Head and Neck Pathology (2019) 13:270–276
https://doi.org/10.1007/s12105-018-0910-x

CASE REPORT

Oral Manifestation of Lymphomatoid Granulomatosis

Alessandro Antônio Costa Pereira[1] · Christian Barros Ferreira[2] · João Adolfo Costa Hanemann[3] · Livia Maris Ribeiro Paranaiba[1] · Patricia Peres Iucif Pereira[4] · Carla Isabelly Rodrigues-Fernandes[5] · Celeste Sánchez-Romero[5] · Oslei Paes de Almeida[5] · Felipe Paiva Fonseca[5,6]

Received: 26 January 2018 / Accepted: 12 March 2018 / Published online: 14 March 2018

Abstract
Lymphomatoid granulomatosis (LYG) is a rare B-cell lymphoproliferative disorder driven by Esptein–Barr virus (EBV) that most commonly affects the lungs, although extra pulmonary sites like the central nervous system, skin, liver and kidney can also be involved. It is microscopically characterized by an angiocentric and angiodestructive growth pattern, predominantly composed by small T-cells, although a smaller population of atypical large B-cells is considered the true neoplastic component. Oral cavity involvement of LYG has rarely been described and the diagnosis of this neoplasm is very difficult. The aim of this report is to present a rare case of LYG affecting an 86-year-old female patient that was diagnosed due to an extensive, ulcerated and painful oral lesion affecting the hard palate. Detailed microscopic evaluation together with a large immunohistochemical study were necessary to achieve the correct diagnosis of LYG.

Keywords Lymphoma · Oral cavity · Lymphomatoid granulomatosis · Palate

Introduction

Lymphomas consist of a heterogeneous group of neoplasms with different incidence rate, biological behavior and prognosis; they may originate from either the primary lymph organs (bone marrow and thymus) or the peripheral lymphoid tissues (lymph nodes, spleen and Peyer's patches) [1]. Lymphomas are broadly classified into Hodgkin's lymphomas (HL), which often presents as a nodal disease, and non-Hodgkin lymphomas (NHL), diagnosed in extra-nodal sites in up to 40% of the cases [2].

Although the head and neck region is considered the second most frequently affected site by extra-nodal NHL, oral cavity involvement by primary or disseminated lymphomas accounts for less than 5% of all malignant neoplasms diagnosed in this anatomical location [3, 4]. The great majority of the head and neck NHL are derived from B-cell lineage, and diffuse large B-cell lymphoma (DLBCL) represents the most common subtype, comprising 30–35% of all cases [5, 6]. Similarly, most cases in the oral cavity are also represented by DLBCL corresponding to more than 50% of the oral lymphomas in some series [3, 4, 7]; however, many other less common subtypes may also affect the mouth.

Lymphomatoid granulomatosis (LYG) is a rare, aggressive, angiocentric and angiodestructive lymphoproliferative disorder of neoplastic B-cells associated with a large population of reactive small T-cells that commonly involves extra-nodal sites, mainly the lungs. According to the World Health Organization (WHO) classification of hematopoietic and lymphoid tumors, it is associated with Epstein–Barr virus (EBV) infection, which is important not only to its pathogenesis, but also to determine its grading, which will be used to define the most appropriate management [8–10].

✉ Felipe Paiva Fonseca
felipepfonseca@hotmail.com

[1] Department of Pathology and Parasitology, Institute of Biomedical Sciences, Federal University of Alfenas, Alfenas, Brazil

[2] Cônego Monte Raso Hospital, Baependi, Brazil

[3] Department of Clinics and Surgery, School of Dentistry, Federal University of Alfenas, Alfenas, Brazil

[4] School of Dentistry, Universidade José do Rosário Vellano, Varginha, Brazil

[5] Department of Oral Diagnosis, Piracicaba Dental School, University of Campinas, Piracicaba, Brazil

[6] Department of Oral Surgery and Pathology, School of Dentistry, Federal University of Minas Gerais, Av. Antônio Carlos 6627, Pampulha, Belo Horizonte 31270-901, Brazil

The occurrence of LYG in the oral cavity is extremely rare and usually represents the dissemination of a pulmonary disease; however, it may occasionally lead to the initial diagnosis of the neoplasm [11, 12]. In this report, we present a case of LYG involving the oral cavity and review the literature of this malignancy involving the mouth.

