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ORIGINAL ARTICLE

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Clinicopathological profile of non-hodgkin lymphomas affecting the parotid glands

Abstract:

Objetivo: The aim of this study is to investigate the clinicopathological and immunohistochemical features of a series of lymphomas involving the parotid glands. **Methods:** All cases diagnosed in one pathology service from January 2008 and December 2018 were retrospectively retrieved, and the formalin-fixed paraffin-embedded tissue blocks were assessed for diagnostic confirmation. Clinical data were obtained from patients' medical files. **Results:** We obtained twelve cases of NHL in the parotid glands representing nine MALT lymphomas, two follicular lymphomas (FL), and one diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS). There was a predilection for the female sex (10F:2M), and in all cases it was possible to confirm the involvement of the parotid glands by macroscopic evaluation, imaging studies, or histologic assessment. Clinically, most of the lesions presented as asymptomatic swellings in the parotid region, although associated pain was reported in one case of FL, and three patients with MALT lymphoma had sicca symptoms. **Conclusion:** In conclusion, NHL affecting the parotid glands are usually of mature B cell lineage, usually representing low-grade subtypes, and frequently simulate other benign or malignant conditions.

Keywords: Lymphoma; MALT lymphoma; Follicular lymphoma; Sjogren's syndrome; Parotid gland.

INTRODUCTION

Non-Hodgkin lymphomas (NHL) encompass a wide range of subtypes distinguished by diverse histological, genetic, and clinical features[1]. According to the latest Global Cancer Statistics report, in 2020 NHL accounted for approximately 260,000 deaths worldwide[2]. Lymphomas affecting the parotid glands (PGs) constitute a significant proportion of NHL cases involving salivary glands, estimated at approximately 79%[3].

Clinical relevance statement
Lymphomas of the parotid glands represent a challenging diagnostic that can frequently simulate other benign or malignant conditions and a careful evaluation of all parotid swell-ings is mandatory to provide an accurate diagnosis for affected patients.

Unlike other salivary glands, lymphomas affecting the parotid gland can originate not only in the parenchyma, but especially from the intraparotid lymph nodes[4]. Frequently, they manifest as painless swellings without specific symptoms[4,5]; moreover, these parotid lymphomas should be thoroughly assessed and clinically correlated, since they may also represent an indication of Sjögren's syndrome (SS)[6,7]. Microenvironment in SS may contribute to transformation to marginal zone lymphoma, a low-grade tumor, and

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one of the most prevalent NLH in parotid glands[8]. Thus, lymphomas arising in the parotids often exhibit a favorable prognosis due to their increased tendency to present as low-grade malignancies[4].

In the current study, we attempted to investigate the clinicopathological and immunohistochemical features of lymphomas affecting the parotid glands, and to compare our results with currently available literature.

MATERIAL AND METHODS

Ethics statement

This study was approved by the Ethics Committee of the Federal University of Minas Gerais, Brazil (CAAE: 58900722.1.0000.5149). All procedures were in accordance with the ethical standards of the committee for human experimentation (institutional and national) and with the Declaration of Helsinki of 1975, revised in 2008.

Sample and data collection

Lymphomas affecting the parotid glands were obtained from pathology files of the immunohistochemistry Laboratory of the Piracicaba Dental School (University of Campinas, Brazil) in a period ranging from January 2008 to December 2018. Cases originating from the neck or the cervical lymph nodes with extension to the parotid glands, and those with no tissue blocks or glass slides available to perform H&E-stained and immunohistochemistry reactions were not included. On the other hand, cases affecting intraparotid lymph nodes and arising in patients diagnosed with Sjögren's syndrome were included.

The original H&E-stained histological sections and immunohistochemistry slides were assessed for at least two pathologists, and cases were classified in accordance to the 4th edition of the World Health Organization guidelines for classification of Tumors of Hematopoietic and Lymphoid Tissues[1]. The clinicopathological data of the cases were obtained from the patient's pathology and/or medical records, and included gender, age, clinical presentation, follow-up time, status at last follow-up and, when possible, information about the primary or disseminated process manifestation of the disease elsewhere in the body.

