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Original Article

Parenchymal changes of salivary glands adjacent to a variety of salivary gland disorders

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Abstract: A fully developed tumor is the first manifestation of a typical salivary gland neoplasm. Identification of precursor lesions and the accompanying clinical findings may improve our understanding of these tumors. The frequency of possible precursor lesions of salivary gland tumors have not been systematically investigated to date. In this study, slides of 661 cases from three pathology laboratories in Ankara, Turkey were reviewed to search for possible precursor lesions. Salivary gland parenchymal changes adjacent to a variety of salivary gland disorders such as metaplastic changes, ductal epithelial hyperplasia, adenomatoid ductal hyperplasia, adenomatoid oxyphilic hyperplasia, adenomatoid hyperplasia of the minor salivary glands, myoepithelial sialadenitis and dysplasia were screened histologically as potentially precursor lesions. Nuclear protein Ki-67 and cellular tumor antigen p53 were also analyzed immunohistochemically in selected cases. Approximately 16% of the cases in this series contained various types of pathologic hyperplasia. Only a minority of these lesions were originally reported, so most of the findings in this study were not part of the original histology reports. The majority of these parenchymal changes were seen in parotids. Adenomatoid ductal hyperplasia was the most frequent possible precursor lesion, and it was found most frequently around pleomorphic adenomas. Although the biological significance of most of the lesions described in this report still remains to be understood completely, efforts to define and detect possible preneoplastic lesions should be intensified. We believe that detection and eradication of the precursors is the best way of decreasing the overall morbidity caused by salivary gland tumors.

Keywords: Salivary gland, precursor lesions, hyperplasia, dysplasia, neoplasm

Introduction

Many, if not most, of the epithelial tumors develop from a precursor stage. A precursor stage may be short and can be easily missed. Therefore, a clinically, fully developed tumor is the first manifestation in most cases, including the tumors of the salivary glands. It is rather difficult to diagnose precursor lesions in internal tissues and organs because they rarely produce clinical symptoms. Awareness of the putative precursors and screenings to detect mass forming precursors may help early diagnosis. One of the best ways of finding precursor lesions is the careful screening of areas surrounding neoplastic lesions.

Numerous attempts have been made to get comprehensive information on a variety of putative precursor lesions of salivary glands [1-6]. These studies have mainly focused on the importance of metaplasia and hyperplasia occuring in salivary glands wich were excised either for chronic inflammation or tumors. Detection of precursor lesions is probably the most efficient approach in improving management of tumors and decreasing their morbidity. Some abnormal proliferative changes in the vicinity of neoplastic lesions can be considered as putative precursors. The actual incidence of these changes have not been systematically investigated to date. On the other hand, there are neither specific clinical nor radiologic findings nor consistent immunophenotypic changes in the potential precursor lesions of the salivary gland tumors which may be used to facilitate early detection.

In this study, we tried to examine the surrounding tissues of the main lesions in samples of

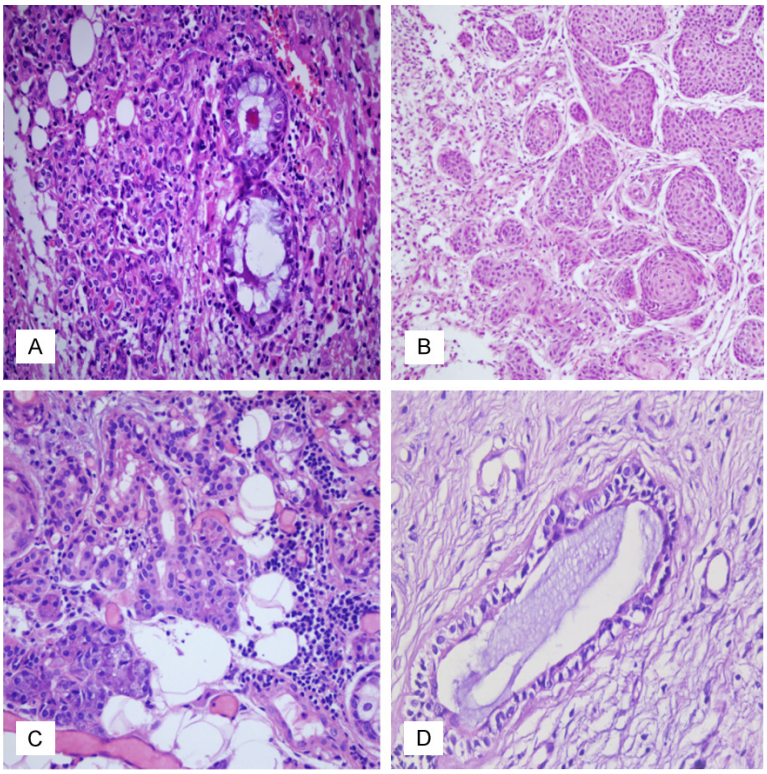

Figure 1. A selection of metaplastic changes. A. Mucinous metaplasia characterised by an increased number of mucous cells lining striated ducts. This example is associated with intercalated duct hyperplasia. B. Necrotising sialometaplasia composed of squamoid changes in acinar epithelium. C. Acinar squamoid and sebaceous metaplasia, associated with chronic inflammation. D. Clear cell change in the myoepithelial layer of excretory ducts (H&E, ×200).

