

## 상악의 단발 림프종모양육아종증

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〈Abstract〉

### Solitary Lymphomatoid Granulomatosis at the Maxilla

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Lymphomatoid granulomatosis (LYG) is an uncommon Epstein-Barr virus (EBV)-associated B-cell lymphoproliferative disorder distinct from lymphoma. LYG primarily occurs in the lung with or without accompanied lesions in the skin, central nervous system, kidney, gastrointestinal tract, nose, eyes, liver and oral cavity. Solitary extrapulmonary LYG is extremely rare, and whether solitary lesions progress onto pulmonary development and dysfunction is controversial. Herein, we report a case on a solitary LYG in the maxilla gingiva with bone exposure in a patient who had been taking methotrexate for rheumatoid arthritis.

**Key words:** Lymphomatoid granulomatosis, Methotrexate, Maxilla, Epstein-Barr virus

## I. INTRODUCTION

Lymphomatoid granulomatosis (LYG) is an uncommon type of EBV-associated B-cell lymphoproliferative disorder (LPD) which commonly arises in various immunosuppressive conditions<sup>1)</sup>. It primarily affects the lung, while it may be concurrently present in other multiple sites such as the skin, central nervous system, kidney, gastrointestinal tract, nose, eyes, liver and oral cavity<sup>2,3)</sup>. Solitary extrapulmonary lesions are extremely rare and are considered as an aspect of

dissemination and systemic involvement<sup>1,2,4)</sup>. There have been a few reports on nervous, cutaneous and oral LYG lesions without a pulmonary lesion development at the time of diagnosis<sup>5-7)</sup>. Whether the extrapulmonary lesions represent an initial sign of systemic disease, or are a true solitary lesion is controversial.

Herein, we report a solitary oral LYG in a patient taking methotrexate (MTX). The initial clinical impression for the oral lesion was Medication-related osteonecrosis of the jaw (MRONJ), while the primary pathologic diagnosis was natural killer (NK)/T-cell lymphoma. We discussed the differential diagnosis of LYG and reviewed the former literature.

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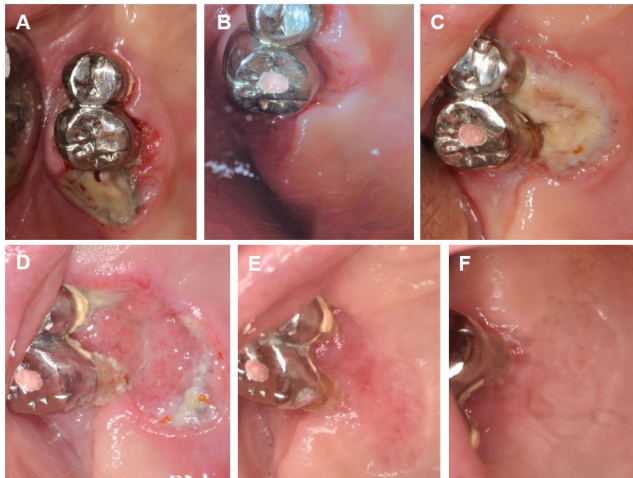
## II. CASE REPORT

A 71-year-old female was referred to our hospital from a primary dental clinic for complaints of discomfort at the maxillary right first molar region. Oral examination revealed gingival necrosis with alveolar bone exposure at the posterior of right maxillary first molar (Fig. 1A). Redness and mild swelling were observed at the marginal gingiva of right maxillary second premolar and first molar. Both teeth had a history of root canal treatment received 5 months ago and showed bad periodontal condition with cortical bone loss and tooth mobility (Fig. 2A and B). The right maxillary second molar had been missing for more than 10 years.

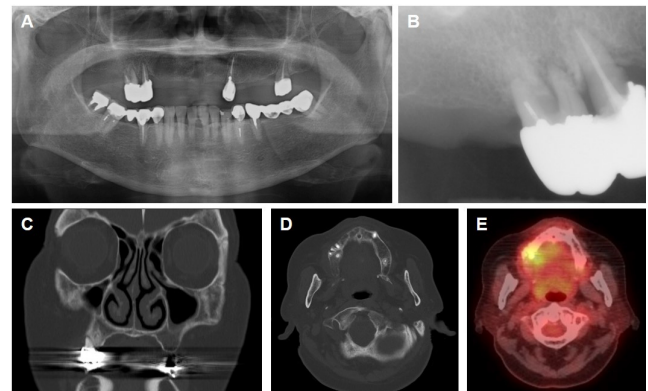
She was on medication for hypertension (amlodipine), rheumatoid arthritis (methotrexate [MTX], 10mg weekly for 14

years and bucillamine) and had been taking bisphosphonate by oral administration for 5 months. She had a past history of recurrent pulmonary tuberculosis treated 30 years ago. The possibility of MRONJ first came to our mind, because the patient was an elderly-women taking bisphosphonate and had signs of bone exposure and resorption. Additional radiologic and laboratory tests were made. Multi-detector computed tomography (MDCT) was taken on the maxilla, and C-terminal telopeptide (CTX) and osteocalcin serum level tests were evaluated. For her well-being, cefpodoxime, metronidazole and nonsteroidal anti-inflammatory drugs (NSAIDs) were prescribed to decrease the pain and inflammation.

