


CASE REPORT

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Follicular lymphoid hyperplasia of the posterior maxillary site presenting as uncommon entity: a case report and review of the literature

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Abstract

Background: Follicular lymphoid hyperplasia (FLH) is characterized by an increased number and size of lymphoid follicles. In some cases, the etiology of FLH is unclear. FLH in the oral and maxillofacial region is an uncommon benign entity which may resemble malignant lymphoma clinically and histologically.

Case presentation: We report the case of a 51-year-old woman who presented with an asymptomatic firm mass in the left posterior maxillary site. Computed tomography scan of her head and neck showed a clear circumscribed solid mass measuring 28 × 23 mm in size. There was no evidence of bone involvement. Incisional biopsy demonstrated benign lymphoid tissue. The patient underwent complete surgical resection. Histologically, the resected specimen showed scattered lymphoid follicles with germinal centers and predominant small lymphocytes in the interfollicular areas. Immunohistochemically, the lymphoid follicles were positive for CD20, CD79a, CD10, CD21, and Bcl6. The germinal centers were negative for Bcl2. Based on these findings, a diagnosis of benign FLH was made. There was no recurrence at 1 year postoperatively.

Conclusions: We diagnosed an extremely rare case of FLH arising from an unusual site and whose onset of entity is unknown. Careful clinical and histopathological evaluations are essential in making a differential diagnosis from a neoplastic lymphoid proliferation with a nodular growth pattern.

Keywords: Follicular lymphoid hyperplasia, Immunohistochemistry, Maxilla, Differential diagnosis, Lymphoma

Background

Follicular lymphoid hyperplasia (FLH) is characterized as a non-neoplastic lymphoproliferative disease, and is also known as nodular lymphoid lesion and pseudolymphoma. This rare disease is known to affect various organs including the skin, lungs, stomach, breasts, intestine, spleen, pancreas, and liver [1, 2]. In the head and neck region, involvements of the orbit, thyroid, and oral cavity have been demonstrated. Morphologically, the lesion may show the features of FLH. The clinicopathological features of lymphoid hyperplasia in the oral mucosa were initially reported by Adkins in 1973 [3]. The author

indicated the hard palate as the most commonly affected site. FLH of the hard palate may be confused clinically and histologically with malignant lymphoma. The condition most commonly affects elderly patients and presents as a painless, slowly growing non-ulcerated mass in the posterior hard palate [1]. The pathogenesis of FLH in the oral cavity is presently unknown. However, it has been suggested that the reactive proliferation is associated with some unknown antigenic stimulation. On the other hand, it may be considered that its occurrence in the submucosal tissue in the oral and maxillofacial areas except in the palate is extremely rare. Although it is also important to have a differential diagnosis from malignant lymphoma or the systemic disease of multicentric lymphadenopathy in this area, a definitive diagnosis of

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FLH could only be made clinically and histopathologically. We describe the case of a patient with FLH found in the posterior maxilla arising from an uncommon site, and review its histopathological features by immunohistochemical analysis.

Case presentation

A 51-year-old woman was referred to the Department of Oral and Maxillofacial Surgery at Tokyo Medical University Hospital for a closer evaluation and treatment of an asymptomatic firm mass in the left posterior maxillary site. Intraoral examination revealed a palpable mass located in the posterior lateral region of the left maxilla (Fig. 1a). The overlying mucosa was intact and normal in color. The firm mass was not movable. Laboratory data were within the normal limits. Computed tomography (CT) scan of her head and neck showed a clear circumscribed solid mass measuring 28 × 23 mm in size between the lateral aspect of the posterior maxilla and the anterior region of the masseter muscle with no evidence of maxillary bone involvement (Fig. 1b). There was no lymphadenopathy in the cervical region. Magnetic resonance imaging scans revealed homogeneously enhanced signal intensity on T1-weighted images after gadolinium administration (Fig. 2a) and high signal intensity on Short T1 Inversion Recovery images (Fig. 2b). Incisional biopsy demonstrated benign lymphoid tissue. CT examination was conducted in the chest and abdominal region taking into consideration Castleman's disease as a differential diagnosis. However, systemic lymphadenopathy was not recognized. The submucosal mass

was completely excised under general anesthesia. In the course of the surgical resection, the mass was observed to be adjacent to the buccal fat pad.

