Mantle cell lymphoma involving the oral and maxillofacial region: a study of 20 cases

Marcus Vinícius Ribeiro Carvalho [1], Carla Isabelly Rodrigues-Fernandes [1], Cinthia Veronica Bardález López de Cáceres [1], Ricardo Alves Mesquita [2], Manoela Domingues Martins [3], Elena María José Román Tager [4], Roman Carlos [5], Fábio Ramôa Pires [6], Liam Robinson [7], Willie F P van Heerden [7], Vitor Bonetti Valente [8], José Cândido Caldeira Xavier-Júnior [9], Daniel Galera Bernabé [8], Hélder Antônio Rebelo Pontes [10], Ciro Dantas Soares [11], Mauro Henrique Melo da Costa [12], Pablo Agustin Vargas [13], Felipe Paiva Fonseca [14]

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

[2] Department of Oral Surgery and Pathology, School of Dentistry, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil.

[3] Department of Oral Pathology, School of Dentistry, Federal University of Rio Grande do Sul, Porto Alegre, Brazil.

[4] Department of Oral Diagnosis, Piracicaba Dental School, University of Campinas, Piracicaba, Brazil; Pathology Section, Centro Clínico de Cabeza y Cuello/Hospital Herrera Llerandi, Guatemala City, Guatemala.

[5] Pathology Section, Centro Clínico de Cabeza y Cuello/Hospital Herrera Llerandi, Guatemala City, Guatemala.

[6] Oral Pathology, Dental School, Rio de Janeiro State University, Rio de Janeiro, Brazil.

[7] Department of Oral Pathology and Oral Biology, School of Dentistry, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa.

[8] Oral Oncology Center, São Paulo State University (UNESP), School of Dentistry, Araçatuba, Brazil.

[9] Pathology Institute of Araçatuba and School of Medicine, Centro Universitário Católico Unisalesiano Auxilium, Araçatuba, Brazil.

[10] Oral Pathology Service, João de Barros Barreto University Hospital, Federal University of Pará, Belém, Brazil.

[11] Getúlio Sales Diagnósticos, Natal, Brazil.

[12] Private practice, Campinas, Brazil.

[13] Department of Oral Diagnosis, Piracicaba Dental School, University of Campinas, Piracicaba, Brazil; Department of Oral Pathology and Oral Biology, School of Dentistry, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa.

[14] Department of Oral Diagnosis, Piracicaba Dental School, University of Campinas, Piracicaba, Brazil; Department of Oral Surgery and Pathology, School of Dentistry, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil; Department of Oral Pathology and Oral Biology, School of Dentistry, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa. Electronic address: Felipepfonseca@hotmail.com.

Abstract

Objective: To investigate the clinicopathologic features of mantle cell lymphoma (MCL) involving the oral and maxillofacial region.

Methods: The MCL cases were retrieved from the pathosis database of 6 pathology laboratories. Original hematoxylin and eosin slides and immunohistochemical reactions were reviewed for confirmation of the initial diagnosis. Clinical data of the cases were obtained from the patients' pathosis and/or medical charts.

Results: Twenty cases were included in the study, showing a male predominance and a mean age of 66 years. The oral cavity (12 cases) and the oropharynx (5 cases) were the most commonly involved subsites. Most cases presented as asymptomatic swellings, with 2 cases showing bilateral involvement of the palate. The classic histologic variant predominated (12/20 cases). All cases expressed CD20 with nuclear cyclin D1 positivity. SOX11 was seen in 9/13 cases, CD5 in 6/16 cases, Bcl2 in 16/19 cases, CD10 in 2/20 cases, and Bcl6 in 4/16 cases. Ki67 showed a mean proliferation index of 40.6%. The Epstein-Barr virus (EBV) was negative in all cases investigated. Follow-up data was available for 7 patients, with 5 currently alive and 2 deceased.

Conclusion: Mantle cell lymphoma, albeit rare, may manifest in the oral and maxillofacial region. Its histologic heterogeneity demands a high degree of diagnostic skill from pathologists.

Statement of Clinical Relevance

Oral and maxillofacial mantle cell lymphoma is rare, demands a broad immunohistochemical analysis, including cyclin D1 and SOX11 expression, and must prompt clinicians and pathologists to investigate the possibility of a leukemic manifestation of the disease.

