion progressed and caused massive bleeding three weeks after the withdrawal of MTX. Therefore, she visited the emergency department of our hospital. Although the patient was conscious, a gait disorder due to dizziness was observed. Since vigorous bleeding was observed around the lesion, she was admitted to our department (Figure 4). Bleeding equivalent to class III as per the Advanced Trauma Life Support (ATLS) classification was observed [8]. The pterygoid venous plexus and posterior superior alveolar artery were considered as the blood vessels causing bleeding. Hemostasis was performed using a microfibrous collagen hemostatic material and tie-over

Figure 1: Intraoral findings during the initial examination showing the exposed necrotic bone covered with necrotic soft tissue in the right upper molar area.
under local anesthesia. Two units of concentrated red blood cells (RCC) were transfused since the blood tests revealed low hemoglobin (Hb) level (Hb: 7.8 g/dL). The next day, her Hb level further reduced to 6.3 g/dL, and transfusion of 2 units of RCC was added. Three days after admission, she was transferred to the Department of Hematology, and rituximab, cyclophosphamide, vincristine, and prednisolone (100 mg/day) (R-COP) chemotherapy was initiated. Doxorubicin was not used because of myocardial infarction history and cardiotoxicity. After 3 courses of chemotherapy, the separated sequestrum (34 × 23 × 18 mm size) in the right posterior maxilla was removed under local anesthesia (Figure 5). After 8 courses of chemotherapy, she achieved complete remission. Two years later, there was no recurrence of MTX-LPD, and her RA remained well controlled without MTX. Anemia was not observed (hemoglobin level 13 g/dL). Moreover, there was no recurrence of necrotic bone exposure or gingival swelling.

**DISCUSSION**

In 1991, Ellman et al. first reported a lymphoproliferative disorder in patients with RA receiving MTX, and MTX-LPD was recognized as one of the side effects [9]. Although extranodal lesions have been reported in 40% of MTX-LPD cases, cases of the oral region are relatively rare. After performing a comprehensive English literature search, it was noted that 26 cases of MTX-LPD in the oral region have been reported, and 13 of them were accompanied by ONJ (Table 1) [4–6, 10–24]. The average age was 70.9 years, and the male-to-female ratio was 1: 2.7, which...
Table 1: Clinical characteristics of 26 patients with MTX-LPD in the oral region

| Case | Age/Gender | Location | Administration period of MTX (y) | Histology | EBV infection | MTX withdrawal | Chemotherapy | Recurrence | Outcome of MTX-LPD | BP | Bone exposure | Treatment for ONJ | Conservative or surgical | Reference |
|------|------------|----------|---------------------------------|-----------|--------------|---------------|--------------|------------|-------------------|-----|--------------|----------------|------------------------|-----------|
| 1    | 72/F       | Gingiva  | NA                              | Pol. BC   | +            | −             | −            | NED        | NA                 | NA  | +            | −              | NA                     | [10]      |
| 2    | 69/F       | Gingiva  | NA                              | Wegener's lymphoma | NA     | +            | −             | NED        | NA                 | +   | NA          | −              | NA                     | [10]      |
| 3    | 73/F       | Oral cavity | 2                              | Peripheral T-cell lymphoma | NA     | −            | −             | NED        | −                 | −   | NA          | −              | NA                     | [11]      |
| 4    | 73/F       | Oral cavity | 2                              | DLBLCL    | +            | +             | −            | NED        | −                 | +   | NA          | −              | NA                     | [4]       |
| 5    | 70/F       | Palate   | 6                               | DLBLCL    | +            | +             | −            | NED        | −                 | −   | −            | −              | −                      | [12]      |
| 6    | 69/F       | Gingiva  | NA                              | Hodgkin   | +            | +             | NA          | NED        | −                 | −   | NA          | −              | NA                     | [13]      |
| 7    | 76/F       | Gingiva  | 10                             | DLBLCL    | +            | +             | R-THP-COP    | +          | DOD                | −   | −            | −              | −                      | [14]      |
| 8    | 67/F       | Palate   | 9                               | DLBLCL    | +            | +             | −            | NED        | +                 | +   | Conservative | −              | −                      | [15]      |
| 9    | 75/F       | Gingiva  | 5                               | DLBLCL    | +            | +             | R-CHOP      | +          | NED                | NA  | +            | Conservative | −                      | [16]      |
| 10   | 64/M       | Oral cavity | 5                              | DMBCL     | −            | +             | R-CHOP      | +          | NED                | NA  | −            | −              | −                      | [17]      |
| 11   | 60/M       | Gingiva  | 20                             | DLBLCL    | +            | +             | −            | NED        | −                 | +   | NA          | −              | −                      | [18]      |
| 12   | 71/M       | Buccal   | 7                               | DLBLCL    | +            | +             | −            | NED        | −                 | −   | −            | −              | −                      | [19]      |
| 13   | 76/F       | Gingiva  | NA                              | Hodgkin   | +            | +             | NA          | NED        | −                 | −   | NA          | −              | −                      | [19]      |
| 14   | 67/M       | Palate   | NA                              | NA        | +            | +             | NA          | NED        | NA                 | −   | −            | −              | −                      | [19]      |
| 15   | 74/F       | Tongue   | 1.5                             | NA        | +            | +             | −            | NED        | NA                 | −   | −            | −              | −                      | [20]      |
| 16   | 74/F       | Tongue   | 5.1                             | NA        | +            | +             | −            | NED        | NA                 | −   | −            | −              | −                      | [20]      |
| 17   | 82/M       | Tongue   | 8                               | NA        | +            | +             | −            | NED        | −                 | −   | −            | −              | NA                     | [21]      |
| 18   | 66/F       | Gingiva  | 3                               | DLBLCL    | NA           | +             | −            | NED        | +                 | +   | NA          | −              | −                      | [22]      |
| 19   | 74/M       | Left mandibular | 7                            | Hodgkin   | +            | +             | −            | NED        | −                 | +   | +           | Conservative | −                      | [6]       |
| 20   | 79/F       | Gingiva  | 21                             | DLBLCL    | +            | +             | −            | NED        | +                 | +   | Conservative | −              | −                      | [6]       |
| 21   | 67/M       | Gingiva  | NA                              | DLBLCL    | +            | +             | −            | NED        | −                 | +   | Conservative | −              | −                      | [6]       |
| 22   | 81/F       | Gingiva  | 4                               | DLBLCL    | +            | +             | −            | NED        | +                 | +   | Conservative | −              | −                      | [23]      |
| 23   | 71/F       | Gingiva  | NA                              | DLBCL     | +            | +             | −            | NED        | +                 | +   | NA          | −              | −                      | [23]      |
| 24   | 77/F       | Gingiva  | 12                             | DLBLCL    | +            | +             | R-CHOP      | +          | NED                | −   | −            | −              | −                      | [23]      |
| 25   | 63/F       | Palate   | 2.5                             | DLBLCL    | −            | +             | −            | NED        | NA                 | −   | −            | −              | −                      | [24]      |
| 26   | 54/F       | Gingiva  | NA                              | DLBLCL    | +            | +             | R-COP       | −          | NED                | −   | −            | −              | −                      | Present case |