Gross examination showed a solid mass measuring 38 × 23 × 17 mm in size, which was encapsulated with fibrous tissue (Fig. 3). Microscopic examination revealed lymphocytic tissue composed of scattered lymphoid follicles with germinal centers and predominant small well-differentiated lymphocytes in the parafollicular area (Fig. 4a). The follicles showed various sizes of the germinal centers surrounded by well-defined mantle zones consisting of small lymphocytes (Fig. 4b). The germinal center contained a mixture of centrocytes and centroblasts with occasional tingible body macrophages (Fig. 4c and d). The nuclei of the centrocytes exhibited the cleaved type. The centroblasts had relatively large nuclei with prominent nucleoli. Penetration of vessels similarly to the hyaline vascular type in Castleman's disease was observed in one part of the germinal centers. Immunohistological analysis demonstrated the positivity of lymphoid follicles for CD20 and CD79a (Fig. 5). In particular, there were expressions for CD10, Bcl6, and Ki67 only in the germinal centers, whereas there was no expression for Bcl2 (Fig. 6a, b, and c). The immunostaining for CD21 was characteristic of a reticular pattern highlighting the follicular dendritic cell networks (Fig. 6d). The parafollicular areas expressed CD3 and CD5, and were weakly positive for Bcl2 (Fig. 7). Both areas showed CD45RO staining, but conversely not CD15 expression. CD45RO and CD15 images were not shown. Based on these findings, a final diagnosis of FLH was made. The patient has been free of local recurrence 1 year postexcision.

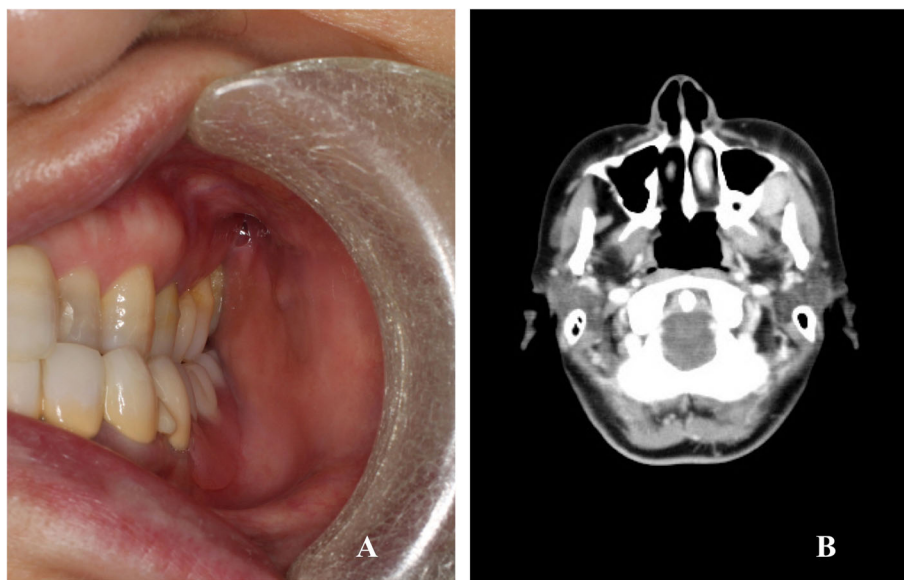


Fig. 1 **a** Intraoral appearance of the mass lesion overlying by normal mucosa in the maxillary posterior site. **b** Computed tomography scan showing a clear circumscribed solid mass between the lateral aspect of the posterior maxilla and the anterior region of the masseter muscle

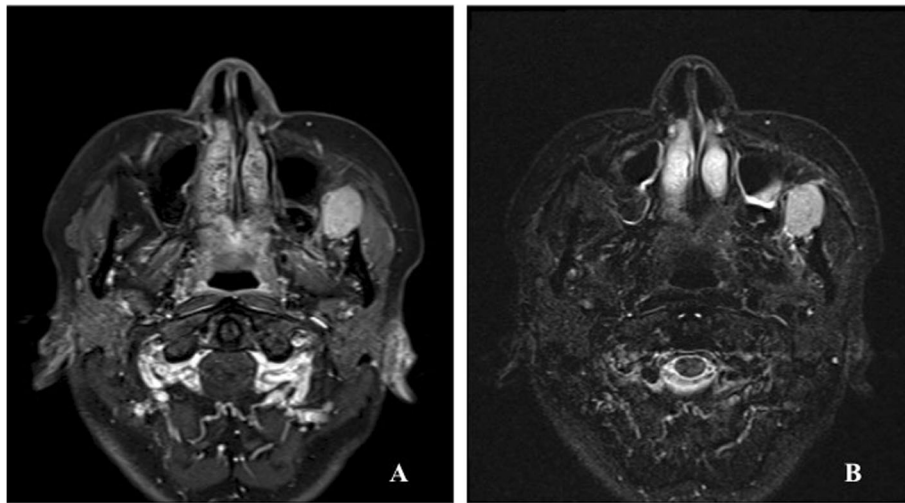


Fig. 2 Magnetic resonance imaging scan showing (a) homogeneously enhanced signal intensity on a T1-weighted image after gadolinium administration and (b) high signal intensity on a Short T1 Inversion Recovery image