A week later, pain symptoms had reduced since the last visit and inflammation signs had been diminished at the site. The CTX level was 0.296 and osteocalcin level was 19.50. The CT image informed that there was cortical bone loss and adjacent soft tissue lesion on the right maxillary second premolar and first molar (Fig. 2C and D). The Department of Oral and Maxillofacial Radiology recommended a biopsy on the lesion to distinguish between inflammatory disease



**Fig. 1.** Clinical image of the right maxillary lesion. A, 1<sup>st</sup> visit. Ulceration and bone exposure were observed in the posterior of #16. Redness and swelling were seen in the palatal marginal gingiva. B, 4 weeks after the 1<sup>st</sup> visit. The lesion showed improvement with healing of the ulcer. C, 6 weeks after the 1<sup>st</sup> visit. The lesion was aggravated on the palatal side and re-biopsy was done. D, 9 weeks after the 1<sup>st</sup> visit. The necrotic area was partially reduced. E, 15 weeks after the 1<sup>st</sup> visit. Necrosis had disappeared, and mild redness was observed. F, 18 weeks after the 1<sup>st</sup> visit. Only a mild indentation of the former lesion was observed.



**Fig. 2.** A, Panoramic view taken on the 1<sup>st</sup> visit. B, Periapical view taken on the 1<sup>st</sup> visit. The right maxillary second premolar and first molar showed cortical bone loss. C, Bone window coronal view of maxillary computed tomography (CT) taken on the 1<sup>st</sup> visit. D, Bone window axial view of maxillary CT taken on the 1<sup>st</sup> visit. Cortical bone loss was observed at the buccal side of the right maxillary second premolar and first molar. E, F<sup>18</sup>-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT axial view showed a hot spot at the right posterior maxilla.

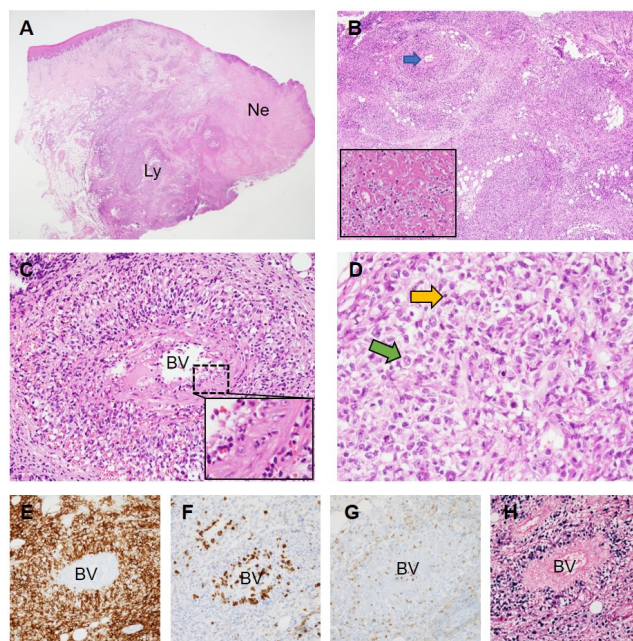
and malignancy. A biopsy was performed on the gingiva avoiding necrosis and necrosis-adjacent tissue. The biopsy specimen revealed chronic non-specific inflammation. The plan was to maintain the antibiotics and NSAIDs to reduce the inflammation.

Four weeks after the first visit, bone exposure had decreased, and inflammatory signs were alleviated but not yet terminated at the lesion site (Fig. 1B). However, during the next two weeks, the lesion aggravated at the adjacent palatal gingiva with diffuse ulceration and necrosis (Fig. 1C) and re-biopsy was performed near the necrosis. The patient complained of severe pain and informed us that she had not been taking her MTX prescription after the first visit. MTX withdrawal had been directed by her primary dentist and rheumatologist in fear of MTX associated MRONJ which has been reported before<sup>8)</sup>. The two clinicians were not aware of the bisphosphonate prescription which had been made in another hospital, so it had been maintained despite the possibility of MRONJ.

