Facultad de Odontología

Carrera de Odontología

ADENOMA PLEOMORFO EN GLÁNDULAS SALIVALES MENORES: REVISIÓN DE LA LITERATURA

Trabajo de titulación previo a la obtención del título de Odontólogo

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Resumen

Antecedente: Según la OMS, el adenoma pleomorfo (AP) es un tumor benigno con manifestaciones citomorfológicas y arquitecturales variables.

Objetivo: Nuestro objetivo es revisar la literatura de todos los casos informados de AP en glándulas salivales menores desde el 2002 hasta el 2022. Se revisará la edad, sexo, localización, características clínicas, radiográficas e histológicas, pronóstico y opciones de tratamiento.

Materiales y métodos: Se realizó una búsqueda bibliográfica en PUBMED con las palabras clave: pleomorphic adenoma y minor salivary glands.

Resultados: Se incluyeron 24 reportes de casos en inglés después de aplicar los criterios de inclusión. La edad promedio de aparición del AP fue de 33,7 años. La relación hombre-mujer fue de 19:11. El sitio de mayor ocurrencia fue el paladar duro (29%). El 16,66% de casos presentaban dolor. 27 de los 30 casos (90%) estaban encapsulados y 28 casos fueron tratados mediante resección quirúrgica (93,33%).

Conclusión: El AP constituye hasta dos tercios de todas las neoplasias de las glándulas salivales. Presenta una predilección por el sexo femenino, aparece más comúnmente en la parótida y en el paladar, el tratamiento de elección es la escisión quirúrgica y su pronóstico es bueno.

Palabras Clave: Adenoma pleomorfo. Glándulas salivales menores. Diagnóstico. Pronóstico. Tratamiento.

Abstract

Background: According to the WHO, pleomorphic adenoma (PA) is a benign tumor with variable cytomorphological and architectural manifestations.

Objective: Our objective is to review the literature of all reported cases of PA of minor salivary glands from 2002 to 2022. Age, sex, location, clinical, radiographic and histological characteristics, prognosis and treatment options will be reviewed.

Materials and methods: A literature search was carried out in PUBMED with the keywords: pleomorphic adenoma and minor salivary glands.

Results: Twenty-four case reports in English were included after applying the inclusion criteria. The average age of appearance of the PA was 33.7 years. The male-female ratio was 19:11. The most frequent location was the hard palate (29%). 16.66% of cases presented pain. 27 of the 30 cases (90%) were encapsulated and 28 cases were treated by surgical resection (93.33%).

Conclusion: PA constitutes up to two thirds of all salivary gland neoplasms. It presents a predilection for the female sex, it most commonly appears in the parotid gland and in the palate, the treatment of choice is surgical excision and its prognosis is good.

Keywords: Pleomorphic adenoma. Minor salivary glands. Diagnosis. Prognosis. Treatment.

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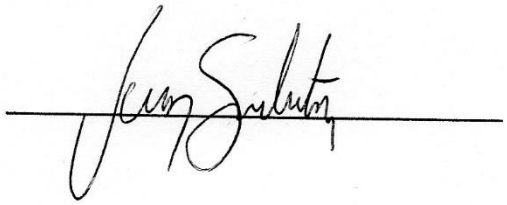

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Introduction

Salivary gland neoplasms are rare and constitute a large and heterogeneous group of tumors. The 2017 World Health Organization classification of head and neck tumors recognizes 41 different types of salivary gland tumors, including 22 malignant tumors, 11 benign neoplasms, and 8 tumors in other categories (1). Among all these diagnostic possibilities, the pleomorphic adenoma (PA) is classified as the most frequent tumor, both in adults and children, and constitutes one to two thirds of the neoplasms found in the salivary glands (2,3). Willis was the first to use the PA terminology, which a few years ago was also referred to as a mixed tumor, enclavoma, branchioma, endothelioma, among others. It is usually found more recurrently in the parotid glands (85%), followed by the minor salivary glands (10%) and the submandibular glands (5%) (2). Pleomorphic adenoma can occur at any age, even in newborns, but most commonly affects women (in a 2:1 ratio), between 30 and 60 years of age (4–6). Until now, there is controversy regarding the real etiology of PA, some authors mention that one of the most accepted risk factors for the development of these tumors is head and neck radiation (3,5).