minor and major salivary glands, in detail. Various types of metaplasia, ductal epithelial hyperplasia, adenomatoid ductal hyperplasia, adenomatoid oxyphilic hyperplasia, adenomatoid hyperplasia of the minor salivary glands, myoepithelial sialadenitis and dysplasia were noted. We believe that awareness of these changes with their associated distinct clinical findings, as well as morphologic and molecular evaluations, may provide further information about determining our approach to many salivary gland tumors.

Material and methods

Hematoxylin and eosin stained slides of biopsy or excision materials of 661 cases seen betweeen 2005-2017 in three pathology laboratories were reviewed. Of these, Gülhane Military Medical Academy, Faculty of Medicine, Department of Pathology contributed 584 (88%), Gören Pathology Laboratory contributed 61 (9%), and TOBB University of Economics and Technology, Faculty of Medicine Department of Pathology contributed 16 (3%) of these cases. Relevant clinical data about location as well as the main histologic diagnosis of the materials were recorded. All histologic slides were reexamined in detail. The surrounding tissues of the main lesion were screened for possible putative precursor lesions.

The presence of mucinous, squamoid, oxyphilic, sebaceous and clear cell metaplasia was recorded for each case (**Figure 1**). Other recorded lesions include the following: ductal epithelial hyperlasia, adenomatoid ductal hyperplasia, adenomatoid oxyphilic hyperplasia, adenomatoid hyperplasia of the minor salivary glands and myoepithelial sialadenitis. Ductal epithelial hyperplasia occurs in various forms such as increased stratification, intraluminal papillary or solid plaque like proliferation, cribriform structures and luminal obliteration due to proliferation. Adenomatoid ductal hyperplasia is an unencapsulated, densely populated ductal proliferation without acompanying desmoplastic stroma. These usually contain intercalated type ducts lined by low cuboidal or columnar epithelium and myoepithelial cells. Adenomatoid hyperplasia of the minor salivary glands is a hamartomatous or choristomatous proliferation forming a mucosal mass. Myoepithelial sialadenitis is characterized by large, irregular ducts with a mixture of epithelial-myoepithelial proliferation and obliterated lumina forming irregularly shaped islands. The degree of ductal and glandular epithelial dysplasia was recorded as either low or high.

Ki-67, a nuclear marker for determination of the growth fraction, and p53, a cellular tumor antigen, a key factor in the pathogenesis of human cancers were analyzed immunohistochemically. The degree of nuclear Ki-67 and

Table 1. Documentation of possible preneoplastic lesions of salivary glands

	Number of cases	Location	Main Diagnosis		
			Inflammatory	Benign Tumors	Malignant Tumors
Possible Preneoplastic Lesions	117	71 P	33	47	24
		19 SM			
		27 M			
Metaplasia	41	19 P	19	10	12
		12 SM			
		10 M			
Mucinous	18	7 P	1	3 PA	1 ACC
		9 SM	7	1 W	1 SDC
		2 M	2		1 SCC
					1 MMM
Squamous	13	6 P	2		2 MEC
		1 SM	5		1 SCC
		6 M			1 LVEP
					1 MMM
					1 MEC
Oxyphilic	5	2 P	1	2 PA	1 MMM
		2 SM	1		
		1 M			
Sebaceous	4	4 P		4 PA	
Clear	1	1 M			1 ACC
Ductal Epithelial Hyperplasia	5	4 P		4 PA	1 MEC
		1 M			
Adenomatoid Ductal Hyperplasia	46	37 P	4	23 PA	1 ACC
		7 SM	4	4 W	1 BCC
		2 M	2	1 PA	1 DC
					2 MMM
					1 SCC
					2 MMM
Adenomatoid Oxyphilic Hyperplasia	5*	5 P		2 PA	
				2 OA	
Adenomatoid Hyperplasia of Minor Salivary Glands	11*	3 T			
		3 V			
		2 P			
		1 B			
		1 AC			
		1 R			
Myoepithelial Sialadenitis	5	5 P	4	1 LH	
Dysplasia	4**	1 P	1 MEC		
		3 M	2 IS- SCC		

Locations: P: Parotid, SM: Submandibular Gland, M: Minor Salivary Gland, T: Tonsil, U: Uvula, B: Buccal area, AC: Alveolar Crest, R: Retromolar area. Benign tumors: PA: Pleomorphic adenoma, W: Warthin tumor, LH: Langerhans Cell Histiocytosis. Malignant tumors: ACC: Adenoid cystic carcinoma, SDC: Salivary Ductus Carcinoma, SCC: Squamous Cell Carcinoma, MMM: Metatatic Malignant Tumor, MEC: Mucoepidermoid Carcinoma, LYEP: Lymphoepithelial Carcinoma, BCC: Basal Cell Adenocarcinoma, OC: Oxyphilic Carcinoma, IS-SCC: In-situ Squamous Cell Carcinoma. *Clinically produced mass. **One case was incidentally detected.

