MUCOEPIDERMOID CARCINOMA OF THE SALIVARY GLANDS. A RETROSPECTIVE STUDY OF 51 CASES AND REVIEW OF THE LITERATURE

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ABSTRACT

The aim of this study is to present the casuistic of mucoepidermoid carcinoma of salivary glands in patients diagnosed at "Dr. Eduardo Cáceres Graziani" National Institute for Neoplastic Diseases, Lima, Perú.

From January 2002 to December 2012, 51 cases were diagnosed as mucoepidermoid carcinoma. The number of female patients was higher, with 28 cases (54.9%), and regarding age distribution, 33.3% of the patients were under 30 years old. Pain was one of the main symptoms, and 74.5% of the mucoepidermoid carcinomas were located in the parotid gland.

It is concluded that epidemiology regarding age and gender of the 51 cases analyzed was in the same range as other studies, and that most cases were located in major salivary glands, in agreement with reports on other populations. Other characteristics showed a homogeneous distribution.

Key words: *Salivary gland neoplasms; mucoepidermoid tumor, epidemiology, neoplasms.*

CARCINOMA MUCOEPIDERMOIDE DE GLÁNDULAS SALIVALES. ESTUDIO RETROSPECTIVO DE 51 CASOS Y REVISIÓN DE LA LITERATURA

RESUMEN

El propósito de este estudio es presentar la casuística del carcinoma mucoepidermoide de glándulas salivales de pacientes diagnosticados en el Instituto Nacional de Enfermedades Neoplásicas "Dr. Eduardo Cáceres Graziani" Lima, Perú, desde el 2002 hasta el 2012.

Realizamos un estudio retrospectivo en el cual fueron incluidos sujetos con diagnóstico primario de carcinoma mucoepidermoide en glándulas salivales. Entre enero de 2002 y diciembre de 2012, se registraron 51 casos. El número de pacientes de sexo femenino fue mayor, con 28 casos (54,9%) y con respecto a la distribución por edades, el 33,3% de los pacientes eran menores de 30 años de edad. El dolor fue uno de los síntomas principales. El 74,5% de los carcinomas mucoepidermoides se localizaron en la glándula parótida.

De los hallazgos obtenidos se concluye principalmente que en lo que respecta a la distribución epidemiológica de edad y género de los 51 casos analizados estas variaron en el mismo rango de otros estudios. También se distingue que el mayor número de casos estuvieron localizados en glándulas salivales mayores, dato en concordancia con otras poblaciones reportadas. Las demás características presentaron una distribución homogénea.

Palabras clave: *Neoplasias de las glándulas salivales; carcinoma mucoepidermoide; epidemiología; neoplasias.*

INTRODUCTION

Neoplasms of the major and minor salivary glands are a challenge for clinicians and histopathologists because they are infrequent and have a wide range of histological, clinical, epidemiological and developmental characteristics[1].

In salivary glands, the most frequent benign tumor is pleomorphic adenoma and the most frequent malignant tumor is mucoepidermoid carcinoma (MC), according to the Armed Forces Institute of Pathology (AFIP) in Washington[2].

MC is defined as a malignant epithelial neoplasm of the salivary glands caused by proliferation of secretory cells, formed by a variable proportion of mucous, epidermoid, intermediate, columnar and clear cells, often with a cystic component. Its

biological behavior is related to the histologic tumor grade (low, intermediate or high)[2-4].

MC was studied, described and reported for the first time by Stewart, Foote and Becker in 1945 with regard to tumors with double metaplasia or double constitution, epidermoid cells and mucous producing cells[5].

Etiology

Little is known regarding the etiological agents of salivary gland neoplasms. Apparently, low-dose radiotherapy used in benign disorders such as acne or obstructive lesions of the lymphoid tissue in the oral cavity or nasopharynx is the main factor involved in the genesis of these tumors. They have not been associated to radiotherapy for the treatment of malignant neoplasms, suggesting that irradiation at high doses is a lower risk factor than irradiation at low doses. Local trauma has also been implicated in the genesis of MC in minor salivary glands[6].