Mantle cell lymphoma (MCL) is a heterogeneous hematolymphoid neoplasm that represents 6% to 10% of all non-Hodgkin lymphomas. It accounted for approximately 3,320 new cases diagnosed in Western countries in 2016, representing 4% of all lymphoid malignancies in the US and 7% to 9% in Europe.[1,2] Older men are the most commonly affected patients, with lymph nodes being the most affected location. The neoplasm frequently manifests as a disseminated disease, usually associated with a poor prognosis, although rarer clinical variants may be associated with a better outcome.[1,3]

Mantle cell lymphoma is histologically complex and may be composed of a monotonous proliferation of small-sized cells (classic and small cell/lymphocytic variants) or intermediate to large cells with abundant mitoses (blastoid variant), with the presence of pleomorphism and prominent nucleoli in some cases (pleomorphic variant).[4,5] This heterogeneous morphology often complicates the diagnosis, demanding a high degree of diagnostic skill from pathologists. The molecular pathogenesis of MCL aids in its diagnosis, because this neoplasm is consistently associated with the t(11; 14) (q13; q32) that leads to strong nuclear expression of cyclin D1 protein in neoplastic B cells, representing the hallmark oncogenic event of this

neoplasm.[5] However, rare cases (<5%) may not express cyclin D1, and in such cases, the expression of SOX11 contributes to the final diagnosis.[2]

In the head and neck region, its prevalence ranges from 1% to 10% of all non-Hodgkin lymphomas. However, cases affecting the oropharynx, major salivary glands, and oral cavity are considered exceedingly rare.6, 7, 8, 9, 10 Therefore, the aim of this study was to investigate the clinicopathologic and immunohistochemical features of an original series of extranodal MCL affecting the head and neck, especially the oral and maxillofacial region.

MATERIAL AND METHODS

Ethics statement

This study was conducted following approval by the Ethical Committee of the Piracicaba Dental School, University of Campinas, Piracicaba, Brazil (process no. 44647421.1.0000.5418). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Sample and data collection

All cases diagnosed as MCL affecting the oral and the maxillofacial region were retrieved from pathosis database of the Universidade Federal de Minas Gerais (Belo Horizonte/Brazil), University of Campinas (Piracicaba/Brazil), Rio de Janeiro State University (Rio de Janeiro/Brazil), Private Pathology Service (Natal/Brazil), Pathology Institute of Araçatuba (Araçatuba/Brazil), University of Pretoria (Pretoria/South Africa), and Centro Clínico de Cabeza y Cuello (Guatemala City/Guatemala). To carry out this search process, the term "mantle cell lymphoma" was used. The original hematoxylin and eosin (H&E) and immunohistochemistry slides and/or the formalin-fixed paraffin-embedded tissues of all cases were obtained for histopathologic review by ≥2 pathologists (oral pathologist and hematopathologist) using the current World Health Organization guidelines for the classification of Tumors of Hematopoietic and Lymphoid Tissues.[4] Additional immunohistochemical reactions were done always that necessary to confirm the diagnosis of MCL. The clinicopathologic data of the cases were obtained from the patients' pathosis and/or medical charts, including sex, age, location of the lesion(s), clinical presentation, and status of the patient at their last follow-up appointment.

Immunohistochemistry

Immunohistochemical reactions were performed on 3 µm sections of the formalin-fixed paraffin-embedded tissues, which were dewaxed with xylene and rehydrated in an ethanol series. The endogenous peroxidase activity was blocked using 10% hydrogen peroxide in a single bath for a duration of 15 minutes. Antigen retrieval was performed via pressure cooker heating with either Tris-HCl (pH 6.0) or Ethylenediamine tetraacetic acid (EDTA) (pH 9.0) solutions for 3 minutes. After washing with a Phosphate **Buffered** Saline (PBS) buffer (pH 7.4), the slides were incubated overnight with the following primary antibodies: CD20 (clone L26, dilution 1: 300; Dako, Carpinteria, CA, USA), CD3 (polyclonal, dilution, 1: 300; Dako), CD5

(clone CD5/54/F6, dilution, 1: 100; Dako), cyclin D1 (clone DCS-6, dilution 1: 100; Dako), SOX11 (clone CLO143, dilution 1: 200; Sigma-Aldrich, St. Louis, MO, USA), Bcl2 (clone 124, dilution 1: 50; Dako), Bcl6 (clone D-8, dilution 1: 300; Santa Cruz, Santa Cruz, CA, USA), CD10 (clone 56C6, dilution 1: 100; Dako), and Ki67 (clone MIB-1, dilution 1: 100; Dako). The slides were subsequently exposed to highly sensitive horseradish peroxidase reagents (ADVANCE; Dako) and diaminobenzidine tetrahydrochloride (Sigma-Aldrich). Finally, the slides were counterstained with Carazzi hematoxylin for 3 minutes. Positive control sections were used for each antibody, whereas the negative control was obtained by omitting the specific primary antibody. The reactions were jointly evaluated by 3 oral and maxillofacial pathologists and descriptively described for each marker, except for Ki67 whose positivity was obtained by counting the percentage of positive nuclei among 1000 cells in representative hotspot regions under higher magnification.

In situ Hybridization

The presence of EBV was also investigated by in situ hybridization (ISH) in several cases as part of the workflow protocol for lymphoma diagnosis, especially cases composed of intermediate to large cells (aggressive microscopic variants). A fluorescein-labeled peptide nucleic acid probe complementary to 2 nuclear-encoded RNAs Epstein-Barr virus (EBV)-encoded small RNA (EBER) (Y5200; Dako) was hybridized at 55°C for 90 minutes, following which labeling was performed using the peptide nucleic acid probe ISH detection kit (K5201; Dako). A single case of extranodal NK/T-cell lymphoma, nasal type, was used as a positive control. Carazzi hematoxylin was used for subsequent counterstaining. Cases were considered positive for EBV if dark blue staining was detected in the nuclei of the neoplastic cells.