Abbreviations: MTX-LPD, methotrexate-associated lympho-proliferative disorder; MTX, methotrexate; EBV, Epstein–Barr virus; poly. BC, polyclonal B-cell lesion; DLBLCL, diffuse large B-cell lymphoma; DMBCL, diffuse mixed B-cell lymphoma; NED, no evidence of disease; DOD, dead of other disease; BP, bisphosphonate; ONJ, osteonecrosis of the jaw; +, positive; −, negative; NA, not available.
was similar to the epidemiology of RA patients. The patients who developed MTX-LPD had received MTX for 1.5 to 21 years (average 7.2 years). Regarding the site of occurrence, gingiva was the most common site in 14 patients.

Clinical findings in patients with bone exposure were similar to those of MRONJ, but at least 5 patients had not taken antiresorptive agents [4–6]. Although the mechanism of jaw osteonecrosis in MTX-LPD has not been clarified, it is considered that free radicals of MTX disrupt the mucosal barrier, and immunosuppression reduces the ability to protect against bacterial infection [25, 26]. In addition, inhibition of bone turnover by suppression of osteoclast differentiation and osteoblast proliferation, and inhibition of angiogenesis because of MTX may also be involved in osteonecrosis [27–29].

Recently, there have been several reports of ONJ caused by MTX in the absence of lymphoproliferative disorder or antiresorptive and antiangiogenic medications [30]. In our case, it could be considered that immunosuppression-induced bacterial infection after bone exposure due to soft tissue ulcer may have caused osteonecrosis, since findings of lymphoma invasion in the bone were not observed.

Immediate discontinuation of MTX and concomitant immunosuppressive drugs leads to regression in half of the patients with suspected MTX-LPD [2, 7]. Moreover, approximately 80% of MTX-LPD cases occurring in the oral region have demonstrated regression by MTX discontinuation (Table 1). Ichikawa et al. reported that Epstein–Barr virus (EBV) was detected in 60% of MTX-LPD cases, and 85% of EBV-positive cases showed spontaneous regression by withdrawing MTX [7]. Patients with spontaneous regression showed significantly higher EBV positivity compared to those without spontaneous regression. In our case, despite EBV-positivity, the disease progressed without regression following MTX withdrawal. It was considered that risk factors, including stage IV-A of Ann Arbor classification, age ≥ 62 years, LDH 431 U/L, pathologic Ki-69 expression in 80% of atypical cells, and numerous mitotic figures might be the reasons for progression of the lesion [31, 32].

Furthermore, in our case, bleeding equivalent to class III as per the ATLS classification was observed because of progression of the lesion [8]. The pterygoid venous plexus and posterior superior alveolar artery are located around the upper molars and maxillary tubercle, and these were considered to be the causative vessels for bleeding. Activation of microangiogenesis by the disease, oral administration of cilostazol for previous myocardial infarction, and the vulnerability of the oral cavity to the external environment were also considered as plausible causes of bleeding. Although hemostasis was achieved by using microfibrous collagen hemostatic material and tie-over under local anesthesia in this case, surgical ligation or catheter embolization may be considered if hemostasis is difficult. Generally, treatment of osteonecrosis is performed conservatively in all cases of MTX-LPD [6, 15, 16, 23]. In our case, conservative therapy was prioritized for continued treatment of DLBCL, and sequestrectomy was performed under local anesthesia because of separation of the sequestrum after 3 courses of R-COP. Treatment of ONJ should be considered according to the general condition of the individual patient and the status of MTX-LPD treatment.

CONCLUSION

Approximately 80% of MTX-LPD cases occurring in the oral region show regression after MTX discontinuation, but we experienced a case in which bleeding occurred with progression of the lesion without spontaneous regression after discontinuation. Careful follow-up is required during the MTX discontinuation period.

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