Although pleomorphic adenoma most commonly occur in the parotid gland, it can be encountered in minor salivary glands located in the hard and soft palate, upper and lower lip, jugal mucosa, tongue, floor of the mouth, and even there are cases of its appearance in the lacrimal glands of the eye (2,7). It is a tumor that presents a slow growth, in most cases, it is asymptomatic, and when it is located in the parotid gland, it does not usually compromise the facial nerve (2,8).

PA is a lesion that is histologically heterogeneous and has a wide range of clinical behaviors. Its name derives from the architectural pleomorphism that can be observed under the light of the microscope (9,10). In very general features, this tumor has three basic components that allow its recognition; an epithelial component, a myoepithelial cell component, and a mesenchymal component. Histological presentation of PA shows a variable pattern of epithelium in a loose fibrous stroma of the myxoid, chondroid or mucoid type, where the myoepithelial cells have a polygonal or spindle-shaped shape, with a pale eosinophilic cytoplasm (2,9). Therefore, it is pertinent to emphasize that the certainty diagnosis of PA must be made through a histological study.

Our objective is to review the literature of all reported cases of PA of minor salivary glands from 2002 to 2022. Age, sex, location, clinical, radiographic and histological characteristics, prognosis and treatment options will be reviewed.

Methodology

Search strategy:

A literature search in English was performed, using the PUBMED database to identify case reports of PA of minor salivary glands. Case reports and literature reviews from 2002 to 2022 were included. The following keywords were searched: Pleomorphic Adenoma, minor salivary glands, diagnosis, prognosis, treatment, together with the Boolean operators: and, not, and we also performed a reference check of articles found for other reported cases.

Inclusion and exclusion criteria:
Inclusion criteria:

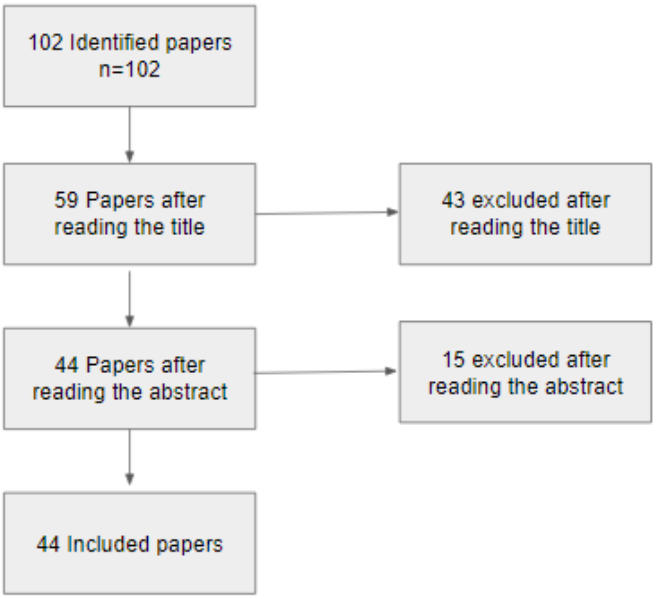
- Case reports of PA of minor salivary glands.
- Literature reviews of PA of minor salivary glands.
- Systematic reviews of PA of minor salivary glands.
- Meta-analysis of PA of minor salivary glands.
- Documented literature in English.
- Documented literature of the last 20 years.

Exclusion criteria:

- Literature based on letters to the editor, opinions, protocols, clinical trials, randomized controlled studies.
- Literature in a language other than English.
- Literature that does not meet the inclusion criteria.

Data extraction:

Two reviewers independently collected all data using a data extraction sheet. For each case report included in the review, we collected information regarding: year of publication, author, absence or presence of pain, location, age, gender, whether the lesion was encapsulated or multinodular, and the treatment chosen by each of the included case reports. (Flowchart 1)



Flowchart 1: Literature search flowchart for PA review in minor salivary glands.

Source: Author.