Case Report

An 86-year-old female patient was referred to our department complaining of dysphagia and oral pain associated with an oral lesion with 4 months of duration. Patient's past medical history included high fever and lethargy 1 month ago, but with no other relevant systemic complaint and the patient did not have any immunodeficiency diagnosed either. Extra-oral examination did not detect any palpable lymph nodes. Intra-oral examination revealed an extensive swelling with a central area exhibiting a deep ulcer with a yellowish irregular surface affecting the left side of the hard palate (Fig. 1a). Computed tomography (CT) scans revealed a large hyperdense mass obliterating the left maxillary sinus (Fig. 1b). Right kidney and the liver also demonstrated hyperdense nodular images, as well as the lungs, which revealed a large bilateral mass (Fig. 1b).

An incisional biopsy was performed and microscopic exam showed a polymorphous lymphoid infiltration, composed by scattered histiocytes, a large number of small lymphocytes, and few large atypical lymphoid cells presented in an angiocentric and angiodestructive distribution pattern exhibiting large areas of necrosis. Perineural invasion was also easily observed (Fig. 2).

Immunohistochemistry confirmed the lymphoid nature of the disease with a diffuse positivity for LCA. Small T-cells predominated and were demonstrated with CD45RO and CD3 reactions. Many cells were also positive for CD43 (Fig. 3). Macrophages and plasma cells expressed CD68 and VS38c positivity, respectively. Perforin and granzyme cytotoxic granulations were negative, as well as CD56 and CD30. Scattered large atypical B-cells were revealed with CD20 antibody and a slightly more diffuse staining was obtained using CD79a. S100 and CD34 were negative evidencing only normal neural and vascular structures, respectively. Proliferative index measured by Ki67 staining in those areas with a higher number of CD20-positive cells achieved approximately 20% and some of the larger atypical cells were also positive for Ki67. EBER (Epstein–Barr encoding region) in situ hybridization was used to demonstrate EBV presence, which was observed to be restricted to few, predominantly large cells consistent with neoplastic B-cells (Fig. 4). These immunohistochemical findings together with the angiocentric/angiodestructive microscopic features and the patients' clinical presentation led to the diagnosis of LYG and, according to the current WHO grading system, the lesion was classified as LYG grade 2. The patient was referred for oncological therapy, but she died before any treatment could be performed.

Discussion

LYG was first described in 1972 as a lymphoreticular proliferation characterized by a polymorphous lymphocytic infiltrate containing small lymphocytes, plasma cells and atypical lymphoid mononuclear cells [13]. Currently, LYG is understood to be a neoplasm of B-cells driven by EBV, even though T-cells predominate in the infiltrate, in which the neoplastic lymphoid cells form infiltrative nodular lesions and destruction of blood vessels. The term "granulomatosis"

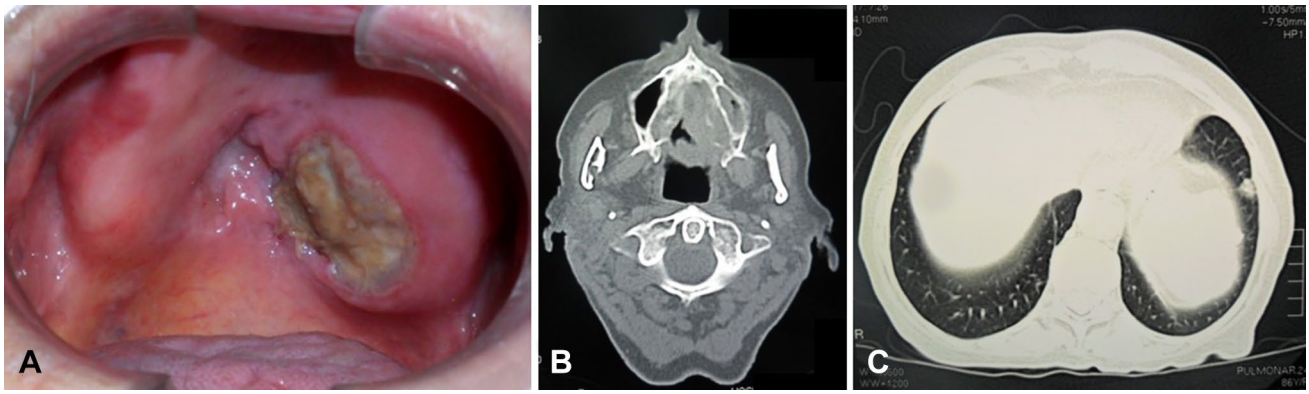

Fig. 1 Intra-oral clinical presentation and pulmonary computed tomography scan of LYG. **a** The patient exhibited a large painful swelling involving the left side of the hard palate, with the central area of the lesion presenting a deep ulcer with an irregular yellowish surface. **b** CT axial section illustrating the involvement of the maxillary sinus by the neoplasm. **c** Pulmonary CT scan revealed a hyperdense bilateral mass