Discussion and conclusions

FLH is recognized as a non-neoplastic proliferative lymphoid lesion and shows very uncommon features. It is also referred to as pseudolymphoma and nodular lymphoid tissue. FLH involves various organs such as the skin, orbit, nasopharynx, larynx, thyroid, lungs, gastrointestinal tract, breasts, spleen, pancreas, and liver [1, 2]. Furthermore, the sites of occurrence of FLH in the oral and maxillofacial regions have included the palate, tongue, salivary gland, and cheek region [4, 5]. Adkins has initially reported the clinicopathological features of lymphoid hyperplasia in the oral mucosa in

1973 [3]. In particular, it was reported that the hard palate was the most commonly affected site. However, to the best of our knowledge, only 21 cases of affected palates have been reported [6]. In a previous report of 21 case series, FLH occurred more frequently in elderly women with an average age of 62 years (range 38–79 years). The mean size of their mass lesions was 2.5 cm (range 1–5 cm) [7]. This condition usually presents as a unilateral, painless, slow-growing, and non-ulcerated mass. These features of age, gender, size, and asymptomatic findings in the present case are almost similar to the clinical characteristics of these case series reported previously. The present case may be considered as extremely unique because it arises from the posterior maxillary site. Besides the present case, another case occurring in the maxillary site has been documented [8]. The clinicopathological characteristics of 27 cases of FLH arising in the oral cavity along with our case were summarized in the Table 1 [1, 4–16]. In case 26, the size of the lesion was not specified, but it was speculated by the surrounding bone destruction that the size was larger than the present case. In the present case, there was no invasion to maxillary bone and because the boundary was clear, complete resection was possible. Both immunohistochemical profiles were similar. Although there was a difference in clinical findings, both showed strong positive for Ki67.

The specific etiology and pathogenesis of FLH have not been fully clarified to date. It has been described that this condition might represent a primary reactive lymphoid proliferation induced by some unknown antigenic stimulation or chronic irritation, for example, from a partial denture [10]. However, a source of persistent



Fig. 3 Surgical specimen of the solid mass measuring 38 × 23 × 17 mm in size, which was encapsulated with fibrous tissue

