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Signs and symptoms of minor salivary gland benign tumors: our experience on 425 cases

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Abstract. *Objective:* This study's aim is to report the diagnostic workup, clinical features, lesion site, histopathological patterns and statistical analysis of a pure series of 425 minor salivary gland benign tumors.
Materials and methods: For each patient selected we analyzed age, gender, histotype, site of neoplasm and clinical signs. 425 patients (238 females and 187 males, the age ranging from 17 to 62) with a cytologic diagnosis of benign intraoral minor salivary glands tumors were reviewed.
Results: In our sample, statistical analysis revealed a higher frequency of pleomorphic adenoma recurrence in the palate. A higher probability to find during the clinical examination are swelling, ulcer or pain like primary signs and symptoms of a benign minor salivary gland tumor.-
Conclusion: To the best of our knowledge, this is the first report regarding a pure series of benign minor salivary glands tumors.

Introduction

Salivary gland tumors are uncommon. The reported incidence in literature is approximately 2-6.5% of all head and neck tumors. The oral cavity has 600-1000 minor salivary glands scattered in the labial, buccal, palatal and lingual mucosa.[1,2] Minor salivary gland tumors are uncommon lesions, representing 9–23% of all salivary gland tumors. Most studies grouped major and minor salivary gland tumors as one, and there is a restricted number of articles that examine minor salivary gland tumors separately. The prevalence of the benign intra-oral minor salivary gland tumors is not well documented in the literature.[1-7] Pleomorphic adenoma is the most common histotype of benign tumor of the minor salivary glands; the majority of these tumors occur in the palate, followed from the buccal mucosa and upper lip.[8-11] Other histotypes of benign tumor of minor salivary glands are the cystadenoma, basal cell adenoma, and cystadenolymphoma.[12-14] From 2006 to 2016 we observed 425 patients affected by minor salivary gland benign tumors referred to Maxillo-Facial Operative Unit, of the University of Naples Federico II and to Otolaryngology Unit of the University of Salerno. The aim of this study is to report the diagnostic workup, clinical features, lesion site, histopathological patterns and statistical analysis of a pure series of minor salivary gland benign tumors.

Materials and methods

In this retrospective study, the test sample has been recruited in two public Universities in Campania, Italy, in the last ten years. For each patient selected

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we analyzed age, gender, histotype, site of neoplasm and clinical signs.

425 patients (238 females and 187 males, the age ranging from 17 to 62) with a cytologic diagnosis of benign intraoral minor salivary glands tumors were reviewed. All patients underwent the following diagnostic protocol: 81 patients (18,9%), affected by the lip and buccal mucosa neoplasm, have executed ultrasound; the remaining of patients (81,1%) affected by neoplasm localized in sites not accessible by conventional ultrasound have executed CT scan, all patients underwent fine needle aspiration cytology (FNAC).

Each neoplasm was totally excised with capsule and with safety margins under local anesthesia. After a blunt dissection, the mucosal tissue was undermined, the tumor was visualized and carefully separated from the nerves and vessels. Hemostasis was achieved and closure was done with silk sutures. After surgery, antibiotics (amoxicillin+clavulanic acid 1 gr BID for 5 days) and corticosteroid (betamethasone 1 mg BID for two days and then QD for two days) was prescribed and the sutures were removed seven days after surgery. All patients were discharged two days after surgery.-

The histopathologic diagnosis was performed, according to WHO classification of 2005.[15] It confirmed the FNAC diagnosis of benign minor salivary gland tumors for all cases.

Each patient was followed postoperatively for one year; clinical examination was performed at 3, 6, and 12 months after surgery.

Statistical analysis

Statistical analysis was performed using R 3.0 for Window.

The frequency of different tumor and the different localization in the oral cavity were expressed as a number and as a percentage and analyzed using Chi-square test. A p-value of <0.05 was considered statistically significant. (Table 1-2)

The distribution of 425 patients affected by different tumor with different signs and symptoms, was expressed as a number and as a percentage and were analyzed using Chi-square test and Cramer's indicator. (Table 3, Table 4)

The Chi-square test was performed using the variable "benign tumor" and each sign and symptom (swelling, ulcer, pain, incorrect fitting prosthesis, cervical lymph nodes involvement) to obtain a statistical dependence.