Risk of bias in individual case reports

The most significant potential bias was the requirement that authors accurately diagnose and report PA of minor salivary glands. When available, histology and cytology reports, along with any other relevant material, were examined by both reviewers for features of major salivary gland PA, metastatic PA, carcinoma ex pleomorphic adenoma, or any other malignant features. If found, these cases were excluded, based on the exclusion criteria.

Results:

Our search strategy allowed us to obtain a total of 102 articles. Of which 43 were excluded after title review and 15 after reading the abstract. Forty-four articles were included for the review, which met the inclusion criteria established by the authors. Of these, 22 case reports were included by the authors: Yousra et al (11), Junior et al (12), Adiyodi et al (13), Iida et al (14), Chhabra et al (15).)., Urs et al (16)., Ahmedi et al (17)., Khan et al (18)., Hmidi et al (19)., Ananthaneni et al (20)., Singh et al (21). , Rahnama et al (22), Goiato et al (23), Erdem et al (24), Goulart et al (25), Hakeem et al (26),

Kim et al (27), Kurokawa et al (28), Chen et al (29), Daniels et al (30), Bablani et al (31), and Jorge et al (32).

Of the 22 case reports (Table 1), the average age of occurance of the pleomorphic adenoma was 33.7 years, with a range between 5 and 62 years. The male-female ratio was 19:11, showing a greater male predilection. The most frequent location of pleomorphic adenoma was the hard palate (29%), followed by the upper lip (26%), soft palate (19%), buccal mucosa (16%), tongue (7%) and left preauricular area (3%). In 5 cases (16.66%) there was pain, in 24 cases (80%) there was no pain, while in 1 case (3.34%) neither presence nor absence of symptoms was reported. 27 of the 30 cases (90%) were encapsulated, 1 was not encapsulated (3.33%), 1 was partially encapsulated (3.33%) and 1 was apparently encapsulated (3.33%). Finally, regarding the treatment option, 28 cases were treated by surgical resection (93.33%), 1 was treated by enucleation (3.33%) and only 1 was treated with partial maxillectomy and immediate installation of prosthetic base with palatal obturator (3.33%).

Table 1. The list of case reports of pleomorphic adenoma.

Investigator	Pain	Location	Age (years)	Gender	Encapsulated	Multinodular	Treatment opted
Yousra y cols., 2021 (11)	Absent	Hard palate	38	M	Yes	No	Surgical excision
Junior y cols., 2020 (12)	Absent	Cheek mucosa	50	F	Partially encapsulated	No	Surgical excision
Adiyodi y cols.,2020 (13)	Absent	Upper lip	44	M	Yes	No	Surgical excision
	Present	Upper lip	44	M	Yes	No	Surgical excision
Iida y cols., 2020 (14)	Absent	Hard palate	57	F	Yes	No	Surgical excision
Chhabra y cols., 2019 (15)	Absent	Tongue	41	M	Yes	No	Surgical excision
Urs y cols., 2019 (16)	Absent	Cheek mucosa	35	M	Yes	No	Surgical excision
Ahmedi y cols.,	Absent	Upper lip	10	F	Yes	No	Surgical

2017 (17)							excision
Khan y cols., 2016 (18)	Absent	Upper lip	60	M	Yes	No	Surgical excision
Hmidi y cols., 2015 (19)	Present	Soft palate	45	F	Yes	No	Surgical excision
Ananthaneni y cols., 2015 (20)	Absent	Cheek mucosa	12	F	Yes	No	Surgical excision
Singh y cols., 2015 (21)	Absent	Upper lip	55	M	Yes	No	Surgical excision
Rahnama y cols., 2013 (22)	Absent	Hard palate	47	F	Yes	No	Surgical excision
Goiato y cols., 2012 (23)	Absent	Hard palate	62	M	Yes	No	Partial maxillectomy and immediate installation of denture base with palatal obturator
Erdem y cols., 2011 (24)	Absent	Hard palate	46	M	Yes	No	Surgical excision
Goulart y cols., 2011 (25)	Absent	Upper lip	32	M	Yes	No	Surgical excision
Hakeem y cols., 2009 (26)	Absent	Soft palate and left lateral pharyngeal wall	20	M	Yes	No	Surgical excision
	No reference	Soft palate	53	M	Yes	No	Surgical excision
Kim y cols., 2009 (27)	Absent	Cheek mucosa	21	F	Apparently capsulate	No	Surgical excision