Epidemiology

Neoplasms of the salivary glands are rare, accounting for less than 2%[7] of all human neoplasms and about 3% of head and neck tumors[7,8]. Malignant tumors of the salivary glands are infrequent and account for about 3% of all malignant neoplasms of head and neck[8].

Malignant neoplasms originating in minor salivary glands are less than 25% of all salivary neoplasms[9,10], and most of the tumors arising in minor salivary glands are malignant[9,11].

MC is the most common malignant neoplasm in major and minor salivary glands[12], accounting fornearly 30% of all malignant neoplasms of the salivary glands. Approximately half the MCs occur in the major salivary glands, with 80% in the parotid gland, 8 to 13% in the submaxillary gland and 2 to 4% in the sublingual gland[13]. Central mucoepidermoid tumors located in the jaws are a recognized entity. Browand and Waldron reported 9 cases and examined the 41 previously published cases[14].

Some authors report that MC is evenly distributed between sexes[15], but most authors report that glandular MC is more frequent in females, with a female:male ratio of 2:1[6,16] or 3:2[17,18].

The onset occurs between the 2nd and 8th decades of life, and it is the most frequent malignant tumor in persons under 20 year of age, in whom there is a predilection for the hard palate. There is also clear predilection for white race[6,16].

Clinical manifestation

Between 70% and 80% of neoplasms in general of the salivary glands are located in the parotid, while the palate is the most common site for neoplasms of minor salivary glands[2]. Similarly, just over 70% of MCs are located in major glands, with the parotid being the most frequent site[19], (with almost half the cases) (Fig. 1 and 2), followed by the submandibular gland and sublingual gland[3]. MCs represent 23% of

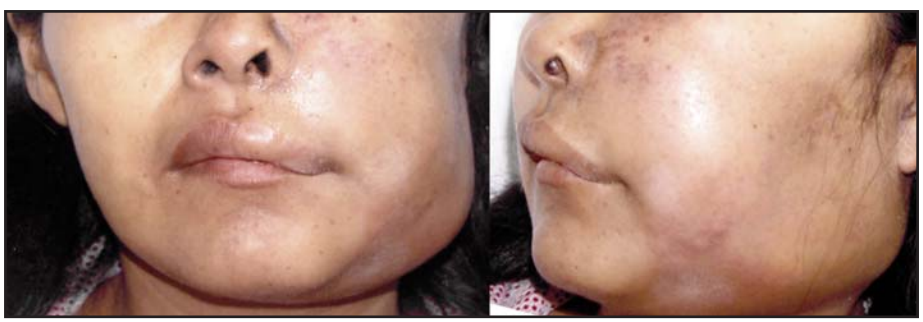

Fig. 1: Female patient, 30 years old. Tumorous lesion in left parotid gland. Patient complained of pain and paresthesia. One year of illness with slow, progressive growth. Diagnosed with high-grade MC and died six months later, after radiation treatment.

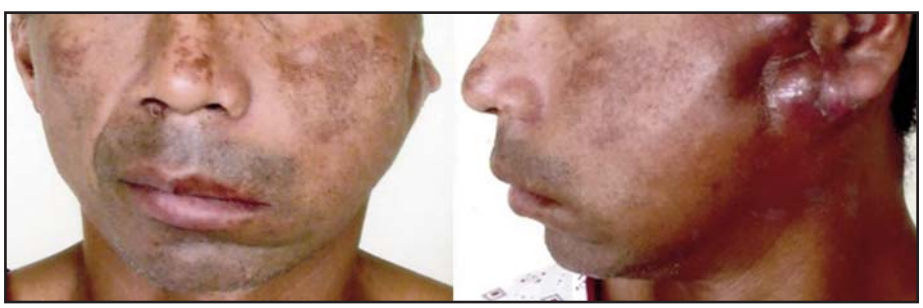

Fig. 2: Male patient, 48 years old. Tumorous lesion in left parotid gland. Patient complained of paresthesia. Diagnosed with high grade MC. Seventeen months after surgery and radiotherapy, presented pulmonary metastasis and died 5 months later.

all tumors in the minor salivary glands[20], with the palate being the most commonly affected site (with almost half the cases in hard palate, the second most frequent location after parotid gland), and they are found less frequently in other minor salivary glands such as those of the tongue, floor of the mouth, gum, lips and cheek mucosa, the ectopic salivary tissue being another location, though exceptional.