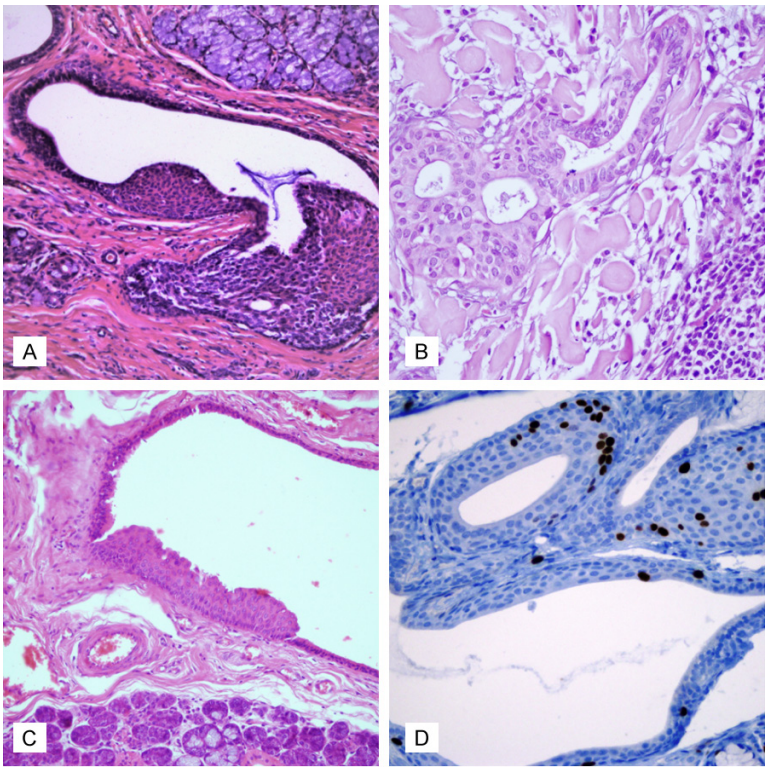

Figure 2. Ductal epithelial hyperplasia is usually seen in excretory ducts. A. Plaque like proliferation of basaloid cells. B. Intraductal proliferation and bridging of ductal epithelial cells. C. Focally increased stratification of columnar epithelial cells. D. Increased Ki-67 activity in the epithelium of hyperplastic ducts (H&E, ×200).

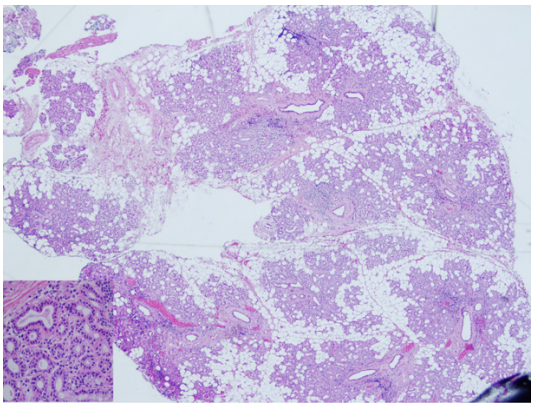

Figure 3. Multifocal, adenomatoid ductal hyperplasia with irregular borders (H&E, ×40). Proliferated intercalated ducts lined by a single layer of cuboidal epithelium (inset, H&E, ×200).

P53 positivity was evaluated in various types of hyperplasia and dysplasia. For these studies new sections were cut from paraffin blocks in cases of ductal epithelial hyperplasia (4 cases), adenomatoid ductal hyperplasia (10 cases), myoepithelial sialadenitis (2 cases) and epithelial dysplasia (3 cases) and stained immunohistochemically. Monoclonal antibodies against Ki-67 (clone SP6, dilution 200, Thermo Fisher Scientific, Fremont, CA, USA) and p53 (DO-7+BP53-12, dilution 100, Thermo Scientific Lab Vision Corp. CA, USA) and the streptavidin-peroxidase technique were used for immunostainings. The degree of nuclear Ki-67 and P53 staining was recorded and representative microphotographs were taken from the hot spots at the same magnification. Positive cells were manually counted and mean percentage of positive cells were grouped as low (< %10) and high (≥ %10). With a calculator program (Microsoft Office Excel 2007, Microsoft Corp., Washington), simple statistics were used when calculating the degree of nuclear Ki-67 and P53 staining. The density of positive tumor cells was compared with the those nonneoplastic cell population in the adjacent non-involved salivary gland parenchyma.