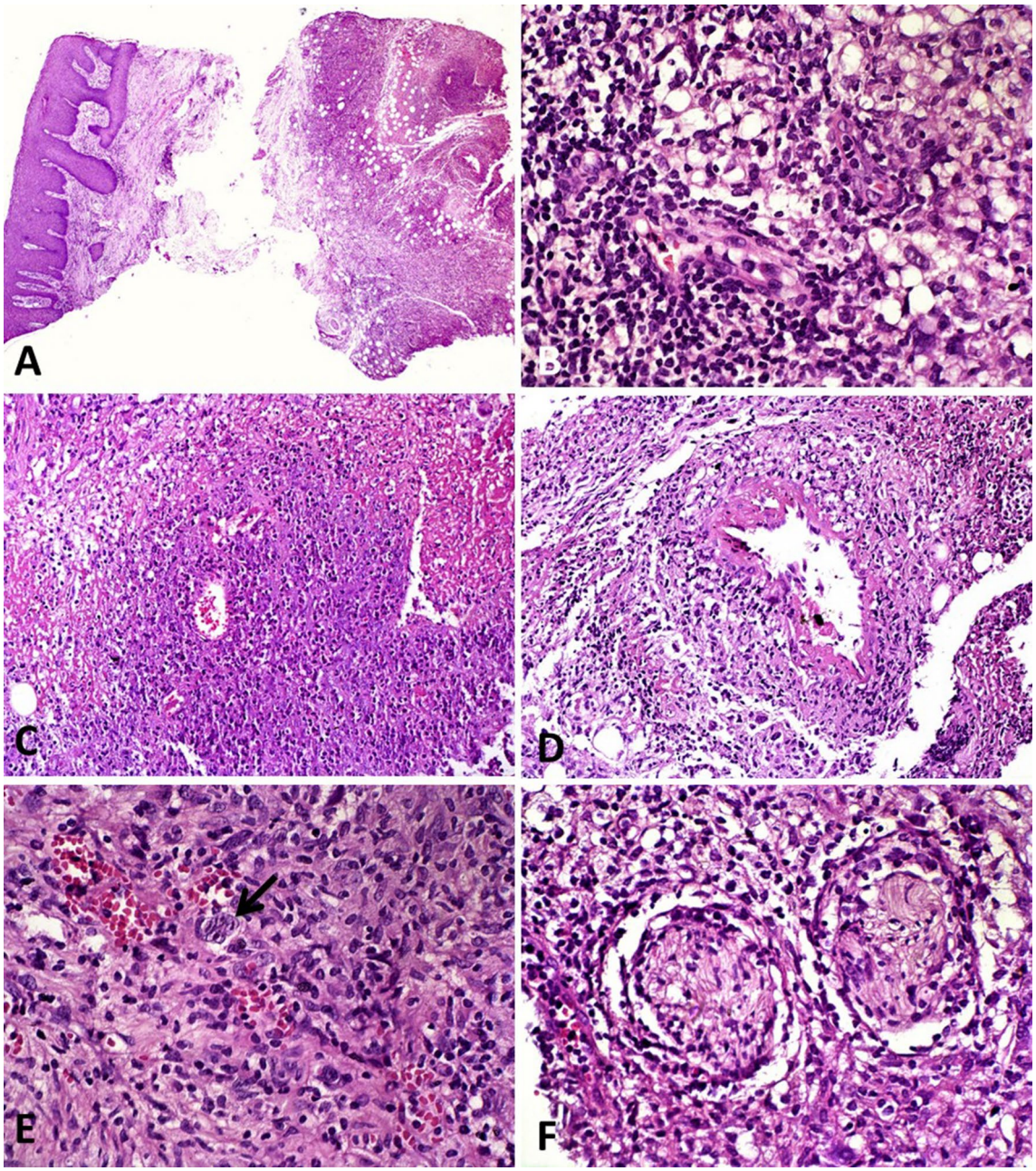

Fig. 2 Microscopic aspect of LYG. **a** Oral mucosa exhibiting lymphoid infiltration in the connective tissue, permeating normal structures (H&E, 25×). **b** The infiltrate consisted predominantly of small lymphoid cells with hyperchromatic nuclei (H&E, 100×). **c** Angiocentric and angiodestructive growth pattern was observed in some areas of the neoplasm. The necrotic background adjacent to the infiltrated and destroyed blood vessels can be seen (H&E, 50×). **d** Higher magnification demonstrating another area of angioinvasion by the atypical lymphoid infiltrate of reactive T-cells and scattered neoplastic B-cells (H&E, 100×). **e** A few atypical large lymphoid cells can be seen as shown by the arrow (H&E, 200×). **f** The atypical infiltrate surrounded small peripheral nerves with invasion into the nerves (H&E, 200×)

refers to the central necrosis of this lymphoid aggregation, and not to a true granulomatous inflammation [12–14].