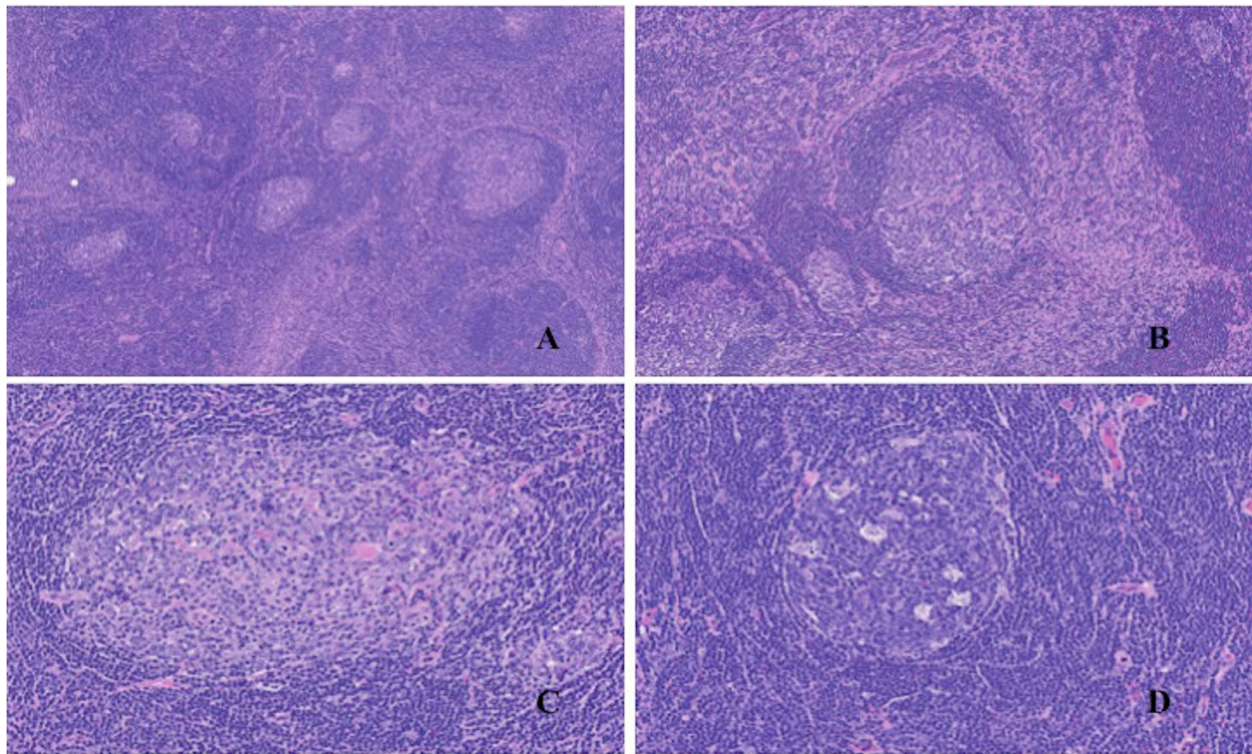


Fig. 4 Microscopic appearance of the hyperplastic lymphoid tissue. **a** Scattered lymphoid follicles with germinal centers (hematoxylin and eosin, 5x). **b** A germinal center surrounded by a well-defined mantle zone consisting of small lymphocytes (hematoxylin and eosin, 10x). **c** Follicle center containing a mixture of centrocytes and centroblasts (hematoxylin and eosin, 20x). **d** Tingible body macrophages in the germinal center (hematoxylin and eosin, 20x)

chronic irritation from a removable denture was not present in a large number of patients [1]. An association with Sjögren's syndrome was not observed, and an association with HIV infection or any other infectious diseases has not been documented. On the other hand, the Epstein-Barr virus may be associated with an unusual form of aggressive and persistent FLH that contains clonal rearrangements of DNA [17].

Regarding the clinical differential diagnoses of the mass in the present case, salivary gland tumors, duct-associated lymphoid tissue, mesenchymal tumors, metastatic tumors, and cheek abscesses were considered initially. When occurring in the palate, some lymphoid lesions including malignant lymphoma can be easily considered in making the differential diagnoses. It is considered that the major importance of FLH is their similarity to oral lymphomas

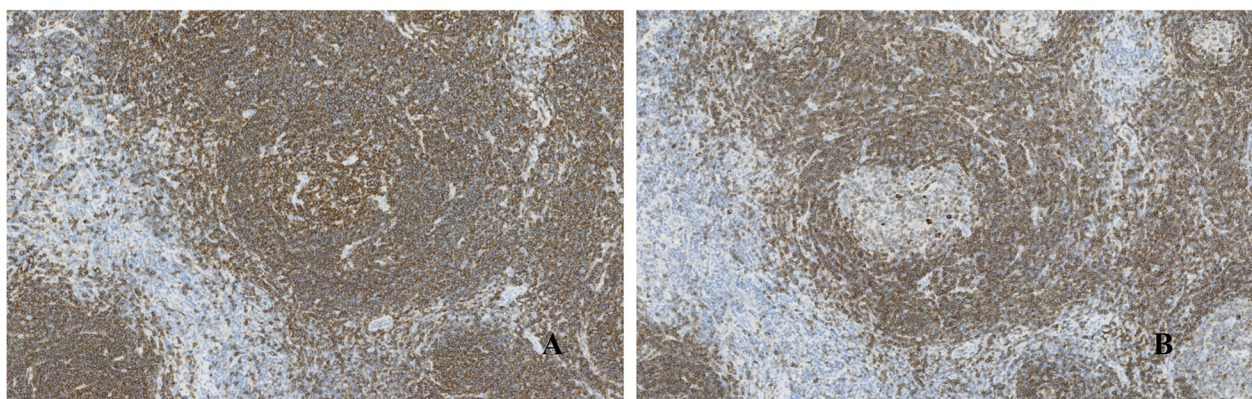


Fig. 5 Immunohistochemical features of the lymphoid follicles. **a** The whole areas of lymphoid follicles were positive for CD20 (10x). **b** The lymphoid follicles except the germinal center were positive for CD79a (10x)