Clinically, in major glands, MCs appear as solitary, asymptomatic enlargements of the parotid body or pole, or of the submaxillary region[8]. In minor glands they appear as blue or purplish-red fluctuating masses with a smooth surface, and are often clinically mistaken for mucoceles[21].

The average latency period is one year, but may vary widely. MCs sometimes grow rapidly after a period of quiescence. In high-grade lesions there is onset of pain, facial paralysis and fixation in neighboring structures[8].

Discovery in minor glands is sometimes accidental during a routine mouth exploration. Rapidly growing tumors are very unusual. The surface is usually smooth, but if it is ulcerated, it is usually associated to more aggressive forms. If it is located at the base of the tongue it may cause dysphagia, while if it affects the bone it may cause insensitivity in teeth[6].

Histology

According to the bicellular theory, salivary gland tumors are formed by[22]:

a) Duct luminal cells and/or acinar cells plus myoepithelial cells,
b) Duct luminal cells or acinar cells, or
c) Myoepithelial cells only.

Histopathology thus identifies mucosecretory, epidermoid, intermediate[8,17,18,21], columnar or clear cells, proliferating alone or in different combinations, in a cystic or solid pattern[8,21].

In addition to this cell pattern, there is extracellular matrix produced by the neoplastic myoepithelial cells, collagen, elastic fibers, glycoproteins, glycosaminoglycans and proteoglycans[23].

The anatomical pathology shows they are partially encapsulated, with full encapsulation being very rare[8,21].

Most authors consider three grades of differentiation[8,21] depending on intracystic component, neural invasion, necrosis, mitotic activity and pleomorphism[24]. The histological grade in this study was classified following AFIP[25], published in the World Health Organization Classification of tumours[26] and shown in Table 1 and Figs. 3, 4 and 5.

Diagnosis

The differential diagnoses considered are: necrotizing sialometaplasia (of the palate), mucocele, inverted papilloma or cystadenoma, cystadenocarcinoma, primary or metastatic epidermoid carcinoma, and low-grade polymorphic adenocarcinoma[17].

The most useful and popular techniques for evaluating neoplasms of the salivary glands are currently Computerized Axial Tomography (CAT) and biopsy by needle aspiration. The latter, however, should be taken with precaution because its diagnostic precision is 60-80%, sometimes requiring a repetition of the aspiration or surgical biopsy. The histological information from the biopsy and delimitation of the lesion provided by CAT enable appropriate medical and surgical management[27].

Treatment

The treatment depends on the location, clinical aspect and histopathological grade. Low-grade MC is generally treated with surgery only, while high-grade tumors also require radiation and dissection of neck lymph nodes[28]. The management of intermediate-grade tumors is controversial, perhaps reflecting the controversy in tumor classification[29].

For tumors in accessory salivary glands, surgical excision is recommended, leaving 1-2 cm safety margins around the tumor[8].

For treatment of tumors in major glands, gland exeresis is recommended (superficial or deep parotidectomy, submaxilectomy)[8].

Cervical lymph notes are removed when lymph nodes are clinically affected (higher incidence of lymph node metastasis in submaxillary location)[8].

Radiotherapy after surgical treatment with tumor-free margins does not increase local control, as it does in advanced cases, cases with infiltrated resection margins and cases located at the base of the tongue[30]. Response to chemotherapy is low (best results have been achieved with methotrexate y cisplatin)[31].

Standard treatment for the main types of salivary gland cancer is surgical resection with adjuvant radiation to reduce failure rates[32-34] and even though

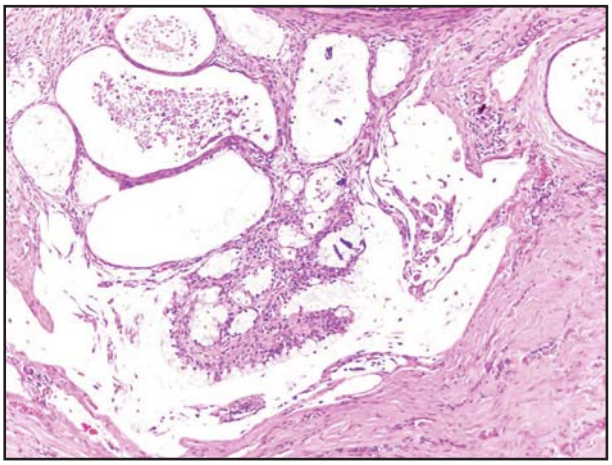

Fig. 3: MC, low grade. Histological image showing cystic structures lined with mucinous, squamous and intermediate cells with slightly atypical nuclei and low mitotic activity. Adjacent connective tissue without perineural invasion (H&E Orig. Mag. 100x).

