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Pleomorphic Adenoma with A Prominent Myoepithelial Cell Component: Case Report with Abbreviated Review of Literature

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1. Abstract

Pleomorphic adenoma, also known as a mixed tumor, is the most common benign tumor involving salivary glands with the parotid and minor palatal glands being common sites of occurrence. Histologically, pleomorphic adenoma can exhibit a wide variation in epithelial and stromal components, such as myxoid, chondroid, osteoid, and clear, spindle-shaped, epitheliod or plasmacytoid myoepithelial cells. In this paper we present a brief focused review of the literature and a case report of a pleomorphic adenoma that involved both the hard and soft palates and featured a prominent plasmacytoid myoepithelial cell component.

2. Introduction

Salivary gland tumors are highly complex due to their extensive spectrum of histologic presentation which, in turn, is the result of various morphologies of tumor cell differentiation, cellular arrangements and extracellular matrix synthesis [1]. The most common tumor of salivary gland origin is the pleomorphic adenoma (PA) with the parotid gland account for approximately 85% of this tumor type and minor salivary glands accounting for 7-8% [2]. Of those intraoral tumors originating in minor salivary glands, PA accounts for about 50% with the palate being the most common site [2].

Myoepithelial cells (MyEC) are a common component of secretory acini and intercalated ducts of salivary glands [3, 4]. MyEC present both an epithelial and smooth muscle phenotype and are likely of ectodermal origin [3, 4]. Commonly, MyEC are described as a major neoplastic cell component of many salivary gland tumors, e.g., myoepithelioma, pleomorphic adenoma, adenoid cystic carcinoma, mucoepidermoid carcinoma and polymorphus low-grade adenoid cyctic carcinoma [4, 5]. Interestingly, neoplastic MyEC, in both benign and malignant tumors, can present as one of several morphotypes, clear, spindle-shaped, epitheliod or plasmacytoid cells [5]. Not unsurprisingly, this variability in MyEC morphology can make for a difficult histopatholgic diagnosis.

Following is a case report in which the initial diagnosis, based on incisional biopsy, was a myoepithelioma and following surgical removal of the entire tumor mass the diagnosis was changed to PA. In both instances, the dominant cellular component was a plasmacytoid MyEC. In addition, a brief review of the literature focused on differential diagnosis, etiology, treatment and prognosis is presented.

3. Case Report

A 41-year-old Caucasian male was referred by his general dentist to a periodontal specialist for evaluation and treatment of periodontal disease. During the periodontal examination, a left-side maxillary palatal swelling was noted that appeared to be unrelated to the existing dentition. The swelling was an asymptomatic, raised, fixed, solid, well circumscribed, dome-shaped mass measuring approximately 1.5 x 1.0 cm (Figure 1). The swelling did not cross the midline but did extend posterior to involve both soft and hard palates. The patient related a slow but progressive swelling in the involved area over a one-year period. The patient's medical and family histories were not significant. However, the patient did admit to a 45 pack-year history of cigarette smoking. Except for a diagnosis of Stage II, Grade C generalized periodontitis [6], intraoral and extraoral examinations revealed no other significant findings.

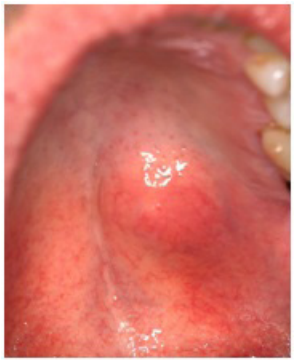

Figure 1: Intra-oral photograph of a circumscribed palatal swelling showing involvement of both the hard and soft palate. Area of swelling measures approximately 1.5 x 1.0 cm.

An incisional biopsy was procured and submitted to the University of Missouri-Kansas City School of Dentistry, Department of Oral Pathology (UMKC) for histologic evaluation and diagnosis. During the biopsy surgery it was noted that subjacent palatal bone appeared intact with no apparent erosion. The biopsy specimen was yellow-brown in color, wedge shaped and roughly 1.5 x 1 x 0.8 cm in size.