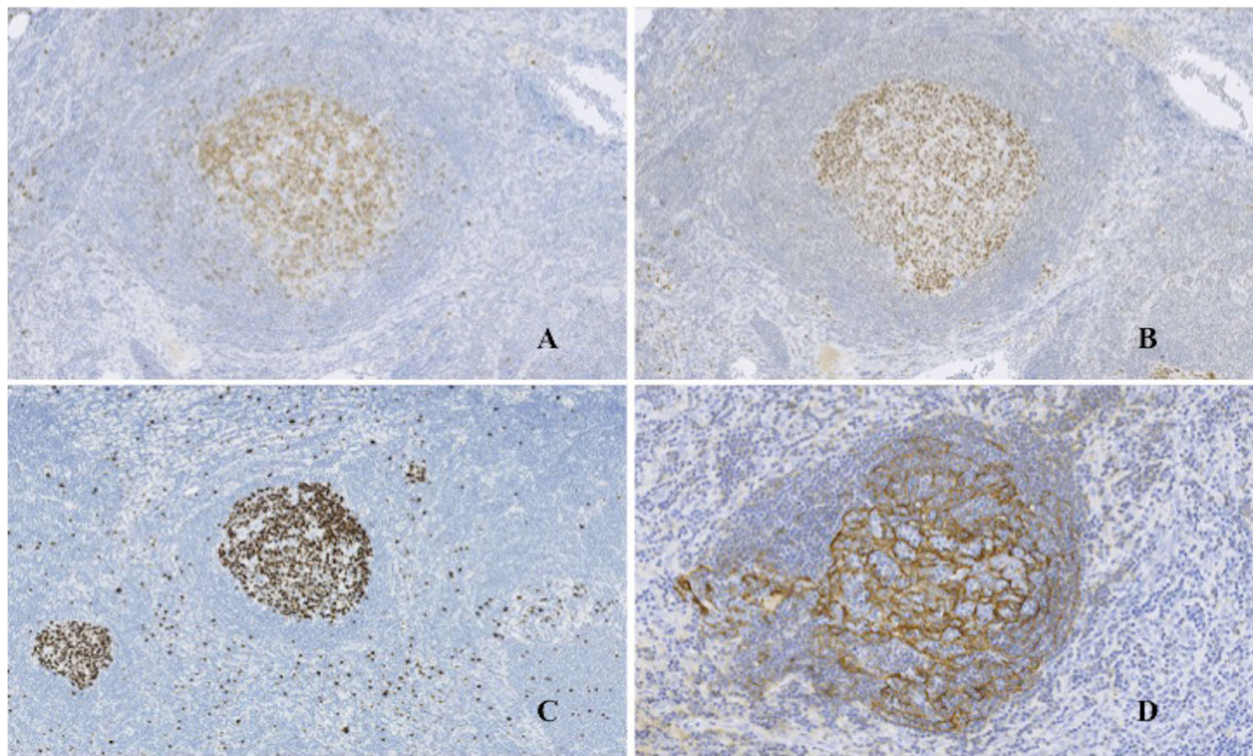


Fig. 6 The germinal centers showed positive immunostaining for CD10 (a), Bcl6 (b), and Ki67 (c) (10x). The immunostaining for CD21 revealed a reticular pattern highlighting the follicular dendritic cell networks (d) (20x)

[18]. Moreover, 25% of non-Hodgkin lymphomas are extranodal, with 3–4% of all cases being located in the head and neck [19].

Considering all of the above-mentioned aspects, the definitive diagnosis of FLH is finally based on pathological examination. Histologically, FLH usually consists of multiple well-circumscribed lymphoid follicles with a clear demarcation of the germinal center and mantle zone. The majority of the lymphoid follicles have germinal centers, and some of these germinal centers are hyperplastic. The germinal centers consist of a mixture of small and large lymphoid cells, with both cleaved and uncleaved cells. Tingible body macrophages are also scattered in the germinal centers. The mantle zone contains small mature B lymphocytes and plasmacytic lymphocytes. There are variable numbers of B lymphocytes, T lymphocytes, and immunoblasts in the parafollicular area. However, Jham et al. have suggested that histological features were not always characteristic [6]. From their report, a vague nodular proliferation with indistinct germinal centers was observed. This pattern was highly suggestive of follicular lymphoma or lymphoma of the mucosa-associated lymphoid tissue (MALT). Kolokotronis et al. also described that there were some cases in which the differential diagnosis

of lymphoma could be very difficult [15]. Not only indistinct germinal centers but also ill-defined mantles and a lack of tingible body macrophages were apparent. When such cases are encountered, further laboratory examination is required to assume a diagnostic process for lymphoma.

The histological diagnosis of FLH should be supported by an immunohistochemical analysis. Regarding the immunohistochemical findings of FLH, lymphoid follicles show positivity for CD20, CD21, CD10, CD79a, and Bcl6. Immunostaining for Bcl2 protein showed positivity in the mantle zone but negativity in the germinal center [1, 7]. The parafollicular areas usually revealed positivity for CD3, CD5, CD15, and CD30. In lymphoma, most neoplastic cells were reported to be positive for Bcl2 in the follicular center [20]. Another report describing 15 cases of extranodal follicular lymphoma indicated that the neoplastic follicle center cells showed coexpression of CD20 with CD10 (13/15 cases) and/or Bcl6 (15/15 cases) [21]. Bcl2 protein was detected in 9 out of the 15 cases [21]. It has also been shown that the Bcl2 oncogene is commonly activated by chromosomal translocations and that B cells undergo neoplastic transformation. This step affects the tumorigenesis of B cell malignancy [20]. Therefore, immunostaining for Bcl2 protein could be a useful marker in the differential diagnosis between