Statistics

A descriptive analysis was performed, with the categorical variables presented as absolute number and percentage, whereas the continuous variables were presented as mean, standard deviation, and range. SPSS software version 22.0 (IBM SPSS, Inc., Armonk, NY) was used for the statistical analyses.

RESULTS

A total of 20 cases of extranodal MCL affecting the oral and maxillofacial region were retrieved. The clinicopathologic features of this sample are summarized in Table I. There was a male predominance (15 males: 5 females) with a male-to-female ratio of 3: 1, and a mean age of 66 years (range 38 to 95 years). Patients reported a disease duration ranging from 2 to 6 months before seeking medical consultation. The oral cavity was affected in 12 cases and the oropharynx in 5 cases. The parotid gland, nasopharynx, and nasopharynx were each affected in 1 case. Bone destruction was observed in 2 cases, whereas a single case showed extension to involve the maxillary sinus. In 4 cases, patients also demonstrated other clinical manifestations including lymphadenopathy (2 cases) and peripheral blood involvement (2 cases). An asymptomatic swelling was the most common clinical presentation, occasionally manifesting as bilateral or multiple synchronous tumors (Figure 1). Six cases presented with ulceration, although nonulcerated smooth-surfaced tumors were also noted.

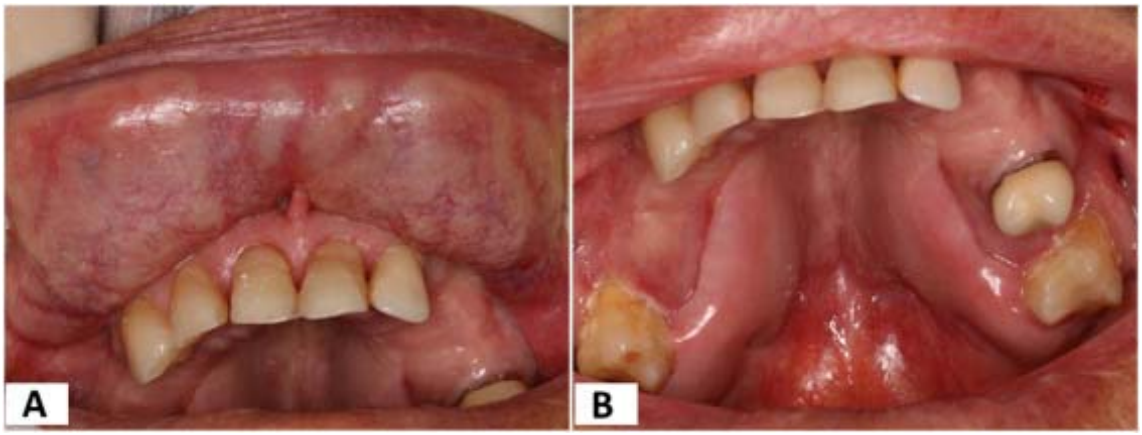

Fig. 1. Clinical manifestation of mantle cell lymphoma. **(A)** Multiple asymptomatic swellings in the oral cavity in case #4. The upper lip was diffusely affected. **(B)** The patient also presented a bilateral manifestation of the disease in the palate as soft, normal-colored asymptomatic swellings.

Histologically, all cases presented with a diffuse growth pattern. Twelve cases were classified as the classic variant of MCL (Figures 2, *A* and *B*), where the neoplastic cells were small with irregular or cleaved nuclei and inconspicuous nucleoli, diffusely infiltrating the affected tissues. Scattered eosinophilic macrophages were identified, but in the absence of a so-called "starry sky" pattern. Mitotic figures were uncommon and necrosis was absent. Five cases were classified as the blastoid variant of MCL (Figures 2, *C* and *D*), containing small to intermediate-sized neoplastic cells with dispersed or condensed chromatin and prominent nucleoli. Macrophages were also noted, again without the "starry sky" pattern. Necrosis was seen focally in 1 case, and mitotic figures were more easily identified in the blastoid variant. Three cases were defined as the pleomorphic variant of MCL (Figures 2, E and *F*), given the prominent nucleoli, the extent of cytologic atypia, and the abundant atypical mitotic figures.