Juan Sebastián, Ordoñez Arce
Martin Alejandro, Arévalo Gárate

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Kurokawa y cols., 2009 (28)	Present	Soft palate	34	M	Yes	No	Surgical excision
Chen y cols., 2004 (29)	Absent	Soft and hard palate	28	M	Yes	No	Surgical excision
	Present	Left preauricular area	39	M	Yes	No	Surgical excision and lobectomy
Daniels y cols., 2002 (30)	Absent	Hard palate	5	M	Yes	No	Surgical excision
	Present	Hard palate	16	M	Yes	No	Surgical excision
Bablani y cols., 2002 (31)	Absent	Cheek mucosa	38	M	Yes	No	Enucleation
Jorge y cols., 2002 (32)	Absent	Soft palate	11	M	Yes	No	Surgical excision
	Absent	Upper lip	15	F	Yes	No	Surgical excision
	Absent	Hard palate	17	F	Yes	No	Surgical excision
	Absent	Upper lip	18	F	Yes	No	Surgical excision
	Absent	Tongue	18	F	No	No	Surgical excision

Discussion:

To date, pleomorphic adenoma continues to be the most frequent benign tumor of the salivary glands and despite the fact that its most common site of appearance is in the parotid, it is not exempt from appearing in minor salivary glands, due to this, it is necessary to report the most common features of this injury.

Although its etiology is still controversial, several authors state that its appearance depends on different risk factors, and is generally related to radiation exposure to the head and neck, even 15 to

20 years after having made such exposure. Almeslet and Bokhari et al. suggest that there are studies linking the appearance of the tumor with the simian oncogenic virus (SV40). In addition to this, it is thought that tobacco consumption, exposure to chemicals and genetic predisposition are factors that can predispose the appearance of this tumor (2,5). From a molecular point of view, there may be a chromosomal translocation of 8q12 and 12q13-15, and if it occurs, PA will present with a more classic morphology and in young patients (3,33).

Pleomorphic adenoma constitutes up to two-thirds of all salivary gland neoplasms. It generally presents between the ages of 30 and 60, even appearing in newborns (6,34). According to the literature, there is a predilection for women (4.4:1), however, this contrasts with our study, since the male-female ratio was 19:11, which is why a greater male predilection was shown. It most commonly appears in the superficial lobe of the parotid, as a swelling of the ramus of the mandible; however, it can also grow between the ascending ramus and the stylomandibular ligament (2,35).

In minor salivary glands, it occurs mainly in the palate, upper lip and buccal mucosa, which coincides with the results of our study, where the site in which the pleomorphic adenoma appeared most frequently was the hard palate (29%). It is a well-defined irregular nodular lesion, with cystic degeneration if it is superficial, generally asymptomatic, slow-growing, with a firm consistency covered by normal mucosa, lacking ulcerations, which commonly appears encapsulated, whose greatest dimension is less than 6 cm. Symptoms and signs depend mainly on the size, location and potential for malignant transformation (Fig. 1) (2,5,12).

This is also found in the findings of Seethala et al, who mention that pleomorphic adenomas of the deep lobe can exceed 5 cm on average. (3)

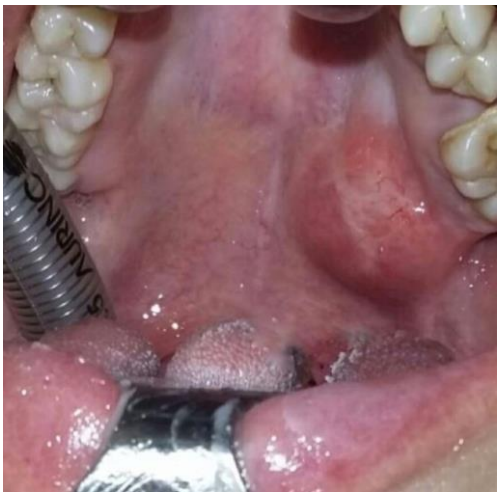

Fig.1: Clinical Image. Nodular lesion on the hard and soft palate, right side. Image courtesy. Dr. Gabriela Patiño Rocha, Maxillofacial Surgeon-Stomatologist, Southern Medical Clinic, Cuenca-Ecuador