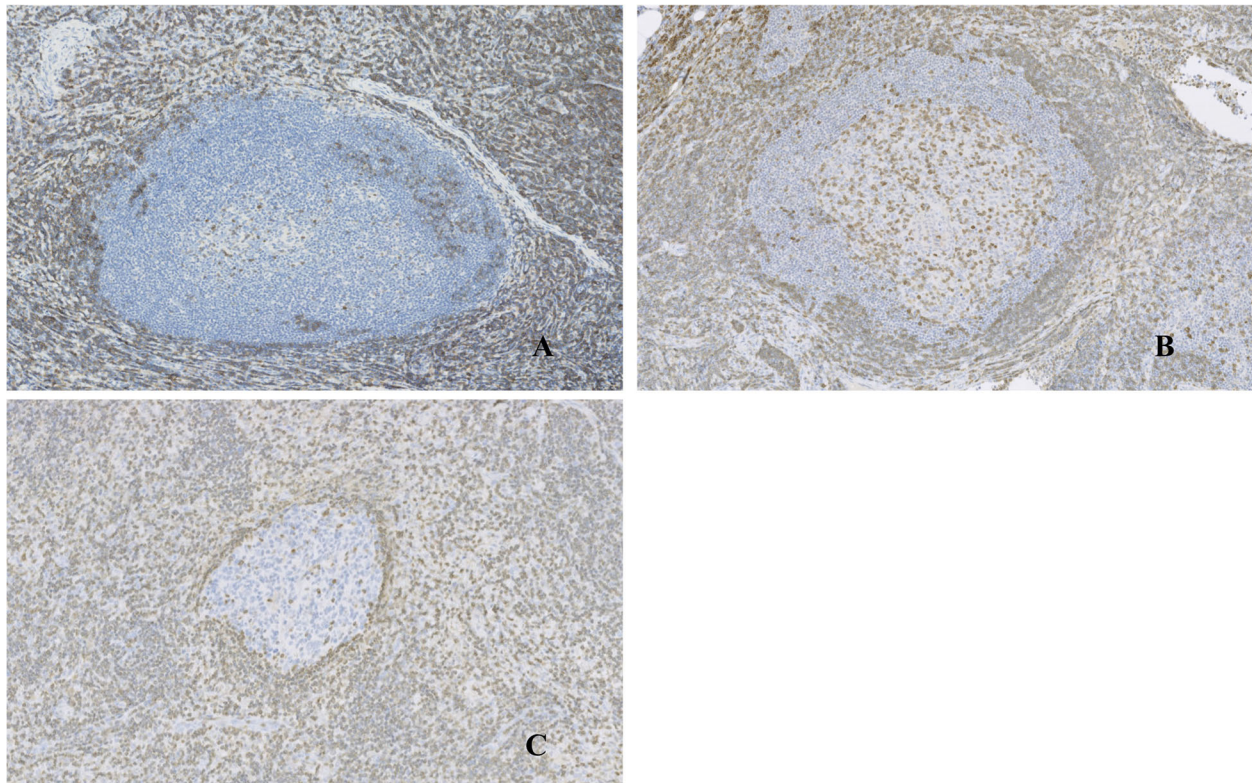


Fig. 7 The parafollicular areas showed immunostaining for CD3 (a) and CD5 (b), and weakly positive immunostaining for Bcl2 (c) (10x)

FLH and lymphoma. However, it has been documented that 10–15% of follicular lymphoma was negative for Bcl2 [8]. Whereas, CD10-positive cells were also observed in the follicle center of lymphoma as well as Bcl2 [20]. CD10 is a 100-kd cell-surface metalloproteinase that appears to be involved in activation and deactivation of peptides through proteolytic cleavage [22, 23]. CD10 expresses on the surface of germinal center cells and lymphomas derived from these cells [24]. It has been suggested that the intensity of CD10 expression can be a useful maker for differentiating between follicular lymphoma and reactive follicular hyperplasia [24, 25]. However, clear expression of CD10 was observed in germinal centers in this case, so it is considered difficult to differentiate only the intensity of expression. In particular, it may be important to distinguish from CD10 expression of interfollicular neoplastic cells except germinal center. In order to arrive at definitive diagnosis, it is necessary to differentiate between FLH and neoplastic lymphoid proliferation with nodular pattern. Therefore, in addition to morphological features, it is important to evaluate immunophenotypes by immunohistochemistry.

The common treatment of FLH is surgical excision of the lesions. Radiotherapy has also been applied as treatment in a single case [9]. In the present case,

the occurrence was from a very rare site, thus biopsy was initially undertaken and then a definitive diagnosis of FLH was established. Thereafter, the lesion was completely excised. A small number of patients have developed recurrences after local excision but they have not shown any evidence of malignization after long-term follow-up [1]. Although a prolonged follow-up has not shown any evidence of a malignant process, the malignant transformation of FLH into lymphoma in the skin and liver has been reported [10, 26]. Although no malignant transformation has been reported, one multisite case within the oral cavity was found to represent MALT-type lymphoma [3].