LYG is diagnosed more commonly in males (male/female ratio 2:1), typically between the fourth and sixth decades of life [15, 16]. Lung involvement is present in virtually all cases more frequently as individual nodules; however, similar to our report, cases describing LYG presenting as large pulmonary masses have also been described [17, 18].

In addition, other organs may also be affected, including the skin, kidneys, central nervous system and liver [19, 20]. As demonstrated in the present report, extra-pulmonary LYG

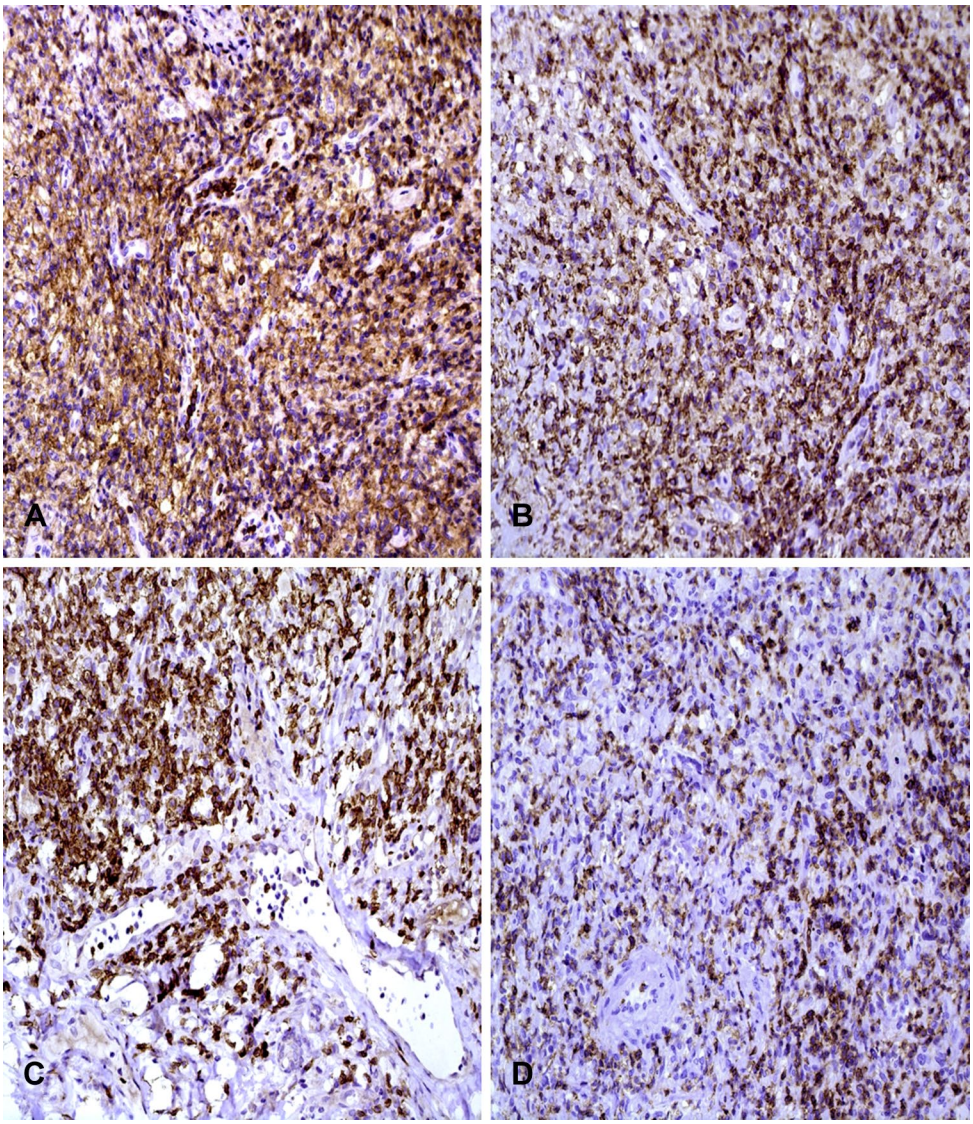

Fig. 3 Immunohistochemical features of LYG. **a** The lymphoid nature of the neoplasm was initially demonstrated with positivity to LCA (DAB, 100×). **b** T-cells predominated in the lesion as shown by positive reactions to CD45RO (DAB, 100×) and **c** CD3 that were also strongly positive around the blood vessels (DAB, 100×). **d** Positive reaction against CD43 was also found (DAB, 100×)

is typically observed in conjunction with lung involvement, although it may rarely be diagnosed as isolated diseases [14].