Formalin-fixed, paraffin-embedded specimens were prepared for routine hematoxylin and eosin (H & E) and immunohistochemical (IHC) staining. The H & E stained sections showed chronically inflamed mucous salivary gland lobules. Within the submucosa was a loosely circumscribed proliferation of rather bland cells with indistinct cytoplasmic boundaries. There were no mitotic figures and the tumor cells were arranged in sheets, nests and trabeculae that, in turn, were separated by dense trabecular bands of hyalinized fibrous connective tissue. The epithelial cell component was dominated by cells exhibiting a plasmacytoid morphology that were often set in a patchy myxochondroid matrix with microcystic change (Figure 2). It was noted that the lesion extended to the surgical margin.

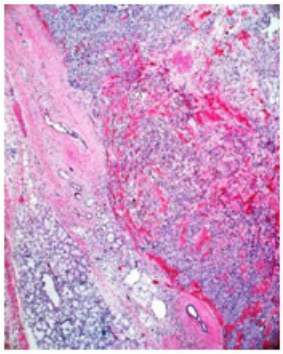

Figure 2: Hematoxylin and eosin stain of incisional biopsy specimen showing a loosely circumscribed proliferation of cells delineated by hyalinized strands of connective tissue (upper right ½ of photo). Remnants of a normal appearing minor salivary gland may be seen at lower left of photo. Original magnification of 50x.

Antibodies for the IHC staining included S100 protein, glial fibrillary acidic protein (GFAP) and pancytokeratin. Tumor cells exhibited a positive immunoreaction to all three IHC stains (Figures 3-5). A positive S-100 stain is common for myoepithelial cells, among other cell types, and a positive GFPA stain can be associated with pleomorphic adenoma [7, 8]. The pancytokeratin stain [9] yielded a strongly positive expression for the presence of cytokeratins CK1-8, 10, 14-16 and 19 (Figure 5). In consideration of the microcystic changes, duct-like structures and positive IHC stains, a diagnosis of trabecular myoepithelioma was rendered.

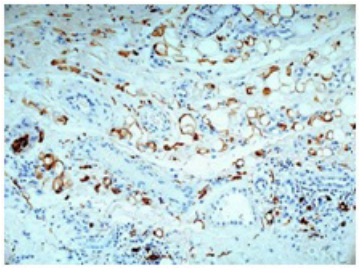

Figure 3: View of S-100 IHC stain showing strong positive expression of S100 protein by myoepithelial cells (a.k.a basket cells). The myoepithelial cells appeared to be associated with mucous acini and microcystic areas. Original magnification of 100x.

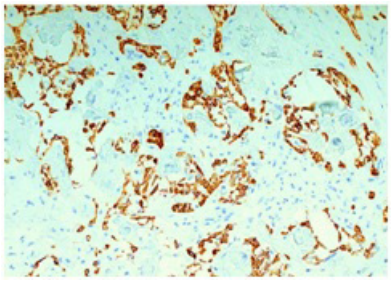

Figure 4: View showing strong positive immunoreaction to the glial fibrillary acidic protein (GFAP) stain. GFAP is a member of the intermediary filament protein family and is expressed in PA and myoepithelioma. Original magnification of 100x.

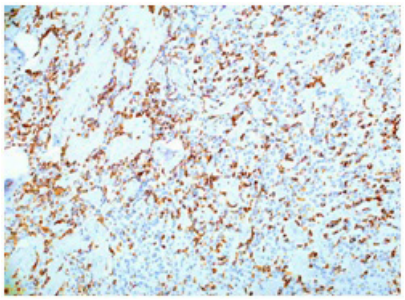

Figure 5: Tumor cell positive immunoreaction to the pancytokeratin IHC stain. This specific stain indicates presence of cytokeratins 1-8, 10, 14-16 and 19. Original magnification of 100x.

Following the histologic diagnosis, the patient was fully informed, both verbally and in written form, of the risks of not pursuing surgical removal of the lesion. He was then referred to an oral surgeon for excision of the remaining lesion. However, the patient chose not to pursue further treatment due to financial reasons. Two years following the initial biopsy procedure the patient was again seen in the same periodontal office with a chief complaint of pain involving the maxillary left 2nd molar and enlargement of the palatal mass. The 2nd molar was removed due to advanced periodontal disease. It was noted at this appointment that the palatal mass exhibited a significant increase in size (approximately doubling in size) compared to the initial presentation of two years previous, measuring approximately 2.5 x 2.0 cm (Figure 6). Examination of the head and neck was negative for lymphadenopathy and there were no subjective symptoms or patient complaints other than the 2nd molar tooth. The patient was again referred to a local oral surgeon but refused treatment. Eventually, after an extended delay of four years from the initial diagnosis, the patient underwent the necessary surgery for removal of the tumor.