The diagnosis of this type of tumor depends on an adequate history and clinical examination, accompanied by complementary tests such as: fine needle aspiration, incisional biopsies and imaging studies (36). Fine needle aspiration allows the differentiation between benign and malignant lesions with a sensitivity of 90%, while biopsies, despite being more invasive, allow a more precise histological typing of the tumor, with a sensitivity of 97%. However, despite the fact that these tumors are generally encapsulated, there may be microscopic extensions to the surrounding tissues, due to dehiscence of the false capsule, which is why some authors suggest avoiding incisional biopsies, to avoid spillage of tumor cells (2,5,37).

Its diagnosis is simple in most cases, however, due to its unusual histological characteristics, its ability to mimic invasion or its atypical or metaplastic cytomorphology, it is necessary to mention its differential diagnoses: palatal abscess, odontogenic cyst, Warthin tumor, parotid ganglion metastasis, non-odontogenic cyst, fibroma, lipoma, neurofibroma, facial nerve schwannomas, neurilemmoma, lymphoma, mucoepidermoid carcinoma, neurofibroma, desmoid tumor, adenoid cyst, malformation infected lymphatic and general neoplasms of the salivary glands. Histopathology remains the gold standard to differentiate them all (2,5,38).

The Ki67 immunohistochemical marker determines cell proliferation through mitotic activity and is a diagnostic and prognostic tool for various neoplasms. This activity is rarely identified in PAs (it does

not usually exceed 5%) compared to their malignant counterparts; however, its increase in isolation is not enough to make a differential diagnosis between a malignant neoplasm and PAs. It must be considered that this marker can be observed at a low level in carcinomas included in the differential diagnosis of PA, such as the classic variant of polymorphous adenocarcinoma (1).

Regarding the imaging findings in PA, these depend on cell density, epithelial proportion and stromal components, type of components presents in the stroma, and secondary histological changes such as: the appearance of fibrosis, lipometaplasia, ossifications, cystic degeneration and infractions (36). Because panoramic radiographs do not usually show changes in the presence of these lesions, confirmation of the tumor is usually done by ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI), depending on the location and size of the tumor. CT and MRI are very useful in evaluating the size, location and extent of the tumor. CT is usually used more frequently since it allows evaluation of bone tissue, especially in cases where there is erosion or perforation that may compromise the nasal cavity or the maxillary sinus, however, the use of MRI presents a better delimitation, an elaborated tumor margin, and shows a relationship of the tumor with the surrounding tissues (2,33). CT reveals well-defined tumors with smooth borders and often lobulated. They usually appear as heterogeneous and relatively hypoattenuating masses in relation to the surrounding soft tissues. Reflecting that they are lesions that present an abundant myxochondroid stroma, in T1, they are hypodense lesions, in T2 weighting they appear as hyperintense lesions. MR imaging reveals well-demarcated tumors that are round or ovoid and usually lobulated. On ultrasound images, the lesions usually appear well confined and hypoechoic (5,36,38).

The name pleomorphic adenoma derives from the diversity of morphological patterns that this lesion presents, but essentially, they are biphasic tumors, which are defined by an integral dual luminal and abluminal myoepithelial ductal component of variable proportions. These tumors are composed of a variable mixture of mesenchymal-type epithelial and myoepithelial cells in a variable myxoid extracellular matrix (Fig. 2) (3).