Results

Of the 661 biopsies, approximately 16% included metaplasia or a type of pathologic hyperplasia. A brief documentation of possible precursor lesions, their locations and any associated lesions are shown in **Table 1**. The majority of the possible preneoplastic lesions was seen in parotids (71 cases), and then minor salivary glands (27 cases), and submandibular glands (19 cases). Adenomatoid hyperplasia of the minor salivary glands was the main histologic diagnosis in eleven cases. These involved different parts of the oral cavity, and they produced a mucosal mass lesion which was the cause of excision. Similarly, in four cases a palpable mass lesion was produced by nodular ductal and oxyphilic adenomatoid hyperplasia. Most of the findings documented in this study were not part of the original histology reports. However, certain potentially important findings

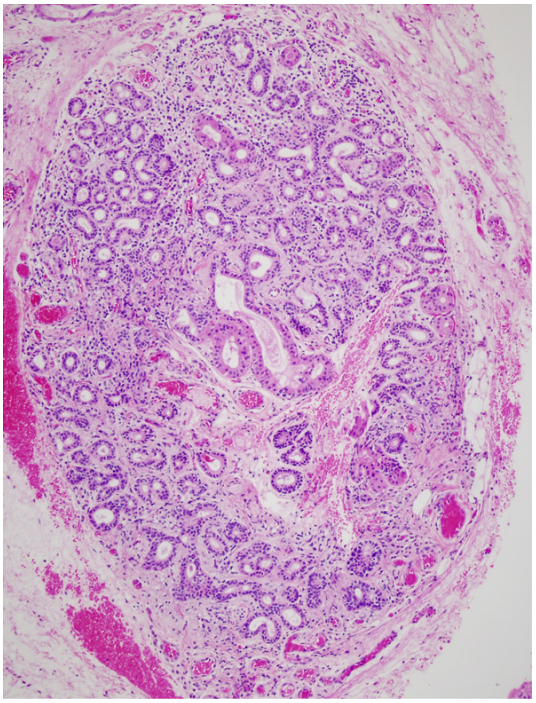

Figure 4. Nodular adenomatoid ductal hyperplasia, a circumscribed, unencapsulated proliferation (H&E, ×200).

were originally reported: Dysplasia (4 cases), myoepithelial sialadenitis (5 cases), sclerosing adenosis-like proliferation (2 cases), adenomatoid oxyphilic hyperplasia (5 cases), necrotizing sialometaplasia (3 cases) and adenomatoid ductal hyperplasia (2 cases).

Most of the metaplastic changes were associated with inflammatory lesions (19 cases). Metaplastic changes were seen in the parotid [19 cases], the submandibular gland [12 cases], and the minor salivary glands [10 cases]. A variety of ductal epithelial hyperplasias (5 cases) including dilatation and distortion of ducts, reserve cell like solid proliferation, focally increased stratification of low columnar epithelium, cribriform adenotubular structures narrowing the lumen, and papillary hyperplasia were noted (**Figure 2**).

Adenomatous ductal hyperplasia was relatively frequent in parotids and it was seen most frequently around pleomorphic adenomas. These can occur as focal, multifocal, poorly defined or circumscribed lobular lesions (**Figures 3**, **4**) without encapsulation and with no stromal desmoplasia. Small, uniform, densely populated intercalated duct proliferation forms the main

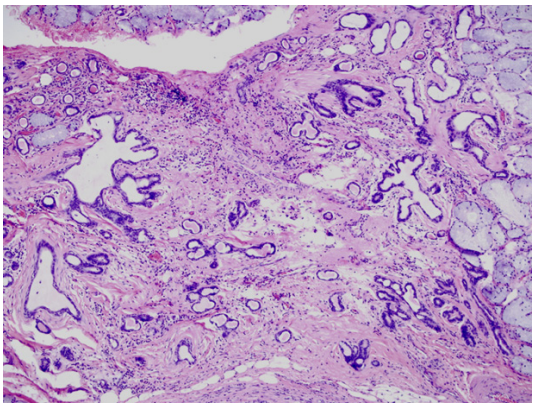

Figure 5. Proliferation of irregular branching ducts within a sclerotic stroma reminiscent of sclerosing adenosis of the breast (H&E, ×200).

component, and some striated ducts accompany the proliferation. The proliferated ducts were usually composed of bilayered, inner cuboidal epithelial and outer myoepithelial cells. Two cases of sclerosing adenosis like adenomatoid ductal hyperplasia, which exhibited both ductal epithelial and associated myoepithelial proliferation within the hyalinized stroma, were interpreted as sclerosing adenosis like proliferation (**Figure 5**). A well circumscribed, unencapsulated, incidental small nodular hyperplasia of mucous duct epithelium was considered as mucinous microadenoma (**Figure 6**). All adenomatoid oxyphilic hyperplasias were seen in parotids (5 cases) and were adjacent to benign tumors. Two of the accompanying tumors were oxyphilic adenomas. One of the adenomatoid oxyphilic hyperplasia cases produced a mass which was the only histologic abnormality found in the excised material. Most of the adenomatoid oxyphilic hyperplasias were composed of multiple nodules, without encapsulation. They were irregularly distributed within the normal salivary gland parenchyma and interstitial fat (**Figure 7**).