Pathologic evaluation revealed areas of severe necrosis and cell-rich portions (Fig. 3A). The cell-rich portions were composed of monocytes, predominantly lymphocytes infiltrating the adjacent tissue (Fig. 3B). Characteristically, the lymphocytes frequently displayed an angiocentric pattern and angioinvasive properties (Fig. 3C). The lymphocytes were a mixture of large atypical lymphocytes and small lymphocytes (Fig. 3D). Other than the lymphocytes, plasma cells and other inflammatory cells were seen in the background as well. NK/T-cell lymphoma was our primary pathologic diagnosis. To confirm our diagnosis, molecular pathology staining was proceeded.

By immunohistochemistry, the large atypical lymphocytes were revealed to be CD20-positive B cells (Fig. 3E), while the small lymphocytes were CD3/T-cell intracytoplasmic antigen (TIA)-positive T cells (Fig. 3F and G). The atypical B cells were figured to be the main aspect of the lesion, while T cells were considered as reactive background. Epstein-Barr virus (EBV) infection was confirmed in the

atypical B cells by in situ hybridization (Fig. 3H) CD56 was negative (not shown), which ruled out NK/T-cell lymphoma. The final diagnosis was lymphomatoid granulomatosis. It was given a grade 3 for the extensive amount of necrosis, aggregated large atypical CD20-positive B cells and high number of EBV positive cells (50)High power field)<sup>9,10)</sup>.



**Fig. 3.** Histopathologic examination and molecular pathology results of the surgical specimen. A, Lymphocytic infiltrated (Ly) on the submucosal area with extensive necrosis (Ne) and ulceration (Hematoxylin and eosin [HE], original magnification x12.5). B, The lymphocytes have infiltrated blood vessels (blue arrow) and submucosal adipose tissue. Necrosis was noticed (inset) (HE, original magnification x200, inset x40). C, Angiocentric and angioinvasive infiltration of lymphocytes in a blood vessel (BV). (HE, original magnification x200, inset x400). D, The lymphocytes were mainly large atypical lymphocytes (green arrow), and small reactive lymphocytes (yellow arrow), plasma cells and various inflammatory cells were admixed (HE, original magnification x400). E, Dense infiltration of CD20-positive large atypical lymphocytes (Immunohistochemistry staining [IHC], CD20, original magnification x200). F, Reactive CD3-positive small lymphocytes. (IHC, CD3, original magnification x200). G, Reactive lymphocytes are positive on TIA stain as well. (IHC, TIA, original magnification x200). H, High amounts of EBV-positive large lymphocytes are observed, indicating Epstein-Barr virus infection. (In situ hybridization, EBER, original magnification x200)

MTX was considered to be responsible for the immunosuppression causing LYG in our patient. The patient was referred to the Department of Hemato-oncology for proper management and MTX was replaced with tacrolimus. To evaluate presence of LYG lesions at other sites, especially the lung, a body CT was taken. There were no abnormal findings throughout the body CT, other than right kidney's parenchymal thinning on abdomen-pelvis and a post-inflammatory sequela due to previous tuberculosis in the chest. There were no abnormal lymph nodes on the neck. On Positron emission tomography (PET)/CT, focal fludeoxyglucose (FDG) uptake was only observed in the right maxilla, regarded as post-operative changes (Fig. 2E).

After replacing MTX to tacrolimus, the lesion gradually improved and was almost completely healed by the 2 month-follow up (Fig. 1D, E, F). Chemotherapy was not considered unless the lesion showed recurrence or pulmonary lesions occurred.

### III. DISCUSSION

Oral LYG is extremely rare and may be difficult to diagnose at first sight. There have been 11 cases of previously reported oral LYG<sup>6,11-19</sup>. The clinical features previously reported of oral LYG were mainly non-specific (pain, granular tissue, ulceration and redness). Other systemic features, such as fever, weight loss, fatigue, cough, dysphagia, and dysphonia were generally seen in patients with synchronous pulmonary lesions<sup>6,11</sup>. Oral LYG lesions presenting as bone exposure with mucosal necrosis, as seen in our case, may be difficult to distinguish from MRONJ or deep fungal infections (i.e. aspergillosis and zygomycosis)<sup>20,21</sup>. Since the patient had a history of recurrent TB, recurrent pulmonary TB and secondary oral TB should had been considered for differential diagnosis as well<sup>22</sup>. Because of the low incidence and non-specific clinical features, pathologic

confirmation is needed for diagnosis, yet pathologic differentiation may be challenging as well.

