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LETTER TO THE EDITOR

Oral ulceration: an unusual manifestation of lymphomatoid granulomatosis

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Dear Editor,

Lymphomatoid granulomatosis (LYG) is a rare angiocentric and angiodestructive lymphoproliferative disorder (LPD) caused by latent Epstein-Barr virus (EBV) reactivation in immunosuppressed individuals [1]. Methotrexate (MTX) has been associated with the development of LPDs. In contrast to pulmonary involvement occurring in > 90% patients with LYG, involvement of oral cavity is extremely rare [2, 3]. We report two cases of oral cavity ulceration as an initial clinical manifestation of LYG.

Case 1: A 68-year-old man with a history of rheumatoid arthritis (RA) presented with mandibular pain over 1 month in a private dental clinic. He had been treated with MTX and prednisolone (PSL) for 10 years. Intraoral examination revealed an ulcer on the floor of the mouth (Fig. 1a). He was diagnosed with ulcer associated with periodontal disease. One month later, he was referred to us because of refractory oral ulcer. Chest X-ray screening showed bilateral multiple patchy infiltration with middle and lower lung predominance. Computed tomography (CT) showed bilateral multiple ill-defined and poorly enhanced nodules, showing perilymphatic distribution (Fig. 1b). He did not respond to MTX withdrawal. A needle biopsy specimen of an affected lung lesion revealed angiocentric infiltration of middle- to large-sized polymorphic lymphocytes expressing CD20, CD30, and EBV latent membrane protein 1 (LMP-1), with extensive necrosis (Fig. 1c). The patient was pathologically diagnosed with LYG grade III. A biopsy specimen of the affected oral mucosa indicated a LYG involvement. He had complete remission after standard CHOP chemotherapy.

Case 2: A 72-year-old woman with a history of RA was referred to us because of right-sided pain in the tongue over 1 month. She had been treated with MTX and PSL for 15 years. Physical examination revealed an ulcer on the right lateral margin of the tongue (Fig. 1d). Chest X-ray screening showed bilateral multiple lung nodules; CT images showed multiple ill-defined and poorly enhanced nodules on bronchovascular bundles in both lungs (Fig. 1e). MTX was discontinued. A lung biopsy specimen revealed angiocentric infiltration of middle- to large-sized polymorphic lymphocytes expressing CD20, CD30, and LMP-1, with extensive necrosis (Fig. 1f). She was diagnosed with LYG grade III. The oral and lung lesions resolved within 1 month after MTX withdrawal.

Diagnosis and management of oral ulcerative lesions have been challenging due to various causative factors,

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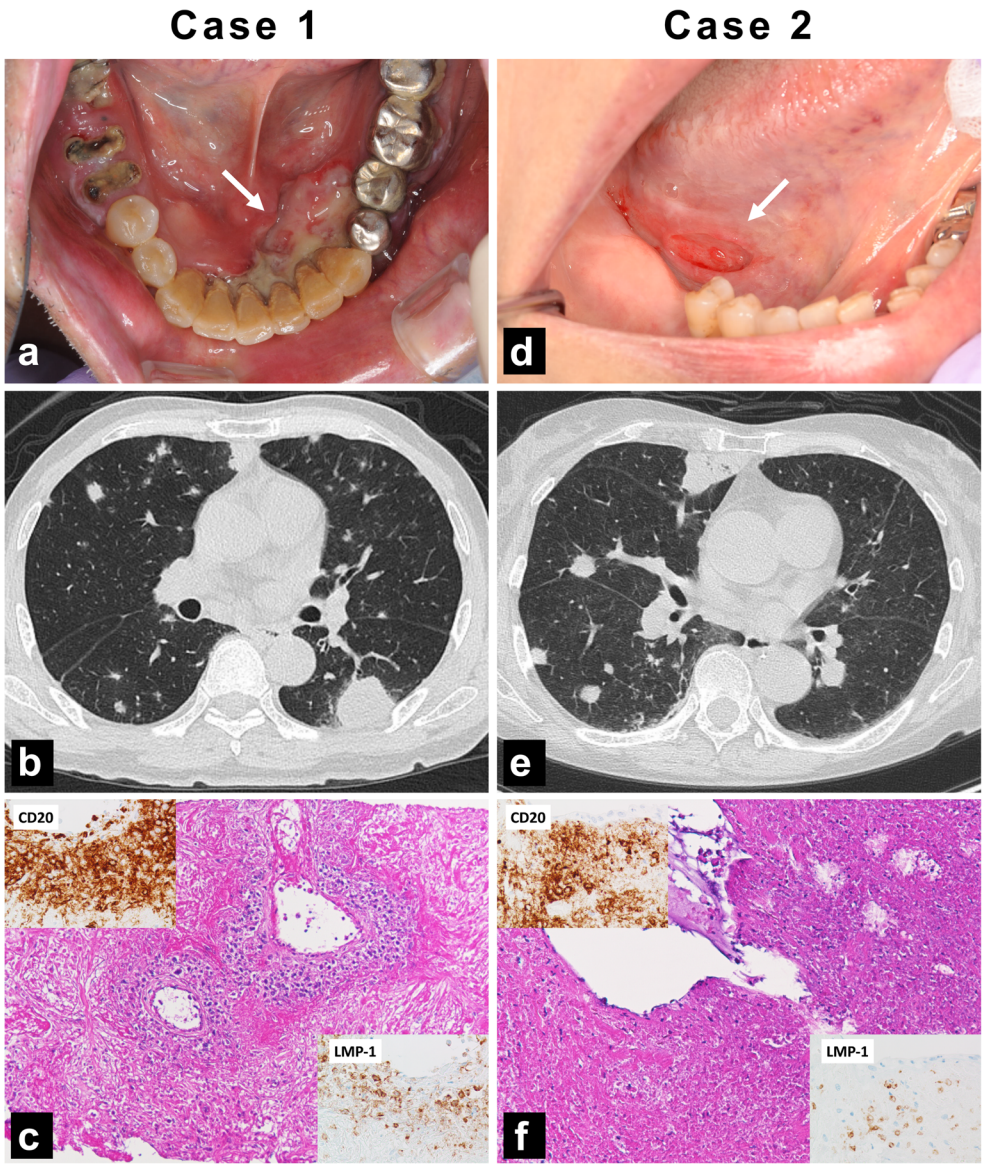