Adenomatoid hyperplasia of the minor salivary glands formed intraoral mucosal mass lesions, and they were the main reason for the biopsy (**Figure 8**). Most of these hyperplasias were located in the tongue, the uvula, and the palatal mucosa.

Myoepithelial sialadenitis was found in five cases in this series. Four of these were associated with Sjögren syndrome. In two the cases showed that a rather extensive epithelial-myo-

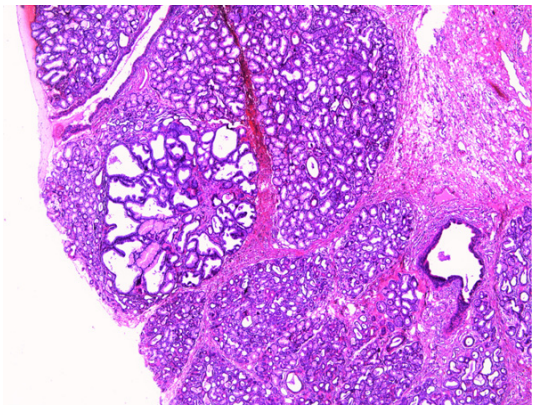

Figure 6. This incidental, circumscribed, unencapsulated, nodular hyperplasia of mucous ducts was considered as mucinous microadenoma (H&E, ×100).

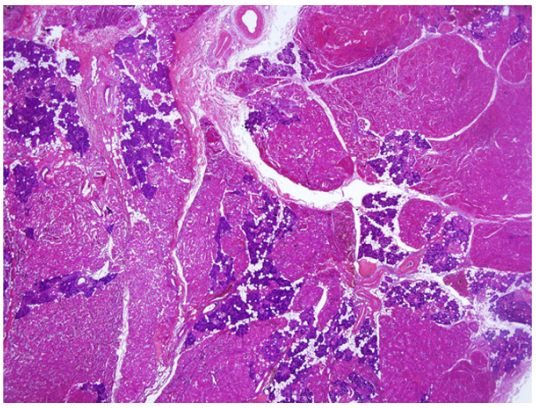

Figure 7. Widespread nodular oxyphilic hyperplasia replacing the normal parenchyma of the salivary gland (H&E, ×40).

epithelial proliferation was present (**Figure 9A**). One of these was within a salivary gland involved by Langerhans cell histiocytosis. This lesion was composed of numerous small basaloid islands (**Figure 9B**).

Dysplasia was recorded in excretory ducts in four cases. Two of these were high grade and were associated with dysplasia of the oral mucosal surface epithelium (**Figure 10A**). The dysplasia in these cases seemed like an extension of the surface dysplasia to the excretory ducts. One of the low grade dysplastic changes was found around a mucoepidermoid carcinoma in a parotid. The last one was an incidental low-grade dysplasia within the minor salivary gland with accompanying atrophic changes and inflammation (**Figure 10B**).

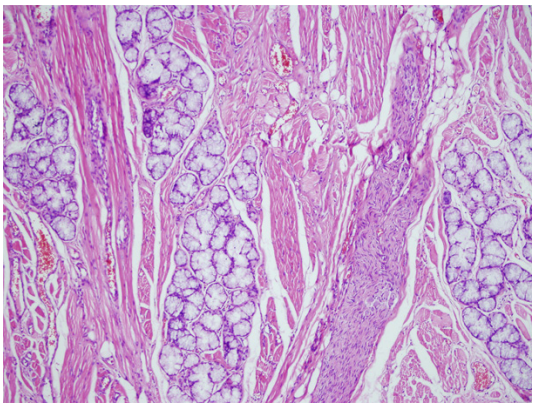

Figure 8. The histologic appearance of adenomatoid hyperplasia of the minor salivary glands in between striated muscle and collagen fibers as well as peripheral nerves (H&E, ×200).

The degree of nuclear Ki-67 and P53 staining was evaluated in various types of hyperplasia and dysplasia. The surrounding normal salivary glands showed practically no staining. An increased (low level) Ki-67 immunohistochemical staining separated adenomatoid ductal proliferations from the surrounding tissues (**Figure 11**). Low level Ki-67 expression was also found in ductal epithelial hyperplasia (**Figure 2D**). High levels of Ki-67 positivity were found in the dysplastic epithelium (**Figure 12A**). Similarly, strongly nuclear p53 immunopositive cells were found in all dysplasia cases (**Figure 12B**). P53 expression was very infrequent and in ductal epithelial hyperplasias, adenomatoid ductal hyperplasias and myoepithelial sialadenitis.