Clinical features of LYG are usually related to the respiratory tract and include cough, dyspnea and chest pain; other non-specific symptoms are common, including fever, malaise, weight loss, fatigue and arthralgia. Diagnosis may be difficult, resulting in delayed treatment of the patients [14, 21].

Oral cavity involvement by LYG has been rarely reported and Table 1 summarizes the main clinicopathological features described previously. Only in two cases, as also shown in the current report, female patients were affected [22, 23]. The mean age of the patients reported with oral involvement was 55.2 years old, even though the youngest patient reported was 15 years old [22]. Unusual clinical symptoms included headache, nasal congestion, dysphonia [23], hoarseness, labial and eyelid edema [24], haemoptysis [11], epistaxis [24] and jaw pain [11, 25]. Hard palate and gingival mucosa were the most affected intra-oral sites [11, 23, 25, 26]. Other case reports that mentioned oral cavity involvement did not specify the affected sites, presenting them as "multiple oral ulcerations" or other similar terms [12, 22, 24, 27]. Although there have been few reports of LYG with oral involvement, it is hypothesized that oral manifestations, as also believed for the involvement of other extra-pulmonary tissues, seems to represent a component of the disease spreading process, although skin lesions may precede the development of lung lesions in 10–15% of the patients [16].

Histological hallmarks of LYG include an angiocentric and angioinvasive T-cell predominant infiltration into vascular walls, associated with variable extents of tissue necrosis. Atypical CD20-positive neoplastic B-cells are EBV-positive [16, 20]. Differential diagnosis of LYG includes multisystem