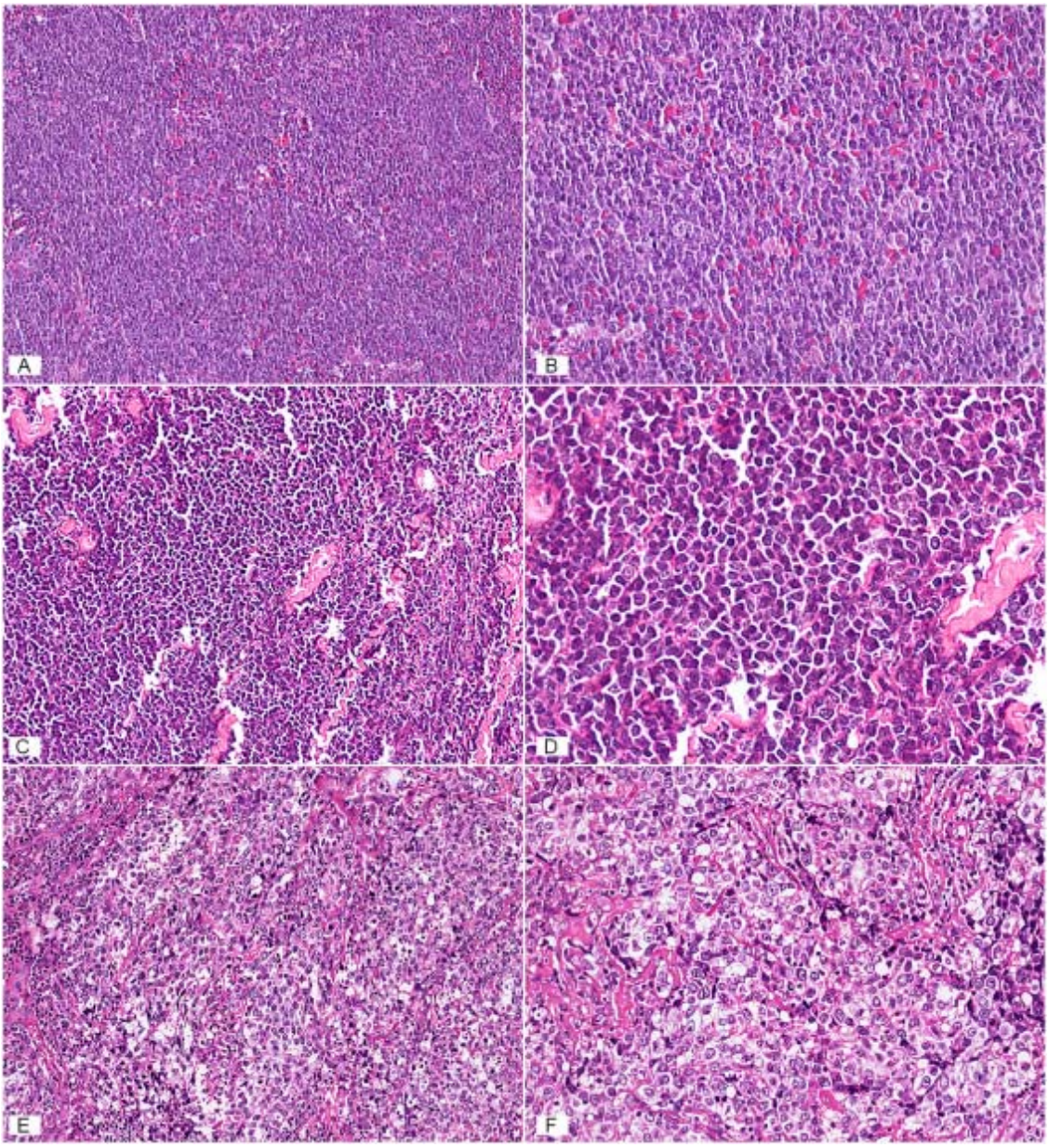

Fig. 2. Microscopic presentation of mantle cell lymphoma affecting the oral and the maxillofacial region. **(A)** Classic variant characterized by a diffuse and monotonous proliferation of small-sized neoplastic cells (hematoxylin and eosin [H&E]; 100 ×). **(B)** Neoplastic cells in the classic variant present as small centrocytes with irregular nuclear contours and inconspicuous nucleoli (H&E; 200 ×). **(C)** Blastoid variant characterized by a proliferation of intermediate-sized neoplastic cells (H&E; 100 ×). **(D)** Higher magnification reveals easily discernable nucleoli and scattered mitotic figures (H&E; 400 ×). **(E)** Pleomorphic variant showing a diffuse and infiltrative growth pattern, with many large, atypical neoplastic cells and mitotic figures (H&E; 100 ×). **(F)** Neoplastic cells with abundant pale to clear cytoplasm and prominent nucleoli with numerous mitotic figures (H&E; 200 ×).

The results of immunohistochemical reactions are detailed in Table II. All cases were strong and diffusely positive for CD20 (Figure 3A), whereas CD3 was negative in the neoplastic cells in all cases. CD5 was only expressed in 6/16 cases (Figure 3B). All cases showed strong nuclear positivity for cyclin D1 (Figure 3C). Bcl2 expression was seen in 16/19 cases (Figure 3D), and

neoplastic cells were rarely positive for germinal center markers such as Bcl6 (4/16) and CD10 (2/20), with no cases showing positivity for both markers simultaneously. SOX11 was expressed in 9/13 cases (69.2%) (Figure 3E). Ki67 expression showed a mean value of 40.6% (range from 15% to 90%) (Figure 3F). All 11 cases investigated for the presence of EBV via ISH were negative.