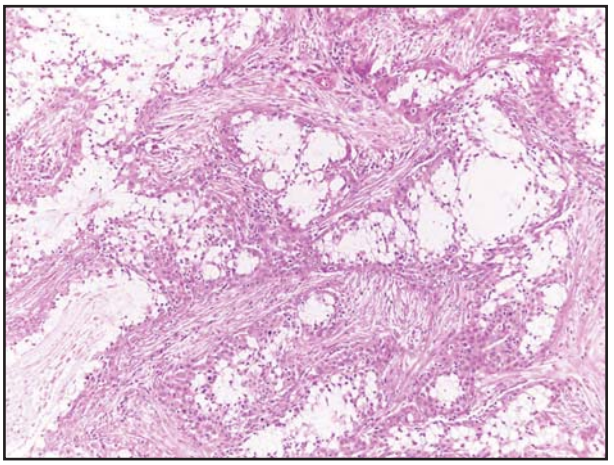

Fig. 4: MC, intermediate grade. Histological image showing tumor with small cystic structures, predominance of intermediate cells, with mucosecretory and epidermoid cells (H&E Orig. Mag. 100x).

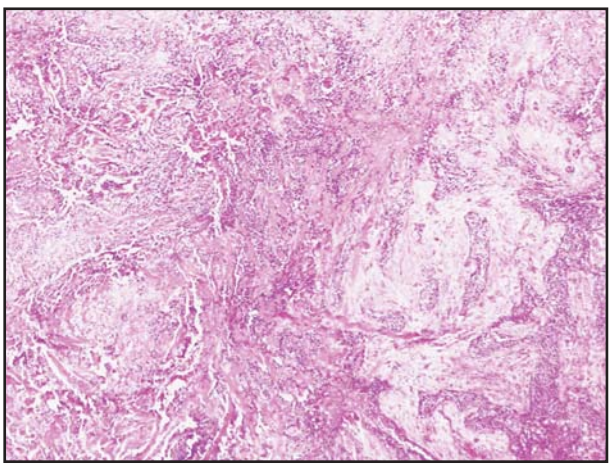

Fig. 5: MC, high grade. Histological image showing proliferations of solid islands of epidermoid and intermediate cells with few mucinous cells, with atypical nuclei and greater mitotic activity (H&E Orig. Mag. 100x).

Table 1: Histopathologic features used in grading MC. World Health Organization[26].

Histopathologic feature	Point value
Intracystic component <20%	2
Neural invasion	2
Mitosis (≥4/10 HPFs*)	3
Necrosis	3
Anaplasia	4
Tumor grade	**Point score**
Low grade	0 - 4
Intermediate grade	5 - 6
High grade	≥7

*HPF, High-Power Fields

the role of adjuvant chemotherapy has not been proven, it has been used to treat distant metastasis and non-excisable disease, and to reduce the effects of local/regional recurrence[35].

Adjuvant radiotherapy has been shown to have an advantage in survival of patients with tumors larger than 4 cm, but little benefit for patients with small tumors, suggesting that, together with the margins involved, tumors larger than 4 cm are an absolute indication for post-surgical radiotherapy[32,36-38].

Further progress in therapy is needed to improve the outcomes of histologic high-grade disease[39].

Prognosis

Prognosis depends on clinical stage[40], (related to anatomical location[41,42]), histologic grade (patients with low or intermediate-grade tumors have local control and favorable survival rates[39]) and treatment[40].

Variable prognostic factors have also been reported, such as neural invasion, vascular invasion, and local or distant metastasis, which are associated to clinical outcome for patients[25].