Discussion

Detection of possible preneoplastic lesions and eradication of them, when possible, is the best way of decreasing the overall morbidity caused by tumors. A variety of aberrant proliferative lesions provides appropriate environments for neoplastic development. Takeda and Yamamoto [1] suggested that some hyperplastic changes might be preneoplastic and might share some features of neoplastic lesions. Different types of proliferative changes occurring in salivary gland parenchyma, such as metaplasia, pathologic hyperplasia, and dysplasia, are the subjects of this study. Many clinical and histopathological appearances of non-neoplastic aberrant proliferative lesions may resemble those of certain neoplasms [2].

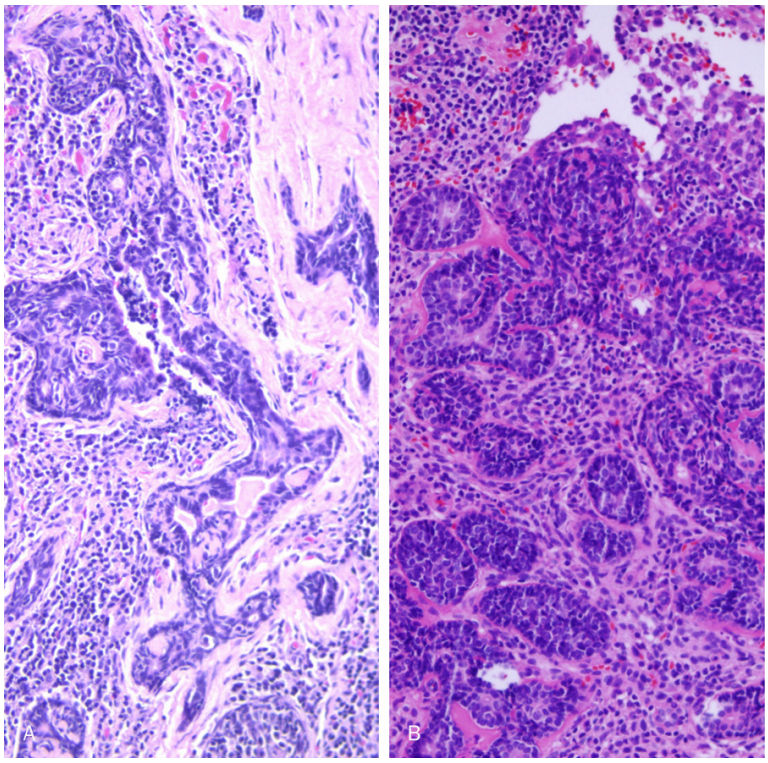

Figure 9. A. Extensive epithelial-myoepithelial proliferation in Sjögren syndrome. B. Islands of epithelial-myoepithelial proliferation within a salivary gland involved by Langerhans cell histiocytosis (H&E, ×200).

The factors that cause metaplasia, if they persist, can predispose tumors to dysplastic change and may even initiate malignant transformation of the metaplastic epithelium [9, 10]. Metaplasia in the internal organs such as the pancreas, breasts, and salivary glands may be more life threatening than those seen in the exposed surface epithelia. The malignant potential of metaplasia is usually related to the presence and degree of dysplasia. In this study, no dysplasia was detected in cases of metaplasia. Oxyphilic metaplasia is similar to that seen in Warthins tumor in being multifocal. We tend to agree with Griffiths and Dekker [11], who suggested they saw no reason why oxyphilic metaplasia should be regarded as any more or less neoplastic than Warthin's tumor.

Ductal epithelial hyperplasia may display architectural changes like intraluminal acanthotic growth, papillary, adenotubular, or cribriform formations [1]. Evaluating cytologic changes in the hyperplastic epithelium as potential risk factors for neoplastic growth is rather difficult and challenging. Most of our cases were encountered in the parotid, around salivary gland tumors, and especially around pleomorphic adenomas. Naumheim [6] suggested that adenomatous ductal hyperplasia might act as a precursor. These changes range from hyperplasia to encapsulated adenomas with hybrid patterns in between which may well represent precursor lesions for some salivary gland tumors [5]. Weinreb [5] believes that large hyperplastic lesions may deserve to be considered incipient adenomas. Eveson and Speight [4] suggested that since epithelial-myoepithelial carcinomas of the salivary gland are frequently associated with adenomatoid ductal hyperplasia, this particular change may be considered a precursor of epithelial-myoepithelial carcinoma. Similarly, Chetty and Luna [2, 12] also proposed that adenomatoid ductal hyperplasias are usually associated with various types of benign and malignant salivary gland tumors and the presence of intercalated duct hyperplasia around epithelial-myoepithelial carcinoma cases could be interpreted as a potential precursor lesion. Adenomatoid ductal hyperplasia is usually an incidental microscopic finding during histologic examination of a salivary gland tumor [12]. Yu and Donath [3] reported extensive adenomatous proliferations forming mass lesions.

Sclerosing lesions of salivary glands include sclerosing polycystic adenosis, sclerosis associated with chronic sialadenitis, and sclerosing adenosis like ductal proliferation. In two of our adenomatoid ductal hyperplasia cases, there were ductal epithelial and myoepithelial proliferations composed of irregular and dilated ducts within a sclerotic and hyalinizing stroma. This appearance is quite different from those of sclerosing polycystic adenosis of salivary glands and sclerosing sialadenitis.