In conclusion, a definitive diagnosis of FLH can be made by careful pathological examination. Nevertheless, there are several cases that may be confused with the diagnosis of lymphoma in terms of histopathological features. In such cases, additional laboratory examinations and molecular analysis may be needed to make an accurate diagnosis. In particular, immunohistochemistry should be considered as an important part for obtaining definitive diagnosis. Although FLH usually has a good prognosis by long-term follow-up, it would be noteworthy that the possible of malignant transformation exist slightly.

Table 1 Clinicopathological characteristics of 27 cases of FLH arising in the oral cavity

| Case | References (year) | Age (years) | Sex | Site | Size (mm) | Symptoms | Image findings | Treatment | Follow-up / Status | Immunohistochemical features | | |
|------|-------------------------------|-------------|-----|----------------------------|----------------|---------------------|------------------------------|-----------------------|----------------------------|------------------------------|-------------|---------------------|
| | | | | | | | | | | Germinal center | Mantle zone | Parafollicular area |
| 1 | Harsany et al. 1980 [9] | 60 | F | Left hard palate | 40 × 20 | Nonpainful growth | No bony involvement | Excision/radiotherapy | 144 months Reduction | NA | NA | NA |
| 2 | | 47 | M | Right hard and soft palate | NS | Nontender swelling | NS | Excision | 48 months Disease free | NA | NA | NA |
| 3 | | 72 | F | Hard palate/Buccal space | 15 × 10/ 25 | Nontender mass | NS | Excision | 108 months NS | NA | NA | NA |
| 4 | | 70 | F | Left hard palate | 18 | Ill-fitting denture | NS | Radiotherapy | 84 months Disease free | NA | NA | NA |
| 5 | Wright and Dunswoth 1983 [10] | 72 | F | Right hard palate | 30 | Swelling | No bone invasion on CT image | Excision | 24 months No recurrence | NA | NA | NA |
| 6 | Bradley et al. 1987 [11] | 76 | F | Left hard palate | NS | Asymptom | NS | Incisional biopsy | 36 months Disease free | NA | NA | NA |
| 7 | | 73 | F | Left hard palate | NS | Asymptomatic mass | NS | Incisional biopsy | 96 months Disease free | NA | NA | NA |
| 8 | | 62 | F | Left hard palate | 35 × 20 | Swelling | NS | Incisional biopsy | 41 months Disease free | NA | NA | NA |
| 9 | | 57 | F | Left soft palate | 30 | Swelling | NS | Excision | 36 months No recurrence | NA | NA | NA |
| 10 | | 41 | M | Left soft palate | NS | Swelling | NS | Excision | 39 months No recurrence | NA | NA | NA |

Table 1 Clinicopathological characteristics of 27 cases of FLH arising in the oral cavity (Continued)

| Case | References (year) | Age (years) | Sex | Site | Size (mm) | Symptoms | Image findings | Treatment | Follow-up / Status | Immunohistochemical features | | |
|------|-------------------------------|-------------|-----|----------------------------------|--------------|------------------|------------------------------|-------------------|-----------------------------|---|---|-------------------------------|
| | | | | | | | | | | Germinal center | Mantle zone | Parafollicular area |
| 11 | | 51 | F | Left hard palate | NS | Swelling | NS | Excision | 24 months Recurrence | NA | NA | NA |
| 12 | | 60 | F | Bilateral palate | Large | Swelling | NS | Incisional biopsy | 120 months Disease free | NA | NA | NA |
| 13 | Davila and Thompson 1988 [12] | 49 | F | Left hard palate | 30 | Slightly rising | No bony involvement | Excision | 84 months No recurrence | NA | NA | NA |
| 14 | Napier and Newlands 1990 [13] | 38 | F | Junction of hard and soft palate | 10 | Swelling | NS | Excision | NS | P: CD45R, CD20, CDw75, CD74, HLA-DR, κ and λ light chains NA | P: CD45RC, CD45R, CD20, HLADR N: CD43, CD45RO, CDw75, κ and λ light chains, AAT | P: CD43, CD45RC, CD45RO NA |
| 15 | | 79 | F | Junction of hard and soft palate | Several tens | Diffuse swelling | NS | Excision | NS | P: CD45R, CD20, CDw75, κ and λ light chains N: CD45RC | P: CD45RC, CD45R, CD20, HLA-DR N: CD43, CD45RO, CDw75, κ and λ light chains, AAT | P: CD43, CD45RC, CD45RO NA |
| 16 | Mopsik et al. 1992 [14] | 63 | M | Right hard palate | 38 × 15 | Swelling | No bone invasion on CT image | Excision | NS | P: κ and λ light chains NA | NA | NA |
| 17 | Menasce et al. 2001 [1] | 51 | M | Left hard palate | 20 | Swelling | No bony involvement | Excision | 48 months No recurrence | P: κ and λ light chains N: Bcl2 | P: Bcl2 NA | NA |
| 18 | | 75 | M | Midline hard palate | 10 | Swelling | NS | Excision | 24 months No recurrence | NA N: Bcl2 | P: Bcl2 NA | NA |
| 19 | | 61 | F | Multifocal | Largest 20 | Swelling | NS | Excision | 192 months No recurrence | P: κ and λ light chains N: Bcl2 | NA | NA |