Other authors mention the same factors that influence survival, such as histologic grade, clinical stage, paralysis of facial nerve and lymph node

metastasis, in addition to location (worse prognosis in submaxillary), age and sex (better prognosis in young people and females). Mucoepidermoid tumor is one of the few tumors of salivary glands in which flow cytometry has high prognostic value, with greater survival in patients with diploid DNA patterns[6].

Regarding histologic grade, it has been reported that at the same histopathological grade, tumors in the parotid gland have better prognosis than tumors in the submandibular gland[43]. Prognosis is better for low-grade lesions and for high-grade lesions when they arein stage I or II[32,36,37,44]. MC prognosis appears to depend largely on tumor grade, with reports of 5-year MC survival rates of 92%-100% for low grade, 62-92% for intermediate grade and 0-43% for high grade tumors[25]. MCs with high grade malignancy have a 50% probability of presenting metastasis[17].

Some molecular factors of malignant cells also influence survival rate, e.g. p27, which is a highly favorable prognostic factor for MC, whereas Ki67 is not identified as a survival indicator[45].

Even with complete resection, there is still a substantial risk of local recurrence (16%-27%) and distant metastasis (13%-26%)[46,47].

The aim of this study is to present the epidemiology of salivary gland MC through thecasuistic in patients diagnosed at the "Dr. Eduardo Cáceres Graziani" National Institute for Neoplastic Diseases from 2002 to 2012.

MATERIALS AND METHODS

This is an observational, descriptive, cross-sectional, retrospective study which included subjects with primary diagnosis of mucoepidermoid carcinoma of the salivary glands diagnosed at "Dr. Eduardo Caceres Graziani" National Institute for Neoplastic Diseases, Lima, Peru, from January 2002 to December 2012. Clinical records with incomplete data were excluded.

The study was approved by the institutional review board (protocol: INEN 13:27) and conducted in accordance with the World Medical Association Declaration of Helsinki on medical research protocols and ethics.

The collected data were transferred to a Microsoft Excel program, on which the table was prepared.

The analysis was performed using Windows XP® Operative System (Washington, USA), with the assistance of the statistical program SPSS (Statistical Package for Social Sciences) version 20.0 for Windows (SPSS, Chicago, IL, USA).

All values found in the different statistical tests were considered with a significance level of 0.05 ($p<0.05$).

RESULTS

Between January 2002 to December 2012, 349 new cases were found of malignant tumors in salivary glands, of which 4.61% (51)cases were mucoepidermoid carcinoma.

All cases were diagnosed by pathological anatomy studies.

Table 2 shows the distribution of the different characteristics evaluated according to sex. There are more female patients (28 cases; 54.9%; female:male ratio 1.2:1). Age range was 12 to 88 years, with 64.71% of patients aged 60 years or less. In most cases (62.75%), tumor size was smaller or equal to 4 cm at the time of the first visit, and the most frequent location was parotid gland (74.51%). No significant difference was found for these characteristics. Among the signs and symptoms evaluated, the presence of paresthesia was statistically significant ($p=0.038$). Considering the TNM (T: primary tumor, N: cervical nodules, and M: distant metastasis) staging system for salivary gland carcinoma, cases were most frequently stage T2 (43.14%), which are tumors measuring 2-4 cm with no macroscopic extracapsular extension, N0 (86.27%), which are lesions without metastasis in regional nodules and M0 (68.63%), which is when there are tumors without distant metastasis. With regard to clinical stage, the largest number of cases was in clinical stage IV C (31.37%), followed by clinical stage II (29.41%). Regarding histological grade, cases were distributed evenly between low and high grade, with 39.22% each, and regarding treatment, surgery combined with radiotherapy was the treatment of choice, with 42.18% of the cases.

DISCUSSION

Most epidemiological studies of MC have found females to be affected more frequently than males, e.g Goode *et al*. studied 234 MC of the major salivary glands, finding that females accounted for 51.3%[43]. In our study, females accounted for 54.9%, a value similar to those reported by Villavicencio *et al*.[48] and Schwarz *et al*.[49]. Some authors report a 3:2 female:male ratio[16,18], and McHugh *et al*. report a

Table 2: Clinical pathological features of subjects with MC of the salivary glands.