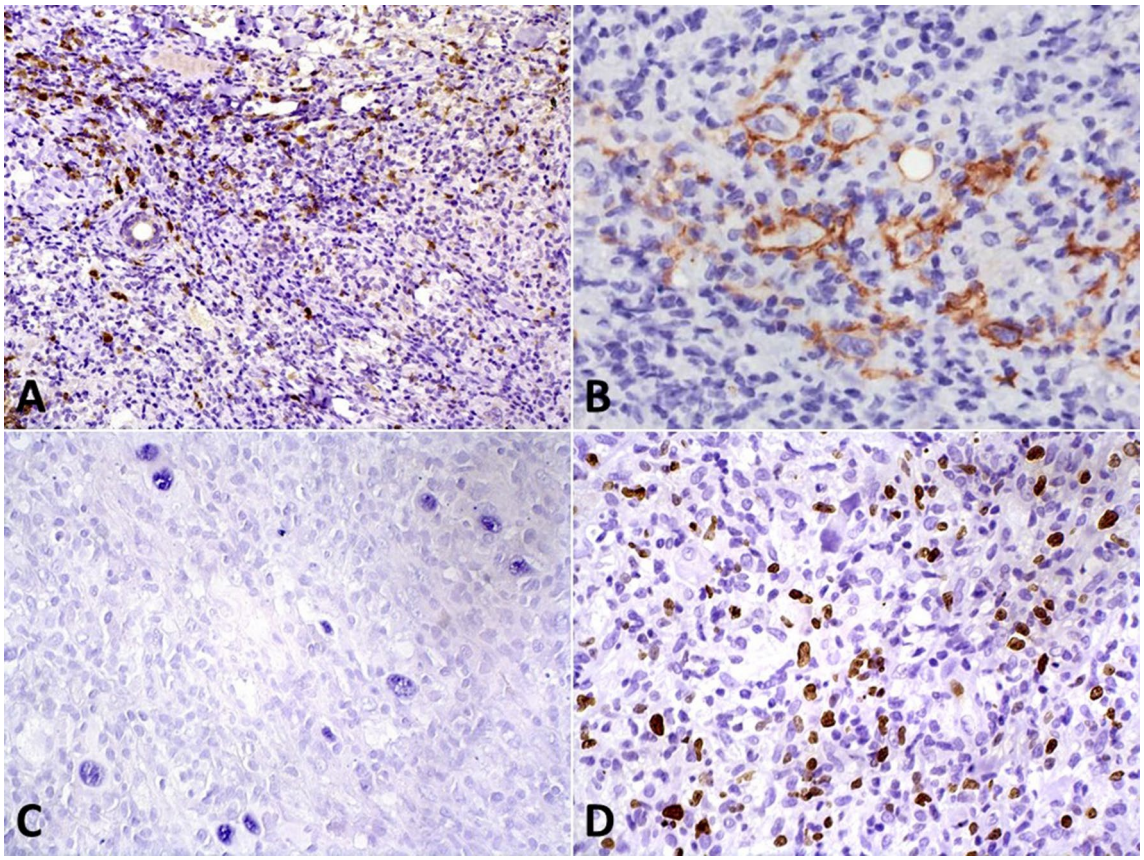

Fig. 4 Immunohistochemical features of LYG. **a** Neoplastic B-cells were a minor component of the lesion and presented as both large atypical and small cells, as shown by CD20 reaction (DAB, 100×). **b** Under higher magnification we can identify few large atypical B-cells staining positively for CD20 (DAB, 400×). **c** EBER in situ hybridization confirmed that EBV-positive neoplastic cells were large, atypical and scarce (EBER, in situ hybridization for EBV, 400×). **d** Proliferative index measured by Ki67 expression achieved approximately 20% in the regions containing a higher number of CD20 positive cells. It was observed that some of the large atypical neoplastic cells were also positive for Ki67 (DAB, 200×)

disorders (e.g., Wegener granulomatosis), and EBV-associated B-cell lymphoproliferative disorders, such as post-transplant lymphoproliferative disorder, HL, EBV-positive DLBCL not otherwise specified (NOS), and particularly T-cell or NK-cell lymphomas (e.g., extra-nodal NK/T-cell lymphoma, nasal type, and peripheral T-cell lymphoma, NOS) [9, 15, 20].

LYG grading is based on the proportion of large atypical EBV-positive B-cells and necrosis, in relation to the background of T-cells [14]. Grade 1 lesions contain few atypical lymphoid cells, rare EBV-positive cells (less than 5 in high-power field), and focal or no areas of necrosis [11]. Grade 2 tumors present an increased number of large atypical B-cells, EBV-positive cells are readily identified (from 5 to 50 in high-power field), and areas of necrosis are commonly observed [15, 16]. Grade 3 lesions show numerous atypical cells, EBV-positive cells are abundant (more than 50 cells in high-power field), and areas of necrosis are extensive [11, 14]. Lesions that exhibit confluent sheets of atypical EBV-positive B-cells and lacking polymorphous inflammatory infiltrate may be better diagnosed as EBV-positive DLBCL and should not be classified as LYG [16].

LYG is most commonly diagnosed in patients with evidence of immune dysregulation or immunodeficiency [20]. It has been reported in conjunction with autoimmune diseases, such as Sjögren syndrome, rheumatoid arthritis, sarcoidosis, and ulcerative colitis [14, 15]. LYG lesions may also occur in the setting of HIV, and in patients submitted to immunosuppression therapy [17, 21]. Immunosurveillance is often defective, as evidenced by low CD4 and CD8 T cells count at diagnosis [14, 28]. Although the incidence of LYG is increased in patients with evident immunodeficiency, other patients with LYG may not present an evident pre-existing condition, as demonstrated in our report [23].

EBV infection has been associated with some malignancies, including nasopharyngeal carcinoma and Burkitt's lymphoma. It is also involved in the pathogenesis of various lymphoproliferative disorders with a broad spectrum

Table 1 Clinical features of LYG with oral involvement previously reported in the literature

Authors	Gender	Age	Oral involvement site	Other involvement sites	Clinical features
Current case (2018)	Female	86	Left maxillary alveolar ridge and hard palate	Lungs, left maxillary sinus, and right kidney	Dysphagia, oral pain, fever, and lethargy
Higashi et al. [12]	Male	79	Multiple oral ulcers	Skin lumbar region	Not present/not informed
Cargini et al. [11]	Male	65	Anterior lower gingiva	Lungs, right axillary fossae, and peri-iliac veins	Persistent pain in the inferior oral fornix and the symphysis mandibular region, and haemoptysis
Alinari et al. [25]	Male	82	Left posterior mandibular ridge	Thoracic lymph nodes	Progressive jaw pain, weight loss, and progressive fatigue
Ammannagari et al. [27]	Male	44	Multiple oropharyngeal ulcers	Lungs and scalp	Cough and dyspnoea
Shanti et al. [23]	Female	32	Hard palate	Lungs	Intermittent dry cough, dysphonia, nasal congestion, and headache
Diez et al. [22]	Female	15	Multiple oral ulcerations	Lungs, skin, liver, and spleen	Fever, dry cough, odynophagia, asthenia, and thoracic pain
Torrelo et al. [24]	Male	40	Recurrent oral ulcers and lips	Lungs, right maxillary sinus, and eyelids	Labial and eyelid oedema, hoarseness, dyspnoea, epistaxis, fever, and weight loss
Cabane et al. [26]	Male	54	Hard palate, buccal mucosa, lingual frenulum, tonsil, the pharynx, gingiva, and lower lip	Not present/not informed	Cardiac rhythm disturbances

of behaviour, like EBV-positive mucocutaneous ulcer, EBV-positive DLBCL, extranodal NK/T-cell lymphoma of nasal type, and LYG [28, 29]. The mechanism of EBV infection is speculated to be associated with an immune deficiency of the host to suppress the virus control [29].