Results

In the 425 patients included in the study were diagnosed pleomorphic adenomas (352 patients), cystadenomas (51 patients), basal cell adenomas (19 patients) and cystoadenolymphoma (3 patient). The affected locus was distributed between the hard palate (343 patients: 308 pleomorphic adenomas, 31 cystoadenomas, 4 basal cell adenomas), the buccal mucosa (69 patients: 40 pleomorphic adenomas, 2 cystoadenolymphoma tumor, 12 basal cell adenomas, 15 cystadenoma), lips (13 patients: 4 pleomorphic adenoma, 1 cystoadenolympomas, 3 basal cell adenoma and 5 cystadenomas). (Table1)

Table 1

Frequency of different benign tumor in different anatomic sites (affected locus) in the oral cavity.

Benign Tumor	Palate		Lips		Buccal mucosa		Total	
Pleomorphic adenoma	308	87,5%	4	30,7%	40	57,9%	352	82,8%
Cystoadenoma	31	9%	5	38,4%	15	21,7%	51	12%
Basal cell adenoma	4	1,1%	3	23,07%	12	17,3%	19	4,47%
Cystadenolimphoma	0	0%	1	7,69%	2	2,9%	3	0,7%
Total	343	80,7%	13	3,05%	69	16,2%	425	100%

Table 2

Analysis of the affected locus of benign salivary glands tumour (Chi-square Test, $P<0,05$)

	Palate	Other sites	p
Pleomorphic Adenoma	308	44	0,00001
Cistoadenoma	31	20	
Basal cell Adenoma	4	15	
Cistoadenolinphoma	0	3	

Table 3
Distribution of 425 patients following benign tumor, signs, and symptoms.

Benign Tumor	Total		Symptoms															
			Swelling			Ulcer			Pain			Uncorrect fitting prosthesis			Cervical lymphonodes involvement				
			Yes		No	Yes		No	Yes		No	Yes		No	Yes		No	
Pleomorphic adenoma	352	302	(85,7%)	50	(14,3%)	116	(33%)	236	(67%)	116	(33%)	236	(67%)	32	(9)	320	(91%)	4	(1,13%)	348	(98,8%)
Cystoadenoma	51	15	(29%)	36	(71%)	22	(43%)	29	(57%)	22	(43%)	29	(57%)	0	(0%)	51	(100%)	4	(7,8)	47	(92,2%)
Basal cell adenoma	19	1	(5,3%)	18	(94,7%)	7	(36,8%)	12	(63,2%)	7	(36,8%)	12	(63,2%)	0	(0%)	19	(100%)	0	(0%)	19	(100%)
Cystadenolimphoma	3	1	(33,3%)	2	(66,6%)	0	(0%)	3	(100%)	0	(0%)	3	(100%)	0	(0%)	3	(100%)	0	(0%)	3	(100%)
Total	**425**	**317**	**(74,5%)**	**106**	**(25,5%)**	**145**	**(34%)**	**280**	**(66%)**	**145**	**(34%)**	**280**	**(66%)**	**32**	**7,5%**	**393**	**(92,5%)**	**8**	**(1,8%)**	**417**	**(98,2%)**

In our sample, 302 patients with pleomorphic adenoma presented intraoral swelling, of these 116 presented also a decubitus ulcer and pain (caused by the wear of prosthesis on the swelling); 32 presented also an unfitting prosthesis; 4 patient presented also reactive cervical lymph nodes; 50 were asymptomatic.

As regards the 51 patients with cystadenoma: 15 patients presented intraoral swelling, 22 presented ulceration of the oral mucosa (caused by biting of mucosa) in association with pain, 4 patients presented reactive lymph nodes.

As regards the 19 patients with basal-cell adenoma 1 of them presented intraoral swelling, 7 presented pain, 7 were asymptomatic.

1 of the 3 patients with cystadenolymphoma presented swelling of the upper lip mucosa, 2 were asymptomatic. (Table 3)

No patient reported early or late postoperative complications. There was uneventful healing without recurrence of pathology.