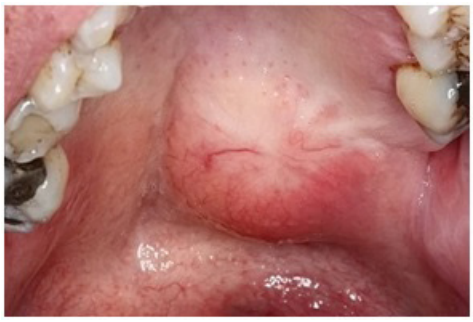

Figure 6: Clinical view of tumor at 4 years following initial incisional biopsy. At this point lesion has doubled in size, measuring 2.5 x 2.0 cm.

The tumor was removed as an intact mass (Figure 7a, 7b) and again submitted to UMKC for histologic examination. Inspection of the surgical wound indicated no tumor erosion of underlying periosteum or palatal bone. The ability to examine the resected tumor mass resulted in a change in diagnosis to a fibrous encapsulated pleomorphic adenoma (mixed tumor). Histologic examination revealed a neoplastic proliferation of benign epithelial and myoepithelial cells in a background of fibro-myxochondroid matrix (Figure 8). The myoepithelial cells exhibited a distinct plasmacytoid morphology (Figure 9). Focal areas of duct formation were observed and there was no evidence of infiltrative growth into adjacent minor salivary glands.

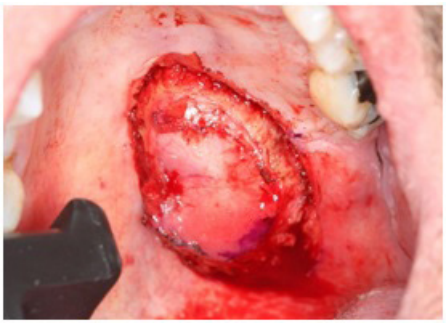

Figure 7a

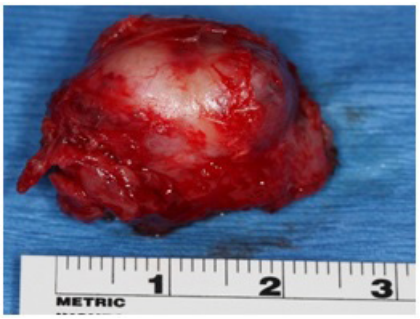

Figure 7b

Figures 7a & 7b: Palatal view showing outline of incision and size of resected tumor mass.

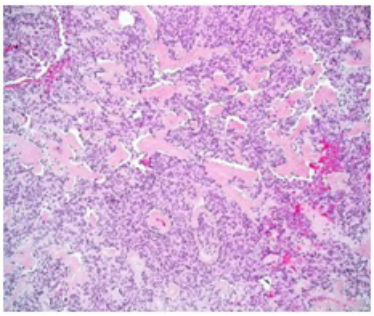

Figure 8: Specimen showing a neoplastic proliferation of benign epithelial and myoepithelial cells in a background fibro-myxochondroid matrix. Original magnification of 50x.

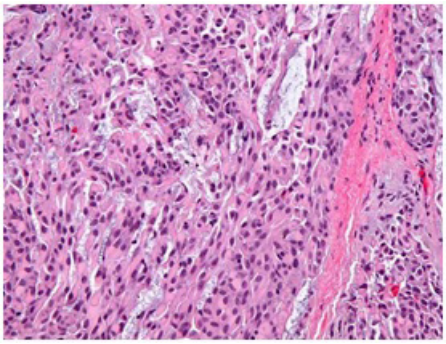

Figure 9: High magnification view showing plasmacytoid morphology of the myoepithelial cells. Original magnification of 400x.

A protective palatal stint was positioned, and the surgical defect was allowed to heal by secondary intention. Healing was followed at weekly intervals and at 4 weeks the surgical defect was healing without complication and had achieved remodeling to roughly a 90% fill (Figure 10).