	Clinical characteristics		Female		Male		*p* Value
			n	%	n	%	
Age (months)	Average		43.107		49.04		
	Minimum		18		12		
	Maximum		79		88		
	Up to 60 years		20	60.6	13	39.4	0.268
	Over 60 years		8	44.4	10	55.6	
Size (cm)	Average		4.25	3.56	5.17	2.96	
	Minimum		1.5		1		
	Maximum		20		12		
	Up to 4 cm		20	62.5	12	37.5	0.157
	Over 4 cm		8	42.1	11	57.9	
Location	Parotid gland		18	47.4	20	52.6	0.165
	Submaxillary gland		5	71.4	2	28.6	
	Minor glands		5	83.3	1	16.7	
Signs	Ulcer	No	24	57.1	18	42.9	0.487
		Yes	4	44.4	5	55.6	
	Pain	No	17	54.8	14	45.2	0.991
		Yes	11	55.0	9	45.0	
	Paresthesia	No	25	62.5	15	37.5	0.038*
		Yes	3	27.3	8	72.7	
	Dysphagia	No	27	56.3	21	43.7	0.439
		Yes	1	33.3	2	66.7	
	Trismus	No	27	54.0	23	46.0	0.360
		Yes	1	100	0	00.0	
TNM (T)	T1		7	70.0	3	30.0	0.235
	T2		13	59.1	9	40.9	
	T3		6	50.0	6	50.0	
	T4A		1	16.7	5	83.3	
	T4B		1	100	0	00.0	
TNM (N)	N0		25	56.8	19	43.2	0.224
	N1		3	75.0	1	25.0	
	N2A		0	00.0	2	100	
	N2B		0	00.0	1	100	
TNM (M)	M0		20	57.1	15	42.9	0.634
	M1		8	50.0	8	50.0	
Clinical stage	I		4	66.7	2	33.3	0.051
	II		9	60.0	6	40.0	
	III		4	57.1	3	42.9	
	IV A		1	50.0	1	50.0	
	IV B		2	40.0	3	60.0	
	IV C		8	50.0	8	50.0	
Histological grade	Low grade		14	70.0	6	30.0	0.068
	Intermediate grade		7	63.3	4	36.4	
	High grade		7	35.0	13	65.0	
Treatment	Sg		10	66.7	5	33.3	0.504
	Sg + Rt		10	47.6	11	52.4	
	Sg + Rt + Cht		0	0.0	1	100	
	Rt + Cht		1	100	0	0.0	
	Rt		7	53.8	6	46.2	

* Statistically significant value
TNM: Classification of Malignant Salivary Gland Tumor Stages.
Cht Chemotherapy; Rt Radiotherapy; Sg Surgery.

1:1.2 male:female ratio[39]. Another recent study is consistent with the above, finding 67% of the cases in females[29].

MC is the most common malignant neoplasm of the salivary glands in persons over 40 years of age[13,50]. Chomette *et al*. report that the onset of MC according to age is variable and may occur between the 2nd and 8th decades of life[6], in agreement with our study, in which on set ranged from the 2nd to 9th decades of life. Villavicencio *et al*. report onset from the 4th to 6th decades of life[48], and Rapidis *et al*. report 3rd to 9th decades of life[17]. Average age in all the aforementioned studies was the 6th decade of life, thus, average age of on set is reported as 52.2 years by Chomette *et al*.[6]; 54.3 years by Villavicencio *et al*.[48], and 56.7 years by Rapidis *et al*.[17]. These values are similar to the average age found in our study, which was 45.78 years. It is worth noting that this study found 8 cases of patients aged 19 years or under over the 10-year study period (0.8 cases per year), similar to findings reported by Techavichit *et al*. of 14 cases over a period of 15 years (0.9 cases per year) in patients aged 19 years or under[51].

Villavicencio *et al*. report that the clinical size of the primary tumor varies according to the anatomical site affected; with median size 8 cm (4 to 10 cm) in submaxillary gland and 3 cm (1 to 5 cm) in minor salivary glands[48]. Rapidis *et al*. found no statistically significant difference between tumor size according to site[17]. Katabi *et al*. report that tumor size was 0.5 to 9 cm, with an average value of 1.77 cm[29]. In our study, the average size was 4.67 cm.