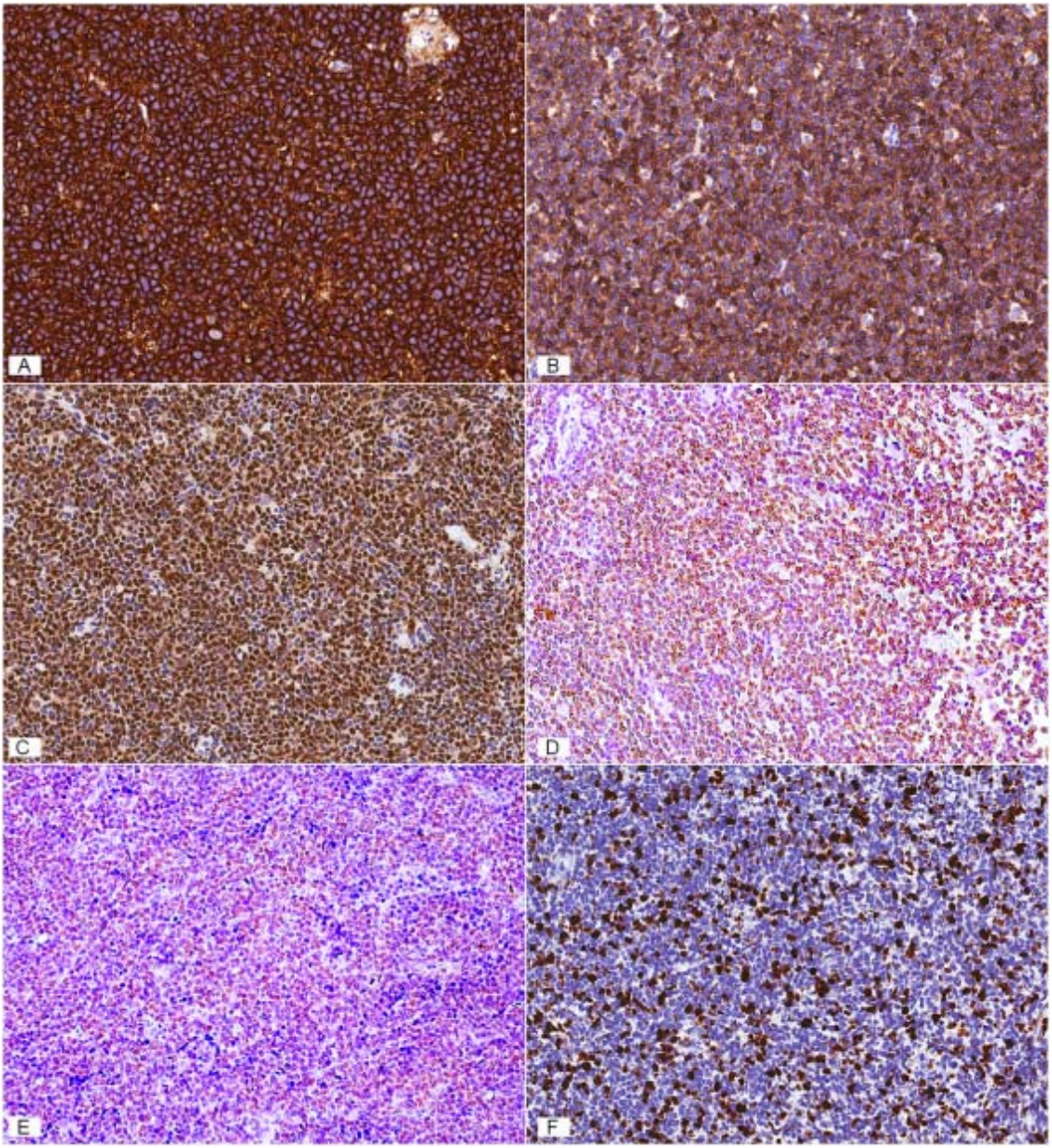

Fig. 3. Immunohistochemical findings of this mantle cell lymphoma series. (**A)** CD20 showed strong and diffuse positivity in all cases (diaminobenzidine tetrahydrochloride [DAB]; 200 ×). **(B)** CD5 positivity was observed in 6 cases, presenting as diffuse membranous staining of the neoplastic cells (DAB; 200 ×). **(C)** Nuclear cyclin D1 positivity was present in all cases (DAB; 200 ×). **(D)** Bcl2 showed cytoplasmic positivity in most of the cases (DAB; 200 ×). **(E)** Nuclear SOX11 positivity was observed in nine out of 13 cases investigated (DAB; 200 ×). **(F)** Ki67 showed a high proliferative index in a blastoid variant of MCL (DAB; 100 ×).