The statistical analysis (Chi test p=0,00001) revealed a dependence connection between the "benign tumor" (histotype) and the anatomic localization. From our analysis of a sample, pleomorphic adenoma is a histologic tumor that occurs in the palate with a major frequency (87,5%). (Table1)

The statistical analysis is significant with a dependence between the variable "benign tumor" and the sign "swelling" and "cervical lymph nodes involvement", respectively with a Chi-square p-value of 0,0 and Cramer's indicator value of 0.55 and Chi-square p-value of 0,001 and Cramer's indicator value of 0.16. (Table 4)

Discussion

Salivary gland tumors are relatively uncommon lesions affecting predominantly major salivary glands. The reported incidence represents about 5% of all head and neck tumors. Minor salivary glands scattered beneath the labial, buccal, palatal and lingual mucosa are about 1000.[1,2] Minor salivary gland tumors are uncommon lesions, representing 9-23% of all salivary gland tumors. Pleomorphic adenoma is most common minor salivary gland tumor in the mouth, but the incidence of other minor salivary gland tumors is difficult to ascertain due to their rarity and their frequency is not well documented in the literature. Also, most series

Table 4

Significant statistical evidence about dependence between benign tumor and swelling, ulcer, and pain. The binding force (Cramer's Value) is strong for swelling and cervical lymph nodes involvement

Symptoms	Chi statistic	Chi p-value	Result	Cramer's V
Swelling	12,97	0,000000	Dependent	0,55
Ulcer	6,73	0,080891	Not Dependent	0,13
Pain	6,73	0,080891	Not Dependent	0,13
Uncorrect fitting prosthesis	7,18	0,066473	Not Dependent	0,13
Cervical lymphonodes involvement	11,29	0,010238	Dependent	0,16

reported in the literature include both major and minor salivary gland tumors, making it difficult to evaluate their real frequency and site distribution.[1-7] From 2006 to 2016 we observed 425 patients affected by minor salivary gland benign tumors referred to our Operative Units. According to literature, the present study reports that benign tumors of minor salivary glands are more common in females (56%) than in males (44%) with age ranging from 17 to 62.[16] The anatomical distribution of minor salivary gland tumors is predominant in the palate followed by an upper lip and buccal mucosa.[4,17] In our study, the predominant localization site is the palate (80,7%) followed by buccal mucosa (16,2%), and lips (3,1%). (Fig.1)

The role of imaging in the diagnosis of benign minor salivary gland tumors is to define: localization, shape and dimension, contour, malignant features, nodal involvement. The ultrasound exam is a primary diagnostic tool for major salivary gland tumors; minor salivary gland tumor of the oral cavity are not all accessible by conventional ultrasound; in these cases, MRI or CT is mandatory to evaluate tumor extent and its radiographic features.[18] The role of fine needle aspiration cytology (FNAC) is critical in the diagnosis and therapy of benign minor salivary gland tumors. The value of FNAC is to obtain a specific diagnosis with a specificity of 95%, the sensitivity of 97, 6% and diagnostic accuracy of 96,3%; it should be considered in the first line investigation of benign minor salivary gland tumors.[19,20] FNAC is a technique involving the collection and evaluation of cells obtained from a thin-gauge needle (typically a 22 to 25 gauge needle). Fine-needle aspiration cytology can be utilized to confirm malignancy, to confirm a benign lesion, or to provide material for ancillary studies. The advantages of fine-needle aspiration include the following: minimally invasive procedure, greater cost-effectiveness, low risk of complication, and comparable diagnostic accuracy in comparison to histology. In our study, 81 patients (18,9%), affected by lip and buccal mucosa neoplasm, have executed ultrasound; the remaining of patients (81,1%) affected by neoplasm localized in sites not accessible by conventional ultrasound have executed CT scan, all patients underwent fine needle aspiration cytology (FNAC). It is essential

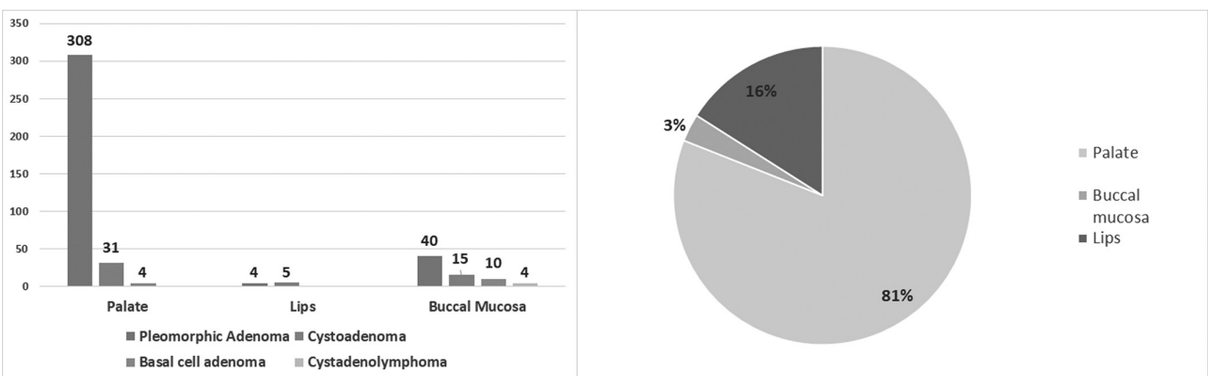

Figure 1

Frequency of different benign tumors in different anatomical sites (affected locus)