An incidental nodule in a lower lip biopsy with well circumscribed uniform population of mucinous ducts lead us use the term "incidental mucinous microadenoma" for this particular

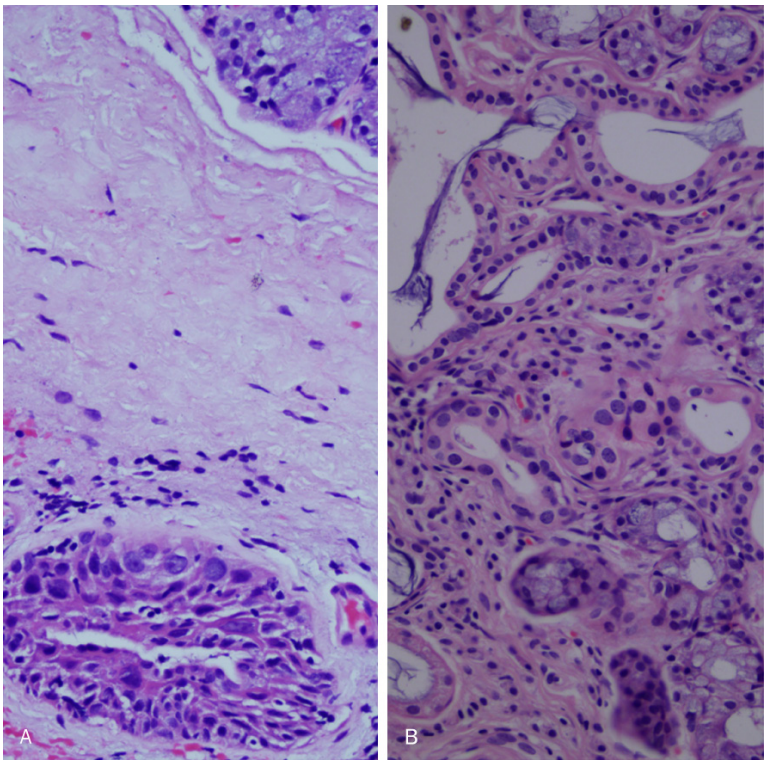

Figure 10. A. High grade dysplasia in excretory ducts which was an extension of oral mucosal dysplasia. Cells have hyperchromatic nuclei with a high nuclear-to-cytoplasmic ratio. B. Low grade dysplasia in intercalated and striated ducts with nucleomegaly and irregular chromatin distribution (H&E, ×400).

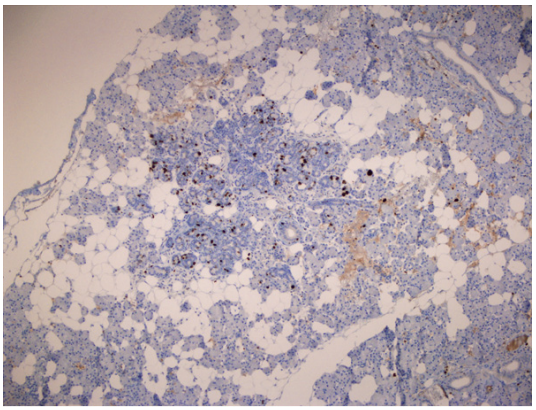

Figure 11. Increased Ki-67 immunohistochemical staining is apparent within the area of adenomatoid ductal hyperplasia in contrast to the surrounding tissue (H&E, ×100).

lesion. Adenomatoid ductal hyperplasia was more frequently encountered in major salivary glands (44 cases) in comparison to the minor salivary glands (2 cases) in the present series.

Multifocal and nodular growth of adenomatoid oxyphilic hyperplasia between normal acini may cause concern for a malignant tumor [4, 7]. Faguin and Powers [13] commented that it might be very difficult to reliably distinguish a true oncocytoma from a hyperplastic oncocytic nodule in the setting of oncocytosis.

Adenomatoid hyperplasia of the minor salivary glands looks similar to sialadenosis of major glands and it is composed of hyperplastic lobules of normal appearing mucinous acini and ducts, like those in normal salivary glands. All of our adenomatoid hyperplasia cases were found in various intraoral minor salivary glands. The absence of uniformity and the presence of normal organization of both the acini and ducts makes adenomatoid hyperplasia of the minor salivary glands a clinically pseudotumoral, histopathologically hamartomatous lesion rather than a neoplasia. Myoepithelial sialadenitis was found in five cases in this series. Four of these were associated with a chronic, lymphocyte rich, inflammatory reaction of Sjögren syndrome, and one was associated with Langerhans cell histiocytosis. Epithelial-myoepithelial reaction was extensive and irregular in both cases. Previous reports of lymphoepithelial carcinoma arising in salivary glands with a benign lymphoepithelial lesion may imply a malignant transformation of epithelial elements of a preexisting lymphoepithelial lesion [14].