Data on therapy was scarcely available; with 2 patients receiving the Rituximab, Cyclophosphamide, Doxorubicin Hydrochloride (Hydroxydaunomycin), Vincristine Sulfate (Oncovin) and Prednisone (R-CHOP) regimen and 1 patient receiving Cyclophosphamide, Doxorubicin Hydrochloride (Hydroxydaunomycin), Vincristine Sulfate (Oncovin) and Prednisone (CHOP) therapy alone. Follow-up data were available for 7 cases, ranging from 1 to 69 months, demonstrating that 5 patients were alive and 2 deceased, 1 of them after the first cycle of chemotherapy and 1 due to unknown reason.

DISCUSSION

Mantle cell lymphoma is a mature B-cell lymphoma with increasing trends in the USA and Europe.[3,11, 12, 13, 14] Lymph nodes are typically the most commonly affected sites for MCL. Extranodal involvement is rarer but may also be found, more usually in the gastrointestinal tract and the head and neck region, which account for 39.7% and 39.1% of all extranodal cases, respectively.[11] Recently, the oropharynx was demonstrated to be the most affected subsite (66%) in the head and neck, whereas the oral cavity was only involved in 8.4% of the cases.[12] The current series further contributed to the understanding of oral and maxillofacial MCL by describing the clinicopathologic features of primary lesions and manifestations of an already leukemic condition. However, we have not reviewed all lymphoma cases diagnosed in the services included in this study, which could possibly lead to the inclusion of additional cases.

Patients with MCL usually present in their sixth to seventh decades of life, with a median age of 70 years.[3,14] This is in accordance with the current series and has also been previously documented for head and neck cases. Males predominate in most of the reported series,[1,15] a feature also documented in the current sample. Cases involving the oral cavity usually present as asymptomatic nonulcerated swellings, with the palate being the most affected subsite.[10,16,17] Two of our cases presented as diffuse bilateral swellings, 1 of which also showed simultaneous involvement of the upper lip. Both cases represented a late manifestation of leukemic disease. Kamel et al.[18] described 71.9% of nodal MCLs affecting multiple sites. In addition, previous reports have also described nonulcerated oral lesions affecting multiple subsites, including the palate bilaterally.[6]

Mantle cell lymphoma is histologically diverse and the current World Health Organization classification of lymphoid tumors recognizes several histologic variants.[4] Although the majority of cases are classified as the classic variant, characterized by small monotonous neoplastic cells, cases composed of larger or pleomorphic cells (blastoid or pleomorphic variants) may also be found.[19] The histologic heterogeneity of MCL results in a broad diagnostic category with a high degree of suspicion required from the pathologist in addition to ancillary tests to reach a final diagnosis. This is exemplified in the current series containing classic, blastoid, and pleomorphic variants.[20] When small to medium-sized neoplastic cells predominate, Chronic lymphocytic leukemia/Small lymphocytic lymphoma (CLL/SLL), follicular lymphoma, Marginal zone lymphoma of the mucosa-associated lymphoid tissue (MALT) lymphoma, lymphoblastic lymphoma, and Burkitt's lymphoma are important diagnoses that must be ruled out using markers like CD5, CD23, CD10, Bcl6, TdT, cyclin D1, SOX11, and the Ki67 proliferative index contribute to the correct diagnosis, whereas the

predominance of large cells make diffuse large B cell lymphoma an important diagnosis to be excluded by investigating cyclin D1 and SOX11 expression.

In recent decades, the molecular pathogenesis of MCL has been better elucidated, leading to important diagnostic improvements. This neoplasm derives from naïve B-cells located in the mantle zone and characteristically expresses mature B-cell markers including CD20 and CD79a, as well as IgD. Both CD5 and Bcl2 are also commonly expressed. CD5-negative cases, although rare, are well described in the literature. In the current series, there was a higher number of CD5-negative cases than previously described.[4,9,21] CD23 is typically negative and helps to differentiate MCL from CLL/SLL. Germinal center markers such as CD10 and Bcl6 are also usually negative; however, they may be aberrantly expressed in approximately 15.8% of the cases,[22,23] as seen in the current series.

The primary molecular event for MCL development is the t(11; 14)(q13; q32) translocation that juxtaposes the *CCND1* gene at 11q13 to the immunoglobulin heavy chain complex at chromosome 14q32. This results in cyclin D1 overexpression leading to cell cycle dysregulation and survival, representing an important diagnostic tool present in >95% of cases. In most cases, the neoplastic cells are diffusely positive for cyclin D1; however, Fuseya et al.[24] recently described a dot-like staining pattern in a single rare case. Moreover, hairy cell leukemia should be excluded in cases if only scattered positive nuclei are seen.[25]