Fig. 1 Imaging findings. **a** An intraoral photograph of the first case shows an ulcer on the floor of the mouth. **b** Chest CT of the first case shows bilateral multiple nodules or mass with perilymphatic and peripheral predominance. **c** Representative histological photograph of the lung needle biopsy specimen of the first case (hematoxylin and eosin, × 100). The angiocentric infiltration of atypical lymphocytes and extensive necrosis are observed. Atypical lymphocytes are positive for CD20 (upper left inset, × 400) and EBV LMP-1 (> 20 cells per high-power field) (lower right inset, × 400). A number of CD3-positive T lymphocytes and CD68-positive macrophages were also present. **d** An intraoral photograph of the second case shows an ulcer on the right lateral margin of the tongue. **e** Chest CT shows bilateral multiple nodules on bronchovascular bundles. **f** Representative histological photograph of the surgical lung biopsy specimen of the second case (hematoxylin and eosin, × 100). Extensive necrosis around the vessel is observed. Immunohistochemistry of CD20 highlights atypical lymphocytes (upper left inset, × 400), and some of these atypical lymphocytes are positive for EBV LMP-1 (> 20 cells per high-power field) (lower right inset, × 400). A number of CD3-positive T lymphocytes and CD68-positive macrophages were also present

such as trauma, infections, systemic diseases, drugs, cancers, and other presenting features. Our experience suggests that a chest X-ray screening and a high-resolution CT are recommended for immunocompromised individuals with refractory oral cavity ulcers. Peribronchovascular distribution of nodules, coarse irregular opacities, small thin-walled cysts, and conglomerating small nodules are radiographic features characteristic of LYG [4].

EBV evokes various malignancies including LPDs, nasopharyngeal carcinoma, Hodgkin lymphoma, nasal NK/T cell lymphoma, and gastric cancer [5]. Recently, EBV-positive mucocutaneous ulcer (EBVMCU) has been proposed as a provisional clinicopathologic entity [1]. EBVMCU occurs in patients with age-related or iatrogenic immunosuppression and often responds well to conservative management. The initial clinical

manifestation in our cases resembled those of the EBVMCU, except for the massive pulmonary involvement. A possible clinicopathologic overlap between LYG and EBVMCU needs to be elucidated.

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Compliance with ethical standards

Written informed consent was obtained from the patients for publication.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, Advani R, Ghielmini M, Salles GA, Zelenetz AD, Jaffe ES (2016) The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 127:2375–2390
2. Cargini P, Civica M, Sollima L, Di Cola E, Pontecorvi E, Cutilli T (2014) Oral lymphomatoid granulomatosis, the first sign of a 'rare disease': a case report. J Med Case Rep 8:152
3. Shanti RM, Torres-Cabala CA, Jaffe ES, Wilson WH, Brahim JS (2008) Lymphomatoid granulomatosis with involvement of the hard palate: a case report. J Oral Maxillofac Surg 66: 2161–2163
4. Lee JS, Tuder R, Lynch DA (2000) Lymphomatoid granulomatosis: radiologic features and pathologic correlations. AJR Am J Roentgenol 175:1335–1339
5. Grywalska E, Rolinski J (2015) Epstein-Barr virus-associated lymphomas. Semin Oncol 42:291–303