Data analysis

A descriptive analysis was performed with categorical variables presented as absolute numbers and percentages, while continuous variables expressed as mean, standard deviation (SD) and range. The SPSS software version 22.0 (IBM, Germany) was used for statistical analysis.

Literature review

A review of the literature was performed with an electronic search in August 2023, using the PubMed/MEDLINE database to retrieve all previous reports of lymphomas affecting the parotid glands containing individual data available for consultation in accordance to the fourth edition of the WHO classification of hematopoietic and lymphoid tissue tumors[1]. The search strategy comprised the following key-words: ("parotid gland" OR "parotid glands") AND ("lymphoma" OR "lymphomas"), and, to expand the search, a manual evaluation on the articles' references was also performed. These articles were included in the software Rayyan (https://www.rayyan.ai/), and three authors reviewed them. Lymphomas affecting other major salivary glands and those without data to diagnose were not included in this review.

RESULTS

A total of 15 lymphomas affecting the parotid glands were identified, but three of them were excluded because an accurate diagnosis could not be performed and were descriptively reported as two low-grade small B cell lymphoma and one high grade lymphoma. Out of the remaining 12 cases, nine cases represented MALT lymphoma, two were follicular lymphomas (FL), and one case was classified as diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS).

The clinicopathological profile of the 12 cases is detailed in Table 1. In summary, females were more affected (10 females:2 males), with the patients' age ranging from 32 to 90 years, with a mean age of 53.6 years. Most of the lesions presented as asymptomatic swellings in the parotid region, but pain was reported in one case (8.0%), while three (25.0%) patients had sicca symptoms (Figure 1). Five patients (42.0%) were affected in the right gland, two (17.0%) in the left gland, one (8.0%) bilaterally, and one (8.0%) in the intraparotid lymph node. It was possible to confirm the involvement of the parotid glands in all cases by macroscopic evaluation, imaging studies, or histologic assessment.

Histologically, MALT lymphoma (9 cases, 75%) consisted of a diffuse proliferation of small-to-medium-sized neoplastic B-cells with the presence of lymphoepithelial lesions in different amounts. Some medium-sized

Table 1. Clinicopathological profile of 12 non-Hodgkin lymphoma cases affecting the parotid glands.

No.	Sex	Age	Diagnosis	Side	Sjögren Syndrome	Immunohistochemistry
1	M	NS	FL	Left	Unknown	CD20+, CD3+, Bcl2+, CD23+, Ki67~30%
2	F	32	MALT	Right	Unknown	CD3+, CD8+, CD10–, Bcl2+, CD43–, CD79a+, CD138+, VS38C+, AE1/AE3+**, EBER r–, Ki67~5%
3	F	58	DLBCL	Right	Unknown	LCA+, CD3–, CD20+, CD23–, CD138–, EMA-, Kappa+, Lambda–, Cyclin D1–, Bcl2+, Bcl6 –, CD10+, TDT–, EBER–, Ki67 ~5%
4	F	35	MALT	Left	Unknown	CD3–, CD20+, CD138+, MUM1+, AE1/AE3+*, Ki67~5%
5	F	90	MALT	Right	Unknown	CD3–, CD20+, CD5–, CD10–, CD43+, CD79a+, Bcl2+, Cyclin D1–, AE1/AE3+*, Ki67~5%
6	M	61	FL	NS	Unknown	LCA+, CD3–, CD20+, CD43+, CD79a+, Bcl2+, Ki67~35%
7	F	69	MALT	NS	Unknown	LCA+, CD3–, CD20+, CD5–, CD10–, CD43–, Cyclin D1–, Bcl2+, Ki67~5%
8	F	81	MALT	Bilateral	Unknown	CD3–, CD20+, CD5–, CD10–, AE1/AE3+*, Ki67~25%
9	F	49	MALT	NS	Yes	CD3–, CD20+, CD10–, AE1/AE3+*, Ki67~10%
10	F	67	MALT	Right	Yes	CD3-, CD20+, CD10-, CD23-, Cyclin D1- Ki67~5%
11	F	44	MALT	Right	Unknown	CD3–, CD20 +, CD10– , CD30–, CD68+, AE1/AE3+*, Bcl2 +, CD18–, Ki67~10%
12	F	58	MALT	NS	Yes	LCA+, CD3–, CD20+, CD5–, CD23–, CD68–, CD79a+, Bcl2+, Cyclin D1–, TDT–, Ki67~5%