Cyclin D1 and translocation-negative cases of MCL are well described, albeit rare, with mutations in the *CCND2* oncogene identified, and subsequent expression of cyclin D2 and cyclin D3. These findings are not of diagnostic significance; rather, nuclear expression of SOX11 is a reliable marker for identifying both cyclin D1-positive and cyclin D1-negative cases.[2,21] In the current series, all cases showed nuclear expression of cyclin D1, whereas 9 of 13 cases expressed SOX11. Although both markers were found in most neoplastic cells, 2 pleomorphic variants showed nuclear expression of cyclin D1 in <70% of the neoplastic population. The prognostic significance of SOX11 is still debatable, usually being associated with a worse prognosis. Unfortunately, we were unable to investigate its significance in the current series, but it is noteworthy that the less-aggressive non-nodal leukemic variant of MCL, characterized by peripheral blood, bone marrow, and splenic involvement in the absence of lymphadenopathy, is usually negative or only weakly positive for SOX11.[26]

Mantle cell lymphoma is usually diagnosed in advanced stages. In contrast, head and neck extranodal MCLs are more commonly diagnosed in early-stage disease, often with a low-risk Mantle Cell Lymphoma International Prognostic Index (MIPI) score. Clinical symptoms in the head and neck region may prompt patients to seek medical consultation timeously, resulting in earlier detection.[1,9,12]

The clinical behavior of MCL is highly variable, with median survival ranging between 3 and 5 years. The survival rate ranges from 29.2% to 54.5%, with improvements following the introduction of rituximab and other novel biological agents.[3,15,18,26] Some authors have demonstrated important differences in prognosis and survival depending on the primary site of involvement. Nodal MCLs usually have a worse prognosis compared with extranodal cases, with head and neck MCLs having a better survival rate compared with gastrointestinal cases.[11,18] In contrast, Breen et al.[12] failed to observe any significant differences among head

and neck subsites. Moreover, the leukemic non-nodal MCL variant is associated with a better prognosis,[26] and the exceedingly rare in situ mantle cell neoplasia has an indolent course with excellent long-term survival.

There is currently no gold standard therapeutic approach for MCL, with patients managed on different chemotherapeutic schemes, with or without radiation and bone marrow transplant.[2,7,27,28] There are many different clinical and histologic parameters that may influence prognosis, including cell proliferation and aggressive histologic variants.[5] The MIPI score is used to stratify patients according to their prognostic risk and includes clinical parameters such as patient age, Eastern Cooperative Oncology Group performance score, lactate dehydrogenase level, and white blood cell count.[2,28,29] Hoster et al.[30] demonstrated that combining the MIPI score with the Ki67 proliferation index might lead to a more sensitive approach for risk stratification. Certain genetic mutations involving the *TP53* gene with subsequent p53 immunoexpression are also associated with a worse overall prognosis.[5]

In conclusion, because of its histologic heterogeneity, MCL should always be considered in the diagnostic work-up of extranodal mature B-cell lymphomas in the oral and maxillofacial region. A broad immunohistochemical panel, including cyclin D1 and SOX11, must be evaluated in all suspected cases. Moreover, an extranodal MCL diagnosis should prompt clinicians to investigate the possibility of a leukemic manifestation of the disease.

Funding

This study was supported by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES/Brazil, Finance Code 001), the São Paulo State Research Foundation (FAPESP/Brazil) (FAPESP #17/14880-3), the Minas Gerais State Research Foundation (FAPEMIG #APQ-00623-18), and the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq/Brazil #406452/2018-0). Manoela Domingues Martins, Ricardo Alves Mesquita, Pablo Agustin Vargas, Fábio Ramôa Pires, and Felipe Paiva Fonseca are fellows of the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq/Brazil).

Disclosure

None.

References

1. Vergote V, Janssens A, Andr e M, et al. Results from the Belgian mantle cell lymphoma registry. Acta Clin Belg. 2017; 72: 172-178.
2. Jain P, Wang M. Mantle cell lymphoma: 2019 update on the diagnosis, pathogenesis, prognostication, and management. Am J Hematol. 2019; 94: 710-725.
3. Epperla N, Hamadani M, Fenske TS, Costa LJ. Incidence and survival trends in mantle cell lymphoma. Br J Haematol. 2018; 181: 703-706.
4. Swerdlow SH, Campo E, Seto M, Müller-Hermelink HK, et al. Mantle cell lymphoma. In: Swerdlow SH, Campo E, Harris NL, eds. World Health Organization Classification of