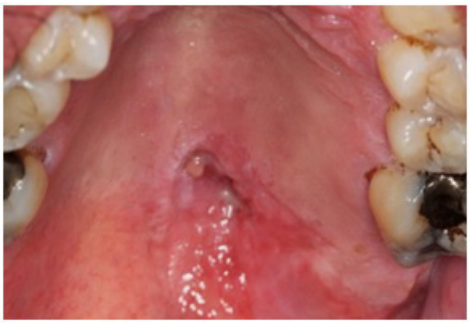

Figure 10: Three weeks' post-surgery showing remodeling of tissue to about a 90% fill of surgical defect.

4. Review

4.1. Clinical Presentation and Etiology

Pleomorphic adenoma in the oral cavity usually presents as an asymptomatic, slow growing, solitary mass that is painless and without ulceration of overlying mucosa. The tumor mass does not invade neighboring structures [2]. While the peak incidence occurs between 4th and 6th decades, pediatric cases have also been reported [10, 11]. As in the current case report, the palate is the most common intraoral site with such location indicating an association with minor salivary glands. There appears to be a slight female gender preference of occurrence (1:1.43) [12].

Although PA is the most common type of salivary gland tumor, little is known about its etiology. With respect to possible etiology, chromosomal rearrangement is frequently encountered in tumor biology and has been reported to occur in PA. The PA Gene 1, PLAG1, is reportedly activated by chromosome rearrangements in both pleomorphic adenoma and myoepithelioma [13, 14]. Using a variety of cytogenetic, molecular cytogenetic and molecular karyotyping based techniques, Thielker et al [15] recently reported chromosomal and/or submicroscopic alterations in 5 of 14 cases of PA, e.g., jumping translocation, gene copy variations involving twist-replated protein 1 (TWIST1) and distal-less homeobox 5 (DLX5) genes [15]. In addition, Choi et al. have reported the differential expression of four genes in PA tumors as compared with the genes in normal tissue. The authors suggest that such findings indicate the genes microfibrillar associated protein 4 [MFAP4], dystonin [DST], solute carrier family 35 [SLC35], and potassium channel tetramerization domain containing 15 [KCTD15]) could be potential biomarkers for a precise diagnosis of PA [16]. Lastly, Mariano et al. [17] report that PA exhibited only a few copy alterations with the most frequent involving chromosomes 8:8p21.3-p12 (gain), 8q12.1 (loss), 8p23.3-q24.3 (gain), and 8q12.1-q21.11 (gain). Other suggested etiologic possibilities include radiation exposure [18] and exposure to the oncogenic simian virus (SV40) [19]. Indeed, either of these factors could be responsible for epigenetic influence in gene expression.

4.2. Diagnosis and Differential

In the present case, the differential diagnoses included: mucocele, palatal abscess, myoepithelioma, schwannoma, fibroma, neurofibroma, leiomyoma, benign fibrous histiocytoma and other salivary gland neoplasms. Initially, the current case was diagnosed as a myoepithelioma–based on incisional biopsy – and changed to PA following histologic examination of the resected tumor mass. In most cases, H & E histology and IHC provide sufficient information required for the diagnosis of myoepithelioma [20]. However, the diagnosis of myoepithelioma can be challenged by cytological heterogeneity, inconsistencies in histological diagnostic criteria, and histological similarities between myoepithelioma and pleomorphic adenoma. Both pleomorphic adenoma and myoepithelioma are benign epithelial neoplasms with modified myoepithelial differentiation and a variety of cytomorphologic features [13].

A major histological difference between the two lesion types is that the origin of myoepithelioma is entirely of myoepithelial cells, though the two conditions can be mixed in some cases. The two conditions also differ in the epithelial and fibromyxoid components in that myoepithelioma should contain no fibromyxoid stroma, and the neoplastic epithelial component should be less than 5%-10% [21]. Differentiating the two conditions is important since myoepithelioma behaves more aggressively than pleomorphic adenoma [22] and can transition into malignant myoepithelioma [21].

As noted, the histology of PA is characterized by heterogeneity involving epithelial, mesenchymal and myoepithelial cells [23]. Such variation in histologic character accounts for the nomenclature of "pleomorphic" adenoma and alternative name of benign "mixed" tumor. The H & E histology and IHC staining results of the present case of PA indicate a plasmacytoid subtype with ductlike features.