LYG management is challenging and depends on the grade of the disease, since the course of the neoplasm is highly variable; most patients progress to an advanced stage with a median survival of less than 2 years, and for patients who present multiorgan involvement the prognosis is usually poor [16]. Various chemotherapy combinations indicated for lymphomas, such as cyclophosphamide, vincristine and prednisone (CVP), cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) combined with rituximab (R-CVP and R-CHOP) have been used for LYG, especially in grade 2 and 3 cases [15, 30, 31]. Some achievement has also been reported with interferon alfa-2b in cases of lower-grade LYG [15, 28].

In summary, LYG is an uncommon EBV-associated B-cell lymphoproliferative neoplasm that predominantly affects the lungs, but that may also be diagnosed in other sites. Oral involvement of LYG is extremely rare and usually represents the pulmonary spread of the disease. Given its unspecific symptoms and histological similarity with other entities, the diagnosis of LYG should be rendered with careful clinical, histological and immunohistochemical evaluation, since the treatment depends on the accurate diagnosis and grading.

Acknowledgements This study was supported by grants of the São Paulo State Research Foundation (FAPESP) Process Number 2017/14880-3.

Compliance with Ethical Standards

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

References

1. Szumera-Ciećkiewicz A, Gałązka K, Szpor J, Rymkiewicz G, Jesionek-Kupnicka D, Gruchała A, Ziarkiewicz-Wróblewska B, Poniatowska-Broniek G, Demczuk S, Prochorec-Sobieszek M. Distribution of lymphomas im Poland according to World Health Organization classification: analysis of 11718 cases from National Histopathological Lymphoma Register project—the Polish Lymphoma Research Group study. Int J Clin Exp Pathol. 2014;7(6):3280–6.
2. Kemp S, Gallagher G, Kabani S, Noonan V, O'Hara C. Oral non-Hodgkin lymphoma: review of the literature and World Health Organization classification with reference to 40 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Oral Endod. 2008;105:194–201.
3. Bhattacharyya I, Chehal HK, Cohen DM, Al-Quran SZ. Primary diffuse large B-cell lymphoma of the oral cavity: germinal center classification. Head Neck Pathol. 2010;4:181–91.
4. Triantafilidou K, Dimitrakopoulos J, Iordanidis F, Gkagkalis A. Extranodal non-Hodgkin lymphomas of the oral cavity and maxillofacial region: a clinical study of 58 cases and review of the literature. J Oral Maxillofac Surg. 2012;70:2776–85.