Tumours of Hematopoietic and Lymphoid Tissues, revised, 4th ed., Lyon, France: IARC; 2017: 285-290.
5. Nabrinsky E, Danilov AV, Koller PB. High-risk mantle cell lymphoma in the era of novel agents. Curr Hematol Malig Rep. 2021; 16: 8-18.
6. Lukach L, Lehman H, Livoff A, Nahlieli O, Michaeli E, Allon I. Mantle cell lymphoma of the oral cavity: an uncommon site for an uncommon lesion, two new cases and literature review. Oral Oncol. 2020; 103: 104578.
7. Marques JAS, Ferreira F, Melo DP, Santos M, Vaz RP. Palatine tonsils primary presentation of blastoid variant of mantle cell lymphoma: case report. Head Neck Pathol. 2021; 15: 588-592.
8. Valente VB, Castro TF, Takamiya AS, et al. Blastoid variant of mantle cell lymphoma in palatine tonsil. Oral Oncol. 2021; 122: 105552.
9. Tashakori M, Kim DH, Kanagal-Shamanna R, et al. Mantle cell lymphoma involving tonsils: a clinicopathologic study of 83 cases. Human Pathol. 2021; 118: 60-68.
10. Wagner VP, Rodrigues-Fernandes CI, Carvalho MVR, et al. Mantle cell lymphoma, malt lymphoma, small lymphocytic lymphoma and follicular lymphoma of the oral cavity: an update. J Oral Pathol Med. 2021; 50: 622-639.
11. Ambinder AJ, Shenoy PJ, Nastoupil LJ, Flowers CR. Using primary site as a predictor of survival in mantle cell lymphoma. Cancer. 2013; 119: 1570-1577.
12. Breen CT, Chao J, Mehra S, Kohli N. Extranodal head and neck mantle cell lymphoma: characteristics, treatment, and survival. Ann Otol Rhinol Laryngol. 2022; 131: 412-419.
13. Issa DE, van de Schans SA, Chamuleau ME, et al. Trends in incidence, treatment and survival of aggressive B-cell lymphoma in the Netherlands 1989-2010. Haematologica. 2015; 100: 525-533.
14. Smith A, Crouch S, Lax S, et al. Lymphoma incidence, survival and prevalence 2004-2014: sub-type analyses from the UK's Haematological Malignancy Research Network. Br J Cancer. 2015; 112: 1575-1584.
15. Leux C, Maynadi e M, Troussard X, et al. Mantle cell lymphoma epidemiology: a population-based study in France. Ann Hematol. 2014; 93: 1327-1333.
16. Chang CC, Rowe JJ, Hawkins P, Sadeghi EM. Mantle cell lymphoma of the hard palate: a case report and review of the differential diagnosis based on the histomorphology and immunophenotyping pattern. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003; 96: 316-320.
17. Guggisberg K, Jordan RCK. Mantle cell lymphoma of the oral cavity: case series and comprehensive review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010; 109: 98-104.
18. Kamel MG, El-Qushayri AE, Sayed AK, Huy NT. Using the primary site as a prognostic tool for nodal mantle cell lymphoma: a SEER-based study. J Comp Eff Res. 2020; 9: 861-876.
19. Jain P, Wang M. Blastoid mantle cell lymphoma. Hematol Oncol Clin North Am. 2020; 34: 941-956.
20. Rodrigues-Fernandes CI, Gon¸calves Junior A, Soares CD, et al. Oral and oropharyngeal diffuse large B-cell lymphoma and high-grade B-cell lymphoma: a clinicopathologic

and prognostic study of 69 cases. Oral Surg Oral Med Oral Pathol Oral Radiol. 2021; 131: 452-462.
21. Loungani L, Mundhe R, Chinoy R. Aggressive cyclin D1 negative blastoid variant mantle cell lymphoma—a case report. Int J Surg Pathol. 2022; 30: 190-194.
22. Pizzi M, Agostinelli C, Righi S, et al. Aberrant expression of CD10 and BCL6 in mantle cell lymphoma. Histopathology. 2017; 71: 769-777.
23. Xu J, Medeiros LJ, Saksena A, et al. CD10-positive mantle cell lymphoma: clinicopathologic and prognostic study of 30 cases. Oncotarget. 2017; 9: 11441-11450.
24. Fuseya H, Yoshida M, Oyama R, et al. Mantle cell lymphoma with dot-like nuclear staining for cyclin D1. Leuk Lymphoma. 2020; 61: 2016-2019.
25. Zhou L, Xu H, Zhou J, Ouyang B, Wang C. A rare case of hairy cell leukemia with co-expression of CD5 and cyclin D1: a diagnostic pitfall. Mol Clin Oncol. 2020; 13: 74.
26. Isaac KM, Portell CA, Williams ME. Leukemic variant of mantle cell lymphoma: clinical presentation and management. Curr Oncol Rep. 2021; 23: 102.
27. Maddocks K. Update on mantle cell lymphoma. Blood. 2018; 132: 1647-1656.
28. Karmali R, Switchenko JM, Goyal S, et al. Multi-center analysis of practice patterns and outcomes of younger and older patients with mantle cell lymphoma in the rituximab era. Am J Hematol. 2021; 96: 1374-1384.
29. Lim SY, Horsman JM, Hancock BW. The mantle cell lymphoma international prognostic index: does it work in routine practice? Oncol Lett. 2010; 1: 187-188.
30. Hoster E, Rosenwald A, Berger F, et al. Prognostic value of Ki67 index, cytology, and growth pattern in mantle-cell lymphoma: results from randomized trials of the European mantle cell lymphoma network. J Clin Oncol. 2016; 34: 1386-1394.