Dysplastic changes which are known to be precancerous were few among the present proliferative lesions. At present, dysplasia is practically the only definitive indicator that a given lesion may have malignant potential. In the present series, two of the dysplasias were of low grade. One was an incidental finding in a minor salivary gland, and the other was found around a mucoepidermoid carcinoma. The two other dysplasia cases were high grade and they were detected in the excretory ducts of the minor salivary glands. Both were associated with high grade dysplasia of the oral mucosal

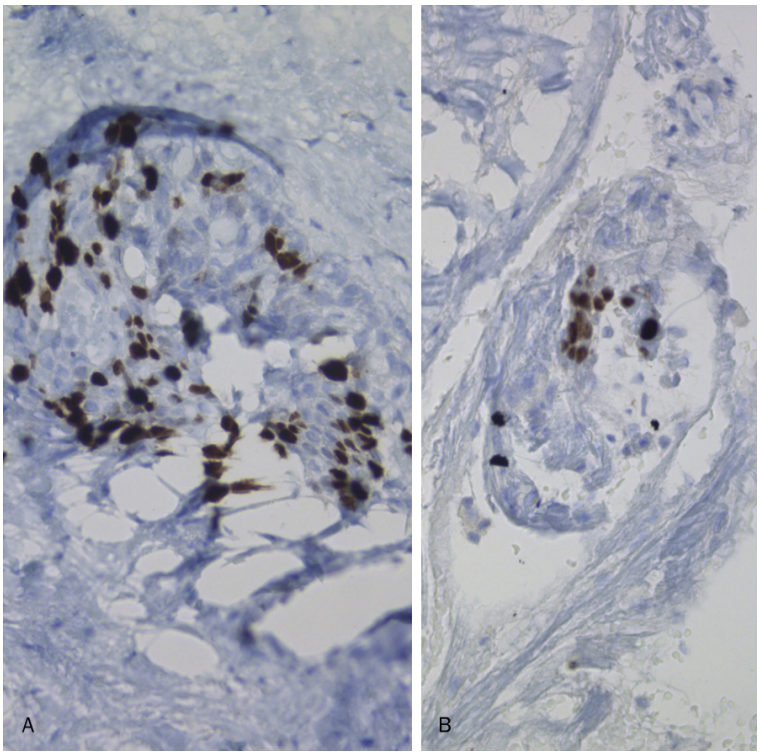

Figure 12. High level Ki-67 (A) and p53 (B) expression in the previously shown (**Figure 10A**) dysplastic excretory duct (H&E, ×400).

epithelium. The excretory duct lesions in these cases can be regarded as an extension of the surface mucosal dysplasia. Squamous cell carcinomas of the oral region are not limited to the oral mucosal epithelium, which consists of a stratified squamous epithelium. For this reason, removal of the adjacent salivary gland tissue is essential in preventing a potential source for the recurrence of oral epithelial dysplasia and oral squamous cell carcinoma [15, 16]. Although there is no specific immunologic or molecular change supporting the diagnosis of preneoplastic potential of a salivary gland tumor, certain markers can still provide valuable information regarding the neoplastic potential of some of the above-mentioned proliferations. Proliferation markers such as Ki-67 and genetic markers like p53 may be used for evaluating the putative risk. Dardick [17] envisaged that a normal salivary gland has an extremely low rate of cell turnover, and the detection of cycling cells in acini and excretory ducts with the use of Ki-67 might point to a relationship with the induction of tumors in these glands. Ki-67 immunostaining was used in some of our cases to analyze the location and the degree of proliferation. Ki-67 activity helped to separate various types of hyperplasia and dysplasia from the surrounding tissues. P53 expression was rarely found as a weak signal in the nuclei of cells of ductal epithelial hyperplasia, adenomatoid ductal hyperplasia and epithelial-myoepithelial proliferations. A strong p53 immunopositivity in the nuclei was observed only in dysplasia cases. In this series, acinar and ductal cells in various types of proliferative lesions showed increased Ki-67 activity which supports the idea that these are capable of proliferation, and they could be possible precursors. An increased expression of p53 and Ki-67 may be a clue for the progression of hyperplasia to neoplasia.

As a result, the biological significance of most of the lesions described in this report still remains to be understood completely. The lack of a uniform terminology and a set of widely accepted criteria are among the obstacles to progress. The present study, designed considering the above issues, focuses especially on morphology as well as on a few relatively well known immunohistochemical markers. It is beyond doubt, however, that a full understanding of carcinogenetic processes involving the salivary glands requires further immunophenotypic and molecular studies like those that had been utilized in tumors of the breast, for example. On the other hand, a detailed and informed examination of morphological findings in and around the neoplastic lesions with the help of a small set of immunohistochemical markers can still help us select patients who need a closer follow up. This approach will also boost our understanding of preneoplasia better in the context of salivary glands.

Disclosure of conflict of interest

None.

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