As the diagnosis of both PA and myoepithelioma relies on both histology and IHC stain results, it is worth noting that cytokeratins 5-7 and 14 and S-100 protein are reliable markers for differentiation of myoepithelioma [24]. The PA in this case was strongly positive for S-100 protein and a more inclusive panel of cytokeratins, i.e., CK 1-8, 10, 14-16 and 19. Further, Perez-de-Oliveira et al. [25] have reported that in 95.2% of PA tumors the stroma is predominantly fibrous, followed by myxoid (66.7%), hyaline (61.9%) and chondromyxoid (33.3%).

Classification of tumor related myoepithelial cell subtypes is based on morphology: 1) spindle, 2) plasmacytoid, 3) epithelioid, and 4) clear [25, 26]. The spindle cell subtype is the most prevalent in myoepithelioma, being characterized by intercalating fascicles

resembling stroma [27]. Epithelioid cells are cords of polygonal cells with centrally located nuclei, whereas clear cells are polygonal in shape with clear cytoplasm rich in glycogen. Plasmacytoid cells are best described as polygonal in shape with eccentric nuclei and a hyaline eosinophilic cytoplasm. Plasmacytoid cell morphology is more common in PA, as seen in the current case [25].

4.3. Treatment and Prognosis

The management of pleomorphic adenoma is by surgical resection to include a margin of non-neoplastic tissues. Marginal resection is important as incomplete excision will generally result in lesion recurrence [28, 29]. Aggressive and extended surgery, unlike enucleation, appears to dramatically decreased recurrence rate of PA from up to 45% to as low as 1% [29-31]. Indeed, several authors have noted that uncertain marginal resection of parotid gland PA [28, 32] and young age at diagnosis [33, 34] are risk factors for recurrence. PA involving minor salivary glands, as in the current case, have been reported to have a low recurrence rate [35]. However, there is little substantiating hard evidence to support this conclusion – it appears based on clinical experience and opinion.

The patient in the current case was a 45 pack-year cigarette smoker, raising the question of an association of smoking as a risk factor for development of PA. Certainly, smoking represents a risk factor for malignant salivary gland tumors [36-38]. However, there appears to be little or no published evidence reporting a similar association of smoking with intraoral PA.

Of further interest is the scarcity of evidence addressing recurrence and/or malignant transformation of palatal minor salivary gland PA. In contrast, there are numerous articles discussing these issues in parotid gland PA that may have some relevance to palatal PA. For example, Aro et al. [39] reported a 15% recurrence rate and a 6% rate of malignant transformation in parotid PA. Witt et al. [40] note that PA may undergo malignant transformation with an increased risk over time. In this regard, if PA is left untreated, recent studies show that the risk for malignant transformation is generally considered to be around 1.1-1.7% [28, 32]. With repeated recurrence and removal, PA gains potential for malignant transformation [40, 41]. Indeed, Suh et al. [41] emphasized that younger patients are at higher risk for recurrences and therefore development of future malignancy.

5. Conclusion

Pleomorphic adenoma, a.k.a. mixed tumor, is the most common benign tumor involving salivary glands with the minor palatal glands accounting for about 5% of occurrences [42]. Histologically, pleomorphic adenoma can exhibit a wide variation in epithelial and stromal components and can be misdiagnosed as a myoepithelioma, a more aggressive tumor reported to undergo neoplastic transformation. Both tumor types exhibit similar clinical presentations when involving minor salivary glands of the hard and/or soft palate. Thus, accurate differential diagnosis, utilizing immunohistochemical stains, is an absolute for proper patient management.