F: female; M: male; MALT: mucosa-associated lymphoid tissue; EBV: Epstein-Barr virus; DLBCL: diffuse large B-cells lymphoma; FL: follicular lymphoma; NS: not specified. *AE1/AE3 was imunopositive in lymphoepithelial lesion.

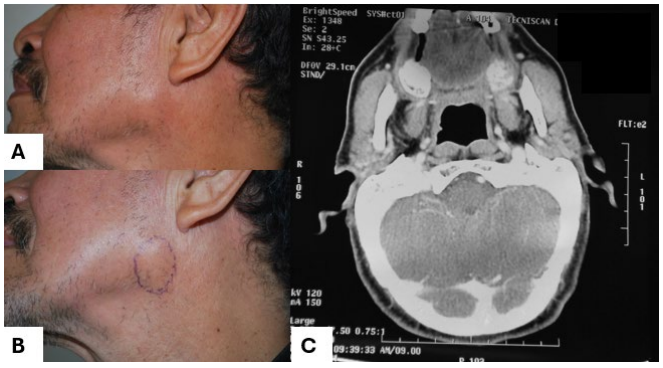

Figure 1. Clinical presentation of lymphomas affecting the parotid gland. A-B) Follicular lymphoma in a 61-year-old man presenting with a painless swelling in the parotid gland (Case #6), and C) In the axial section of the tomography we can observe a bilateral increase in volume of the parotid gland (Case #6).

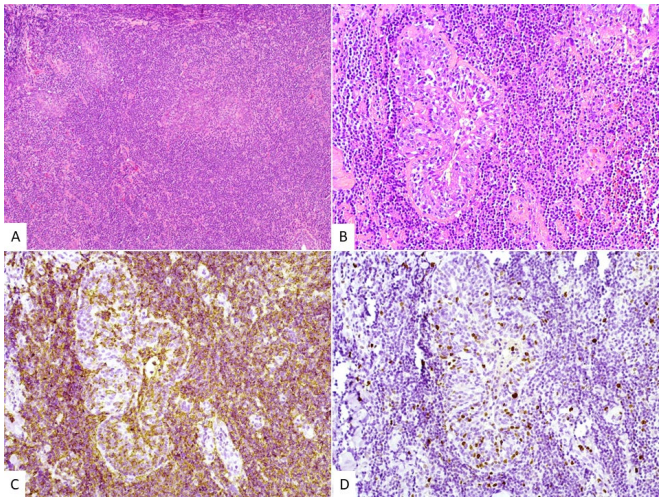

Figure 2. Microscopic findings of MALT lymphoma affecting the parotid gland (PG)(case #6). A) A diffuse proliferation of small-to-moderate-sized neoplastic cells with scant cytoplasm (H&E; 100 ×). B) Presence of neoplastic cells in glandular structures with lympho-epithelial lesions (H&E; 200 ×). C) The neoplastic cells were diffusely positive for CD20 (DAB; 200 ×) and D) Ki-67 (DAB; 200 ×).

cells exhibiting a relatively abundant pale cytoplasm consistent with monocytoid cells were noted. The neoplastic cells diffusely expressed CD20, were negative for CD3, CD5 and Cyclin D1, and had a low proliferative rate (Ki67~ 5 to 10%) (Figure 2). AE1/AE3 immunohistochemistry was assessed in six (67%) MALT lymphomas, and demonstrated lymphoepithelial lesions. Three (33.0%) patients affected by MALT lymphoma had clinical signs and symptoms consistent with SS, and one (11.0%) case was associated with a lymphoepithelial cyst. The two (17.0%) cases of follicular lymphomas exhibited a follicular growth pattern with the neoplastic follicles proliferating in the glandular parenchyma, and one of them was also located in the intraparotid lymph node. They were composed predominantly of centrocytes, with a variable number of centroblasts, and both were diagnosed as low-grade subtypes. The neoplastic cells were diffusely positive for CD20, and revealed positivity for CD10, and Bcl2 proteins in the neoplastic germinal centers (Figure 3). The DLBCL, NOS case was microscopically heterogeneous and characterized by a diffuse proliferation of large atypical B-cells with