Table 1 Clinicopathological characteristics of 27 cases of FLH arising in the oral cavity (Continued)

| Case References (year) | Age (years) | Sex | Site | Size (mm) | Symptoms | Image findings | Treatment | Follow-up / Status | Immunohistochemical features | | |
|---|----------------|-----|----------------------|-----------------|------------------------|------------------------------------|---------------------------------------|-----------------------|---|---|-------------------------------------|
| | | | | | | | | | Germinal center | Mantle zone | Parafollicular area |
| 20 Kolokotronis et al. 2003 [15] | 74 | F | Right hard palate | 25 | Firm swelling | No bony involvement | Excision | 18 months | P: CD20 | P: CD20 | P: CD45RO |
| 22 Carnelio and Rodríguez 2005 [4] | 36 | F | Left tongue | 40 × 30 | Painless ulcer | NS | Excision | No recurrence | N: Bcl2 | N: Bcl2, CD45RO | NA |
| 21 Kojima et al. 2005 [5] | 49 | F | Right cheek | 10 × 10 | Hard mass | NS | Excision | 14 months | P: CD20, CD10, IgD, IgM, CD30 | P: CD20, IgD, IgM | P: CD30, CD57 |
| 23 Jham et al. 2009 [6] | 55 | F | Left hard palate | 50 | Swelling | No bony involvement | Incisional biopsy | 3 months | N: Bcl2 | NA | N: CD15, EMA |
| 24 Gordón- Núñez et al. 2012 [7] | 70 | F | Right soft palate | 20 | Nodular mass | No bony involvement | Excision | 8 months | P: CD20, CD79a, CD10, CD21, Bcl6, CD45 | P: CD20, CD79a, CD45 | P: CD3, CD5, CD30, CD15, CD45 |
| 25 Anjomsboaa et al. 2013 [16] | 46 | F | Right hard palate | 20 × 15 | Nontender firm mass | No intraosseous radiolucency | Intralesional steroid injection | 7 months | N: Bcl2 | NA | P: CD20, Bcl2, Bcl6 |
| 26 Hanemann et al. 2017 [8] | 24 | M | Right maxilla | NS | Swelling | Bone invasion on CT image | Curettage | 36 months | No recurrence | N: Bcl2 | NA |
| 27 Present case | 51 | F | Left maxilla | 38 × 23 × 17 | Palpation mass | No bone invasion on CT image | Excision | 12 months | P: Bcl6, CD20, CD21, CD10, CD79a, Ki67 | P: Bcl6, CD20, CD21, CD10, CD79a, Ki67 | P: CD3, CD5, CD15, CD30 |

Table 1 Clinicopathological characteristics of 27 cases of FLH arising in the oral cavity (Continued)

| Case | References (year) | Age (years) | Sex | Site | Size (mm) | Symptoms | Image findings | Treatment | Follow-up / Status | Immunohistochemical features | | |
|------|-------------------|-------------|-----|------|-----------|----------|----------------|-----------|--------------------|------------------------------|-------------|---------------------|
| | | | | | | | | | | Germinal center | Mantle zone | Parafollicular area |
| | | | | | | | | | | N: Bcl2 | N: Bcl2 | NA |

FLH follicular lymphoid hyperplasia, F female, M male, NS not stated, P positive, N negative, NA not applicable, AAT α1-antitrypsin, EMA epithelial membrane antigen

Abbreviations

CT: Computed tomography; FLH: Follicular lymphoid hyperplasia; MALT: Mucosa-associated lymphoid tissue

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Authors' contributions

MW drafted the manuscript and interpreted the data. AI helped collect pathological data. YY and MK helped collect clinical data. MW and OH carried out surgical resection. YK revised of the manuscript. TS participated in literature review. DC made critical revisions for important intellectual content. All authors read and approved the final manuscript.

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Availability of data and materials

All relevant data are within the paper.

Ethics approval and consent to participate

Because this report involves no experiment, ethics approval is waived.

Consent for publication

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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