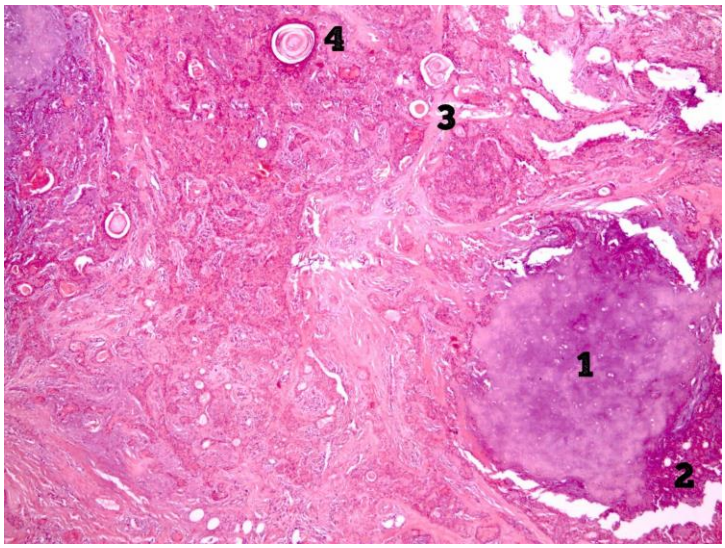

Fig.2: Photomicrograph. 1. Fibrous capsule 2. Myxoid mesenchymal tissue 3. Chondroid tissue (H&E 40x)

Source: Author

Being a lesion of variable morphology, Triantafyllou et al., propose that the components that can present in PA are: A nodular or multinodular, solid or cystic silhouette. epithelial cells (parenchymal). A capsule that varies in thickness and integrity, and may be involved or penetrated. Epithelial cell components, with cells that based on their topography are of type: luminal, non-luminal; based on the morphological phenotype they can be: cuboidal, columnar, fusiform, oval, stellate, angular, transparent, plasmacytoid, oncocytic, squamous (epidermoid), mucosal, seromucous, serous, apocrine, adipocytic, sebaceous; and according to their interpretation they can be: intercalated in the form of a duct and myoepithelial/modified myoepithelial neoplastic. Stromal components, of types: myxoid, chondroid, fibrous/hyalinized, bone and adipocyte, which may contain: mucosubstances, collagen and elastin. A boundary between the cellular content and the stroma which may be demarcated or indistinct. Crystalloids, microliths or pigmentations. Nerves and blood vessels. Non-epithelial cells such as: dendritic cells, lymphoid cells, macrophages, mast cells and myofibroblasts. (Fig. 3) (39).

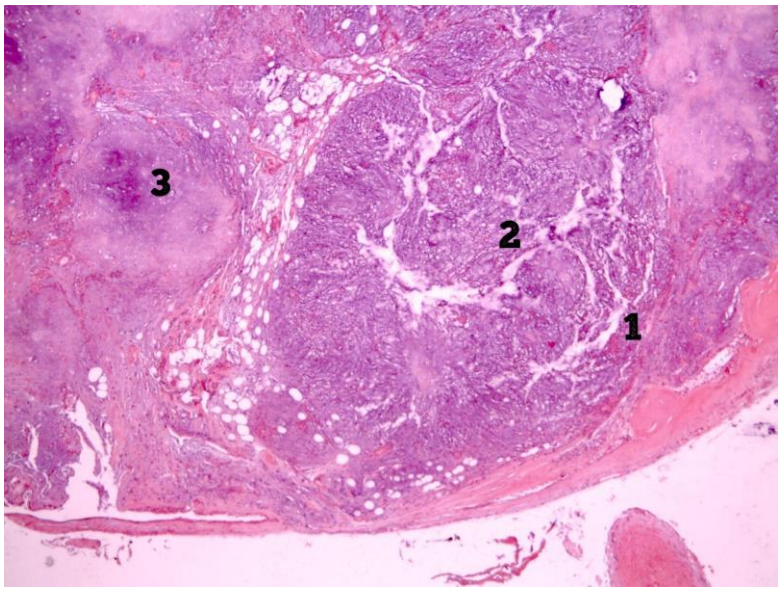

Fig.3: Photomicrograph. 1. Chondroid nodule 2. Epithelial cells 3. Duct 4. Keratin pearl (H&E 100x)
Source: Author