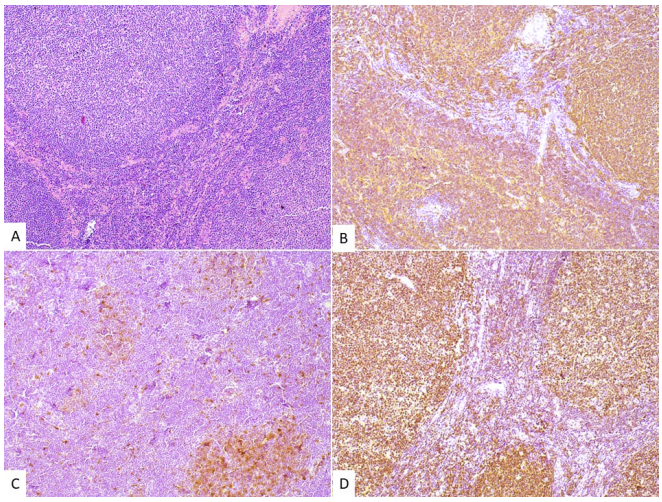

Figure 3. Microscopic features of FL in the parotid gland (PG). A) The neoplasm exhibited a FL growth pattern with follicles focally showing a back-to-back pattern (H&E; 100 ×). B) The neoplastic cells were diffusely positive for CD20 (100x), and C) revealed positivity for CD10 (100x) and D) Bcl2 proteins in the neoplastic germinal centers (100X)

both centroblast and immunoblast features. Immunohistochemically, the neoplastic cells were positive for CD20 and Bcl2, and negative for CD3, Bcl6 and EBER, showing a high Ki67 proliferative index.

In our literature review, 15 articles reporting lymphomas in the parotid glands could be retrieved, accounting for 272 cases. The clinicopathological profile of these cases are detailed in Supplementary Table 1, and references of this table can be found in Supplementary File 1. Briefly, females predominated (162 females:82 males), with the patients' age ranging from 15 to 93 years. Most of the lesions presented as a painless hard swelling. The sicca syndrome, a manifestation of SS, arthralgia, fatigue, Raynaud's phenomenon, and fever were also described. Microscopically, MALT lymphoma, FL and DLBCL predominated, but anaplastic large cell lymphoma (ALCL)[9], adult T-cell leukaemia/lymphoma (ATLL)[9], Burkitt's lymphoma (BL) and small-cell lymphocytic lymphoma (SLL) were also described. The most common treatment applied was surgery, associated with different protocols of radiotherapy and chemotherapy. Only 36 patients died and 240 remained alive at their last follow up.

DISCUSSION

The presence of lymphomas in the salivary glands is uncommon, representing approximately 2% of all salivary gland tumors, and 75% occur in the parotid glands, especially in patients with SS[7,10]. The parotid gland, compared to other major salivary glands, has an important anatomical feature, which is the presence of lymphoid tissue inside of the glandular parenchyma that can potentially be involved by reactive, metaplastic or neoplastic lymphoid processes[11]. Considering the low incidence of lymphomas of the salivary glands and their unspecific clinical manifestations, the diagnostic process is very complex and these neoplasms may simulate the clinical features of many other entities, like benign salivary gland tumours, making their final diagnosis very difficult. In this series of 12 cases, we demonstrated that the most common entities were MALT, followed by FL and DLBCL, NOS; most often manifesting as asymptomatic swellings, which is in accordance with previous studies (Supplementary File 1).