conducting a right diagnosis of minor salivary gland tumors, having an accurate anamnesis to know the times and the type of onset of the tumors and the clinical examination to define the shape, the approximate size, the mobility, the texture and the condition of the tissues that cover the tumor. The differential diagnosis of intraoral benign tumors of minor salivary glands includes buccal abscess, dermoid cysts, sebaceous cyst, neurofibromas, lipoma, mucoepidermoid carcinoma, and polymorphous low-grade adenocarcinoma.[15]

Most patients of our data referred to the hospital had intraoral swelling (75,05%) as a primary symptom. Involvement of reactive cervical lymph nodes is a rare presentation (1,88%). Other clinical signs and symptoms include ulceration of the upper mucosa and pain (34,1%), misplacement of the dental prosthesis (7,52%). In 425 patients of our series, the experienced symptoms were decubitus ulcer due to the unfitting dental prosthesis and pain, intraoral swelling, reactive cervical lymph nodes; 59 patients were asymptomatic.

The surgical treatment provided the total removal of the tumor, closure or reconstruction of the resulting defect and complete restoration of function and aesthetics.[2] After, excision is a mandatory histological typing of salivary gland tumors according to the WHO classification of 2005 histopathological description of tumor, subclassification and differential diagnosis between examined tumor and similar neoplasm.[15]

All patients of our data underwent ~~to~~ total excision of the tumor with immediate closure or reconstruction of the surgical gap.

The histopathological diagnosis was performed for all neoplasm excised and it confirmed the FNAC diagnosis.

In most studies, pleomorphic adenoma is described to be the most common benign minor salivary gland tumor, with a variable frequency ranging from 60% to 80% followed by myoepithelioma tumor, canalicular adenoma, basal cell adenoma, intraductal papilloma, follow in frequency the pleomorphic adenoma. The monomorphic adenoma constitutes about the 19% of benign tumors, followed by cistoadenolymphoma 9% and papilliferum sialoadenoma 2%.[2,3,21] In our study, the predominant histotype was the pleomorphic adenoma (82.8%) followed by cystadenoma (12%), basal-cell adenoma (4.47%), and cystadenolymphoma (0,7%).

The particular tumor that we have observed was a rare case of cystadenolymphoma (Warthin tumor) in a 32 years old man, with a gradual growth, the huge size of about 3 cm, located in the upper lip buccal mucosa. The Warthin tumor of minor salivary glands was described previously only in some case reports.[22,23] Histological analysis confirmed the features of Warthin tumor: solid growth delimited by cystic spaces, oncocytic epithelial cells arranged in a double layer with the underlying reactive lymphoid tissue arranged to form follicles with germinal centers, B and T Lymphocytes.[24]

The statistical analysis of our sample highlighted the dependence between the variable "benign tumor" and the variably affected locus (Chi-square p value=0,0001).

From our analysis of a sample, pleomorphic adenoma is a histologic tumor that occurs in the palate with a major frequency. (Table 2)

The statistical analysis of our sample highlighted the dependence between the variable "benign tumor" and the different signs and symptoms treated like single variables. Particularly, statistical significance was demonstrated between a benign tumor and swelling (Chi p-value of 0,0), and "cervical lymph nodes involvement (Chi p-value of 0,001). (Table 4)

From our analysis, swelling, ulcer, and pain occurred with major frequency in a benign salivary gland tumor. Through the review of the international literature, to the best of our knowledge, we found samples combining the data of minor and major salivary gland tumors; a restricted number of articles examined minor salivary gland tumors separately including benign and malignant tumors; no article report malignant and benign tumors separately.[2,3,21,25]

Conclusion

Our study reports a pure series of 425 cases of benign minor salivary gland tumors.

In our sample, statistical analysis revealed a higher probability to find a benign tumor in the palate and a higher frequency of pleomorphic adenoma recurrence in the palate.

Furthermore, our analysis showed a major probability to find, at the clinical examination, swelling like primary sign and symptom of a benign minor salivary gland tumor while lymph nodes involvement is a rare presentation.

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