LYG belongs to the EBV-associated LPD classification and needs pathological differentiation with various LPDs and other EBV-associated diseases. LYG presents pathologic features of large, sometimes atypical B cell infiltrates mixed with reactive T cells and other inflammatory cells. Angiocentric lymphocytic infiltration and necrosis are commonly observed. The large B cells are frequently infected with EBV<sup>23</sup>. The angiocentric and necrotic characteristics of LYG are similar to those of NK/T-cell lymphoma<sup>24</sup>. Abundant amounts of reactive T cells in LYG may be confused as T-cell lymphoma, especially in early grade 1 lesions with only very few large B cells<sup>25</sup>. The large atypical cells in LYG are CD20-positive and CD56-negative (NK-cell-associated marker), which distinguishes it from NK/T-cell lymphoma<sup>26,27</sup>.

Mononuclear infiltrations with large CD20-positive and EBER-positive cells can give the differential diagnosis ranging from EBV-associated mucocutaneous ulcer to EBV-associated B-cell lymphoma<sup>28</sup>. The mononuclear infiltration in EBV-associated mucocutaneous ulcer is non-tumorous which supports the flat and clean clinical appearance of the ulcer. Furthermore, Reed-Sternberg like cells are routinely present which are not classically noticed in LYG<sup>29,30</sup>. Occasionally, there may be large lesion cells infiltrating blood vessels near the surface ulceration in EBV-associated mucocutaneous ulcer<sup>30</sup>.

Whether EBV-associated B-cell lymphoma and high-grade LYG are a separate classification is a complicated issue. Presently, LYG is considered to be distinct from lymphoma, yet high-grade LYG does have pathological overlaps with subtypes of Diffuse Large B-Cell Lymphoma (DLBCL)<sup>23,31,32</sup>. Angiocentric feature, a characteristic finding of high-grade LYG, is not a regular feature of B-cell lymphoma. Lymphomas are considered to have a monomorphous cell infiltrate distribution compared to the polymorphous background of LYG, although polymorphous infiltrates have been noticed

within certain lymphomas as well<sup>2,25,31,32</sup>. In deficient amounts of biopsy material, the monomorphous tumor cells-aggregated foci may not be included within the captured lesion. Therefore, to differentiate LYG from lymphoma a careful integrated evaluation of previous lymphoma or immunosuppression history, clinical settings (pulmonary and/or multiorgan involvement), cellular features and EBV infection status are needed<sup>9</sup>.

LYG has a wide spectrum of prognosis, from indolent to highly progressive, which is difficult to predict at initial diagnosis. High-grade LYG resembles the clinical progress of lymphoma and generally requires immediate therapy. Moreover, further transformation to lymphoma has been reported in literature by a rate of 7~45%<sup>1,25,33,34</sup>. Meanwhile, Katzenstein et al. proposed that grade 2, 3 LYG should be termed as "lymphoma" to guide the clinician to select active therapeutic options confirmed in lymphoma without risking clinical confusion due to the unpredictable biological behavior of LYG<sup>9</sup>. Corticosteroids, immunotherapy and combined chemotherapy are the known successful choices to improve symptoms of LYG and suspend progression to pulmonary dysfunction, the main cause of death<sup>3</sup>. A low proportion of LYG cases, mainly low-grade cases, go through spontaneous remission or remission after immunosuppressant discontinuance<sup>34,35</sup>.

Persistent methotrexate use has been noticed in cases of LYG<sup>11,17,35-38</sup>. MTX is an anti-metabolic agent with complications of bone marrow suppression, and is known possible to induce various LPDs<sup>39</sup>. Among the 12 reported cases of oral LYG (including this case), 4 cases had a history of MTX prescription<sup>11,17</sup>. Three of the 4 cases showed complete remission after MTX withdrawal even in those with grade 3 LYG yet lacked long-term follow up data. Successful remission after MTX withdrawal has been presented in a few cases other than the oral cavity<sup>36-38</sup>. Nevertheless, continuous progression and relapse of LYG are ongoing problems in current cohorts and case reports despite the

chemotherapeutic application in either MTX and non-MTX-associated cases<sup>11,40,41</sup>. Therefore, long term follow-up is essential in LYG patients.

The prognosis of oral LYG patients depends on its pulmonary status. When an oral lesion is pathologically diagnosed as LYG, a periodic chest evaluation is required even in the absence of pulmonary involvement at initial examination. Cutaneous LYG lesion preceding its pulmonary lesion has been well described<sup>4,40,42</sup>. Moreover, cutaneous lesions are known to present as a first sign of relapse<sup>40</sup>. Our case of oral LYG had alleviated at the first withdrawal of MTX but had progressed once again in the adjacent tissue during the MTX-free period. The LYG lesion has spontaneously regressed since then yet alerts us of the importance of periodic check-ups of this disease. The biologic behavior of oral lesions is yet poorly understood and its association with pulmonary lesion needs further evidence.

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