It is known that the risk of occurrence of MALT is significantly increased in the context of SS, an autoimmune disorder that more often affects the lacrimal and salivary glands, and predisposes patients to develop NHL[12,13]. It is believed that the parotid glands in patients with SS have a microenvironment that plays a pathogenetic role in the final step of primary SS-related lymphomagenesis[7,14-16]. Although any lymphoma subtype can develop in the parotid glands of patients with this condition, it is well known that MALT is the most frequent subtype[17,18], as illustrated in our study where all three patients diagnosed with SS were affected by MALT lymphoma.

The clinical manifestations of lymphomas in the parotid glands are very unspecific, with most of the cases associated with expansive swelling, more often asymptomatic, although pain and paresthesia may occur, especially in higher grade subtypes. In patients diagnosed with SS, parotid swelling has been considered a very early and important key predictor of neoplastic development, and the disease should be assessed for the possibility of a lymphoma[7]. Moreover, some studies demonstrated a correlation between the duration of parotid gland swelling and the risk of lymphoma transformation, reporting that the increase in time make the risk of lymphoma diagnosis increase significantly[7]. Therefore, a careful evaluation of parotitis should be conducted, and even more cautiously when patients already have the diagnosis of SS; in the meanwhile, when patients are diagnosed with lymphomas in the salivary glands, diagnosticians should investigate the possibility of an SS scenario which could not have been established so far.

Although the definitive diagnosis of lymphomas in the parotid glands relies on the microscopic

and immunohistochemical examination of the surgical specimen, there seems to have some advantages of performing salivary gland ultrasonographic examinations or ultrasound-guided salivary gland fine needle aspiration and core needle biopsies, especially in SS individuals[19,20]. These diagnostic approaches allow for an exploratory microscopic investigation even in the absence of evident parotid gland swelling[21], representing a minimally invasive technique with a satisfactory initial diagnostic predictability[22]. Although the definitive diagnosis and subclassification of the lymphoma type normally depend on the histopathological examination of the surgical specimen.

The treatment for lymphomas in parotid glands depends on the microscopic diagnosis, tumor grade and clinical stage, more often consisting of surgery, radiotherapy, chemotherapy, and immunotherapy, alone or in combination. In localized diseases the neoplasms may be successfully treated by more conservative approaches[23], although this type of treatment is considered more effective for low-stage, low-grade indolent forms of lymphomas[24]. Most of the cases in our literature review were affected by FL and MALT lymphomas, and several of them were treated only with radiotherapy (Supplementary File 1).

The prognosis of patients affected by lymphomas in the parotid glands is usually good, with the prognosis of patients affected by MALT lymphomas usually being the most favorable among the lymphoma subtypes described in the literature[25,26]. The risk of death associated with a parotid gland lymphoma is directly impacted by older age, higher grade tumors and advanced stage neoplasms[25]. In our literature review, it was observed that deaths were strongly associated with higher grade diagnoses like ATLL, DLBCL and mantle cell lymphoma (MCL) (Supplementary File 1).

CONCLUSION

In conclusion, we observed that lymphomas of the parotid glands represent a challenging diagnosis that can frequently simulate both benign or malignant conditions. Therefore, a careful evaluation of all parotid swellings, especially in patients with SS, is mandatory to provide an accurate diagnosis for affected patients, which should be systematically evaluated to rule out a disseminated disease.

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AUTHORS' CONTRIBUTIONS

GRA: data curation, formal analysis, methodology, writing – original draft, writing – review & editing. ALMP: data curation, investigation, methodology. LAL: investigation, methodology. CVBLC: data curation, investigation, methodology. JMAL: data curation, investigation, writing – original draft, writing – review & editing. NRG: investigation, writing – original draft, writing – review & editing. PAV: data curation, formal analysis. EMJRT: investigation, methodology, writing – original draft, writing – review & editing. HARP: data curation, methodology. RAM: data curation, formal analysis. SFS: writing – original draft, writing – review & editing. FPF: conceptualization, data curation, funding acquisition, methodology, supervision, writing – original draft, writing – review & editing.

CONFLICT OF INTEREST STATEMENT

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Competing interests: The authors have no relevant financial or non-financial interests to disclose.

Ethics approval: Ethics Committee of the Universidade Federal de Minas Gerais (58900722.1.0000.5149)

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