Although the characteristics of this tumor are very similar in both major and minor salivary glands, it has been reported that the cellular content of PA in minor salivary glands is greater than its counterpart in the parotid (39,40). Nonitha et al. reported a predominance of duct-shaped and solid structures, since trabecular patterns are rarely seen. They also mention a predominance of cuboidal cells, followed by spindle, basaloid, plasmacytoid and squamous cells (6). The stromal component is shown with a pale blue fibromyxoid appearance and is usually made up of myxoid and chondroid stromas, which represent 50% of the tumor mass, with limited areas of hyalinization. In the myxoid stroma, modified myoepithelial cells designated myxoid cells are seen with a stellate morphology that was morphofunctionally modified for mucopolysaccharide synthesis. The chondroid zones showed abundant areas with extracellular matrix rich in mucopolysaccharides with chondroid lacunae. In the PA of minor salivary glands, the appearance of keratin pearls is also common, as well as, a quarter of the PAs present extensive squamous metaplasia that forms structures similar to cysts, of variable size and shape, lined by epithelial cells that resemble to cystic pleomorphic adenoma (3,6,41–43).

Seethala et al., in their study, mention that the majority of PAs of the major salivary glands are encapsulated, but when they occur in the minor salivary glands, they appear partially or without a capsule. This study does not agree with Nonitha et al., who described that the majority of PA of minor

salivary glands are encapsulated and only some cases present partial encapsulation, data that coincide with our study, where 90.64% of the cases, they were encapsulated (3,6).

In the study by Seok et al, it is mentioned that carcinoma ex pleomorphic adenoma arises from primary or recurrent benign pleomorphic adenoma, can be asymptomatic and has clinical presentations similar to those of benign pleomorphic adenoma, so differential diagnosis is necessary (34). Malignancy can arise from PA in three forms: carcinoma ex pleomorphic adenoma (CEPA), carcinosarcoma, and metastatic pleomorphic adenoma (MPA). The latter two are exceptionally rare, with MPA accounting for 1% of all malignant PAs (44).

Surgical excision is the treatment of choice, especially in cases of PA of minor salivary glands, in order not to compromise large amounts of tissue. However, the treatment of recurrent pleomorphic adenomas should include surgical resection in combination with radiotherapy. Bokhari et al mention that submandibular gland tumors are treated with a simple excision procedure with preservation of the adjacent nerve, including the mandibular branch of the trigeminal nerve, the hypoglossal nerve, and the lingual nerve (5). In minor salivary glands, a margin of 5 mm should be obtained. These data coincide with those obtained by our study, since 28 cases were treated by surgical resection (93.33%), 1 was treated by enucleation (3.33%) and only 1 was treated with partial maxillectomy and immediate installation of the base. prosthetic with palatal obturator (3.33%). With the preoperative biopsy it is possible to determine the degree of encapsulation and determine the surgical modality. On the other hand, enucleation should not be considered as the definitive treatment, since it can lead to high local recurrence. As the tumor is radioresistant, radiotherapy is not indicated (2,4,33).

According to Mc Loughlin, radiotherapy is effective in reducing recurrence rates in those with adverse prognostic factors such as multinodular recurrence (7). The prognosis of pleomorphic adenoma is good, with a 95% cure rate and a very low recurrence rate in modern cohorts (0%-5%) (2,3).

The risk of recurrence is between 2.8% and 46.6%, depending on the surgical technique and the location of the tumor, and malignant transformation is found at a rate of 3% to 13.3% (38).

Conclusion:

Pleomorphic adenoma constitutes up to two-thirds of all salivary gland neoplasms. Its average age of appearance is 33.7 years. It has a predilection for the female sex. It is usually found more recurrently in the parotid glands (85%), followed by the minor salivary glands (10%) and the submandibular glands (5%). In minor salivary glands, it occurs mainly on the palate, upper lip and buccal mucosa. It usually appears as a well-defined irregular nodular lesion, generally asymptomatic,

slow-growing, with a firm consistency that commonly appears encapsulated, whose greatest dimension is less than 6 cm. Its histological appearance is highly variable and does not follow a specific pattern. Routine imaging findings are not frequent, however, complementary studies such as CT, MRI and ultrasound can be used for the diagnosis of this lesion. The treatment of choice is surgical excision with safety margins. The prognosis is favorable and rarely these tumors can become malignant.

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