5. Roschewski M, Staudt LM, Wilson WH. Diffuse large B-cell lymphoma—treatment approaches in the molecular era. Nat Rev Clin Oncol. 2014;11:12–23.
6. Deng D, Wang Y, Liu W, Qian Y. Oral and maxillofacial non-Hodgkin lymphomas—case report with review of literature. Medicine. 2017;96(35):1–9.
7. Kolokotronis A, Konstantinou N, Christakis I, Papadimitriou P, Matiakis A, Zaraboukas T, Antoniades D. Localized B-cell non-Hodgkin's lymphoma of oral cavity and maxillofacial region: a clinical study. Oral Surg Oral Med Oral Pathol Oral Radiol Oral Endod. 2005;99:303–10.
8. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, Advani R, Ghielmini M, Salles GA, Zelenetz AD, Jaffe ES. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375–90.
9. Hsi ED. 2016 WHO Classification update—What's new un lymphoid neoplasms. Int J Lab Hematol. 2017;39:14–22.
10. Murthy SL, Hitchcock MA, Endicott-Yazdani TR, Watson JT, Krause JR. Epstein–Barr virus-positive diffuse large B-cell lymphoma. In Baylor University Medical Center Proceedings; 2017. p. 443–444.
11. Cargini P, Civica M, Sollima L, Di Cola E, Pontecorvi E, Cutilli T. Oral lymphomatoid granulomatosis, the first sign of a "rare disease": a case report. J Med Case Rep. 2014;8(152):1–5.
12. Higashi Y, Yoshioka T, Kwai K, Fujii K, Yoshimitsu M, Kusuyama J, Shima K, Tanimoto A, Kanekura T. Lymphomatoid granulomatosis initially presenting as ulcerated subcutaneous and muscle lesions without pulmonary involvement. J Dermatol. 2017;44(5):e107–e108.
13. Mosqueda-Taylor A, Meneses-Garcia A, Zarate-Osorno A, Rivera LMRG, Ochoa-Carrillo FJ, Mohar-Betancourt A. Angiocentric lymphomas of the palate: clinico-pathological considerations in 12 cases. J Oral Pathol Med 1997;26:93–7.
14. Roschewski M, Wilson WH. Lymphomatoid granulomatosis. Cancer J. 2012;18:469–74.
15. Katzenstein ALA, Doxtader E, Narendra S. Lymphomatoid granulomatosis—insights gained over 4 decades. Am J Surg Pathol. 2010;34:e35–e38.
16. Rysgaard CD, Stone MS. Lymphomatoid granulomatosis presenting with cutaneous involvement: a case report and review of the literature. J Cutan Pathol. 2015;42:188–93.
17. Bartosik W, Raza A, Kalimuthu S, Fabre A. Pulmonary lymphomatoid granulomatosis mimicking lung cancer. Interact CardioVasc Thorac Surg. 2012;14(5):662–4.
18. Hadid W, Rifai D, David O, Sadikot RT. A woman in her 40 s with AIDS and lung mass. Chest. 2014;145(1):173–7.
19. Jaffe ES. Lymphoid lesions of the head and neck: a model of lymphocyte homing and lymphomagenesis. Mod Pathol. 2002;15(3):255–63.
20. Song JY, Pittaluga S, Dunleavy K, Grant N, White T, Jiang L, Davies-Hill T, Raffeld M, Wilson WH, Jaffe ES. Lymphomatoid granulomatosis—a single institute experience. Pathologic findings and clinical correlations. Am J Surg Pathol. 2015;39:141–56.
21. Pittaluga S, Wilson WH, Jaffe ES. Lymphomatoid granulomatosis. In: Swerdlow SH, Campo E, Harris NL, editors. WHO classification of tumours of the haematopoietic and lymphoid tissues. Vol. 4. Lyon: IARC; 2008. p. 247–9.
22. Diez JSJ, Hernández-Pérez B, De Paula JMP, Ortega EO. Granulomatosis linfomatoidea: caso clínico de uma enfermedad infrecuente com uma presentación infrecuente. Revista Clínica Española. 2000;200(8):461–3.
23. Shanti RB, Torres-Cabala CA, Jaffe ES, Wilson WH, Brahim JS. Lymphomatoid granulomatosis with involvement of the hard palate: a case report. J Oral Maxillofac Surg. 2008;66:2161–3.
24. Torrelo A, Martin M, Rocamoral A, Allegue F, Ledo A. Lymphomatoid granulomatosis presenting as angioedema. Postgrad Med J. 1992;68:366–8.
25. Alinari L, Pant S, McNamara K, Kalmar JR, Marsh W, Allen CM, Baiocchi RA. Lymphomatoid granulomatosis presenting with gingival involvement in an imune competente elderly male. Head Neck Pathol. 2012;6:496–501.
26. Cabane J, Godeau P, Chomette G, Auriol M, Szpirglass H, Raphae M. Granulomatose lymphomatoïde buccale. Rev Med Interne. 1990;11:69–72.
27. Ammannagari N, Srivali N, Price C, Ungprasert P, Leonardo J. Lymphomatoid granulomatosis masquerading as pneumonia. Ann Hematol. 2013;92:981–3.
28. Eminger LA, Hall LD, Hesterman KS, Heymann WR. Epstein–Barr virus: dermatologic associations and implications—Part II. Associated lymphoproliferative disorders and solid tumors. J Am Acad Dermatol. 2015;72:21–34.
29. Castillo JJ, Beltran BE, Miranda RN, Young KH, Chavez JC, Sotomayor EM. EBV-positive diffuse large B-cell lymphoma of the elderly: 2016 update on diagnosis, risk-stratification, and management. Am J Hematol. 2016;91(5):529–37.
30. Jung KH, Sung HJ, Lee JH, Lee KY, Shin JS, Kim KM, Kim YS, Shin C, Kim JH. A case of pulmonary lymphomatoid granulomatosis successfully treated by combination chemotherapy with Rituximab. Chemotherapy. 2009;55:386–90.
31. Gangar P, Venkatarajan S. Granulomatous lymphoproliferative disorders—granulomatous slack skin and Lymphomatoid granulomatosis. Dermatol Clin. 2015;33:489–96.