MC is a neoplasm that usually affects major salivary glands, although 10% can arise in minor or accessory salivary glands in the head and neck area[24], including maxillary sinus, nasopharynx, nasal cavity, oropharynx, larynx and trachea. Our study was consistent with this observation, finding 74.51% of the cases in parotid gland, 13.73% in submaxillary gland and 11.76% in minor glands. Ellis *et al*. report that 74.5% of neoplasms of the salivary glands in general are found in the parotid gland[2], with a percentage identical to the one found in our study. The location of MC in our study was also consistent with Villavicencio *et al*. who reported 74.5% in major salivary glands (32 cases in parotid and 3 cases in submaxillary gland)[48]; Védrine *et al*., who reported 18 cases, of which 77.78% (14 cases) were in parotid gland, 11.11% (2 cases) in submaxillary gland and 11.11% (2 cases) in minor salivary glands[7]; Schwarz *et al*. who reported 60% (24 cases) in parotid gland, 10% (4 cases) in submandibular gland and 30% (12 cases) in minor glands[49], and Rapidis *et al*. who reported 18 cases, of which 66.6% (12 cases) were in major salivary glands (10 in parotid and 2 in submaxillary)[17]. Regarding location in minor salivary glands, Triantafillidou *et al*. report 56.25% in palate[40], while in our study, 100% of the minor salivary gland cases were located in the palate.

Signs and symptoms are varied, with none appearing as characteristic or pathognomonic, but the most outstanding in our study was pain, in agreement with Villavicencio *et al*., who report pain in 55.3% of their 47 cases[48]. It is worth noting that it is statistically significant (p=0.038) that most patients do not report paresthesia as a symptom at the time of the initial clinical examination.

Regarding the clinical stage of MC, Schwarz *et al*. report declining percentages for increasing stages, with 40% (16 cases) Type I, 30% (12 cases) Type II, 15% (6 cases) Type III and 15% (6 cases) type IV[49]. In our study, the highest number of cases was found for the last stage, IV (16 cases), followed by stage II (15 cases).

In most epidemiological studies presenting data on the histological grade of the disease, the distribution of the number of MC cases generally declines as the level of histologic grade rises, i.e. there is an inverse relationship. Rapidi *et al*. report a decline according to histological grade, with 9 tumors classified as low grade, 5 as intermediate grade and 4 as high grade[17]; Katabi *et al*. report 90.38% (47 cases) low grade, 3.85% (2 cases) intermediate grade and 5.77% (3 cases) high grade[29]; Védrine *et al*. report 68.75% (11 cases) low grade, 18.75% (3 cases) intermediate grade and 12.5% (2 cases) high grade[7], and Schwarz *et al*. report 67.5% (27 cases) low grade, 7.5% (3 cases) intermediate grade and 25% (10 cases) high grade[49]. Our study found equal numbers of cases for low grade and high grade with 39.22% (20 cases) each, and 21.56% (11 cases) intermediate grade. This higher percentage of cases with high histological grades may be due to the health culture in the Peruvian population, since people tend to consult a professional only when the disease is at an advanced stage.

Treatment is fairly well established, with most papers reporting surgical treatment and adjuvant radiation therapy, similarly to our casuistic, which shows that 41.18% was treated thus, which depends on the histologic grade. This is also reflected by follow-up case research such as Chen *et al*., which follows a series of 61 cases, all of which were treated with surgery and postoperative radiation, for over 10 years[52], and other papers which report casuistic of surgical treatment only, such as Rapidis *et al*., who treated 9 cases of parotid gland tumors with superficial or total parotidectomy, all with radical dissection of neck or suprahyoid dissection, with one parotid gland case being treated with hemimandibulectomy and suprahyoid dissection[17].

Based on the abovementioned findings, other studies were conducted which, in addition to the epidemiological contribution regarding this salivary gland disease, present the respective patient follow-up analyses for survival.

It is concluded that the epidemiology regarding age and gender of the 51 cases analyzed was in the same range as other studies, and that most cases were located in major salivary glands, in agreement with reports on other populations. Other characteristics showed a homogeneous distribution.

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