References

1. Nonitha S, Yogesh TL, Nandaprasad S, Maheshwari BU, Mahalakshmi IP, Veerabasavaiah BT. Histomorphological comparison of pleomorphic adenoma in major and minor salivary glands of the oral cavity: A comparative study. J Oral Maxillofac Pathol. 2019; 23(3): 356-62.
2. Regezi JA, Sciubba JJ, Jordan RCK. Salivary gland diseases. In: Oral Pathology: Clinical Pathologic Correlations. St. Louis: Elsevier; 7th Edition. 2017. pp. 202-204.
3. Hamada T, Matsukita S, Goto M, Kitajima S, Batra SK, et al. Mucin expression in pleomorphic adenoma of salivary gland: A potential role for MUC1 as a marker to predict recurrence. J Clin Pathol. 2004; 57(8): 813–21.
4. Satpathy Y, Spadigam AE, Dhupar A, Syed S. Epithelial and stromal patterns of pleomorphic adenoma of minor salivary glands: A histopathological and histochemical study. J Oral Maxillofac Pathol. 2014; 18(3): 379-85.
5. Balachander N, Masthan KMK, Babu NA, Anbazhagan V. Myoepithelial cells in pathology. J Pharm Bioallied Sci. 2015; 7(Suppl 1): S190-3.
6. Tonetti MS, Greenwell H, Kornman KS. Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. J Periodontol. 2018; 89(Suppl 1): S159-72.
7. Curran AE, Allen CM, Beck FM, Damm DD, Murrah VA. Distinctive pattern of glial fibrillary acidic protein immunoreactivity useful in distinguishing fragmented pleomorphic adenoma, canalicular adenoma and polymorphus low grade adenocarcinoma of minor salivary glands. Head Neck Pathol. 2007; 1(1): 27-32.
8. Zarbo RJ, Regezi JA, Batsakis JG. S-100 protein in salivary gland tumors: An immunohisto-chemical study of 129 cases. Head Neck Surg. 1986; 8(4): 268-75.
9. Nagao T, Sato E, Inoue R, Oshiro H, Takahashi RH, et al. Immunohistochemical analysis of salivary gland tumors: Application for surgical pathology practice. Acta Histochem Cytochem. 2012; 45(5): 269-82.
10. Dombrowski ND, Wolter NE, Irace AL, Cunningham MJ, Vargas SO, et al. Pleomorphic adenoma of the head and neck in children: Presentation and management. Laryngoscope. 2019; 129(11): 2603-9.
11. Bradley PJ, Eisele DW. Salivary gland neoplasms in children and adolescents. Adv Otorhinolaryngol. 2016; 78: 175-81.
12. Valstar MH, de Ridder M, van den Broek EC, Stuiver MM, van Dijk BAC, et al. Salivary gland pleomorphic adenoma in the Netherlands: A nationwide observational study of primary tumor incidence, malignant transformation, recurrence, and risk factors for recurrence. Oral Oncol. 2017; 66: 93-99.
13. Zhu S, Schuerch C, Hunt J. Review and updates of immunohisto-

chemistry in selected salivary gland and head and neck tumors. Arch Pathol Lab Med. 2015; 139(1): 55-66.

14. Rotellini M, Palomba A, Baroni G, Franchi A. Diagnostic utility of PLAG1 immunohisto-chemical determination in salivary gland tumors. Appl Immunohistochem Mol Morphol. 2014; 22(5): 390-4.
15. Thielker J, Weise A, Othman MAK, Carreria IM, Melo JB, et al. Molecular cytogenetic pilot study on pleomorphic adenomas of salivary glands. Oncol Lett. 2020; 19(2): 1125-30.
16. Choi J-S, Cho B-H, Kim H-J, Kim Y-M, Jang J-H. Identification of new genes of pleomorphic adenoma. Medicine (Baltimore). 2019; 98(51): e18468.
17. Mariano FV, Fidalgo F, Casarim ALM, Martins AS, Scarini JF, et al. Somatic copy number alterations in pleomorphic adenoma and recurrent pleomorphic adenoma. Oral Surg Oral Med Oral Pathol Oral Radiol. 2020; 129(1): 59-64.
18. Bokhari MR, Greene J. Pleomorphic adenoma. StatPearls. 2020.
19. Martinelli M, Martini F, Rinaldi E, et al. Simian virus 40 sequences and expression of the viral large T antigen oncoprotein in human pleomorphic adenomas of parotid glands. Am J Pathol. 2002; 161(4): 1127-33.
20. Karthik RS, Sivakumar JS, Cholan R, Shanmugapriya, Rajan VS, et al. Myoepithelioma. J Pharm Bioallied Sci. 2015; 7(6): 779-81.
21. Gore CR, Panicker N, Chandanwale S, Singh BK. Myoepithelioma of minor salivary glands – a diagnostic challenge: report of three cases with varied histomorphology. J Oral Maxillofac Pathol. 2013; 17(2): 257-60.
22. Kleihues P, Sobin LH. World Health Organization classification of tumors. Cancer. 2000; 88(12): 2887.
23. Guerra G, Testa D, Montagnani S, Tafuri D, Salzano FA, et al. Surgical management of pleomorphic adenoma of parotid gland in elderly patients: role of morphological features. Int J Surg. 2014; 12(Suppl 2): S12-S16.
24. Hungermann D, Roeser K, Buerger H, Jakel T, Loning T, Herbst H. Relative paucity of gross genetic alterations in myoepitheliomas and myoepithelial carcinomas of salivary glands. J Pathol. 2002; 198(4): 487-94.
25. Perez-de-Oliveira ME; Leonel ACLDS; de Castro JFL; Carvalho EJA; Vargas PA, et al. Histopathological findings of intraoral pleomorphic adenomas: A retrospective study of a case series. Int J Surg Pathol. 2019; 27(7): 729-35.
26. Di Palma S, Simpson RHW, Skalova A, Fonseca I, Leivo I, et al. Major and Minor Salivary Glands. In: Cardesa A, Slootweg PJ, Gale N, Franchi A, eds. Pathology of the Head and Neck, Berlin, Heidelberg; Springer; 2017, p. 244.
27. Testa D, Galera F, Insabato L, Vassallo A, Mesolella M, Galli V. Submandibular gland myoepithelioma. Acta Otolaryngol. 2005; 125(6): 664-6.
28. Valstar MH, de Ridder M, van den Broek EC, Stuiver MM, van Dijk BAC, et al. Salivary gland pleomorphic adenoma in the Netherlands: A nationwide observational study of primary tumor incidence, malignant transformation, recurrence, and risk factors for recurrence. Oral Oncol. 2017; 66(3): 93-99.
29. Colella G, Cannavale R, Chiodini P. Meta-analysis of surgical approaches to the treatment of parotid pleomorphic adenomas and recurrence rates. J Craniomaxillofac Surg. 2015; 43(6): 738-45.
30. Riad MA, Abdel-Rahman H, Ezzat WF, Adly A, Dessouky O, Shehata M. Variables related to recurrence of pleomorphic adenomas: outcome of parotid surgery in 182 cases. Laryngoscope. 2011; 121(7): 1467-72.
31. Witt RL. The significance of the margin in parotid surgery for pleomorphic adenoma. Laryngoscope. 2002; 112(12): 2141-154.
32. Andreasen S, Therkildsen MH, Bjorndal K, Homøe P. Pleomorphic adenoma of the parotid gland 1985-2010: a Danish nationwide study of incidence, recurrence rate, and malignant transformation. Head Neck. 2015; 38(Suppl 1): 1364-9.
33. Zbaren P, Tschumi I, Nuyens M, Stauffer E. Recurrent pleomorphic adenoma of the parotid gland. Am J Surg. 2005; 189(2): 203-7.
34. Wittekindt C, Streubel K, Arnold G, Stennert E, Guntinas-Lichius O. Recurrent pleomorphic adenoma of the parotid gland: analysis of 108 consecutive patients. Head Neck. 2007; 29(9): 822-8.
35. Ahmedi JR, Ahmedi E, Perjuci F, Ademi R, Gashi A, Agani Z, et al. Pleomorphic adenoma of minor salivary glands in child. Med Arch. 2017; 71(5): 360-3.
36. Sadetzki S, Oberman B, Mandelzweig L, Chetrit A, Ben-Tal T, Hakak AJ, et al. Smoking and risk of parotid gland tumors: a nationwide case-control study. Cancer. 2008; 112(9): 1974-82.
37. Israel Y, Rachmiel A, Gourevich K, Nagler R. Salivary malignancies-medical, demographic and diagnostic analysis. J Cranio Maxillo Fac Surg. 2019; 47(3): 500-4.
38. Sawabe M, Ito H, Takahara T, Oze I, Kawakita D, et al. Heterogeneous impact of smoking on major salivary gland cancer according to histopathological subtype: A case-control study. Cancer. 2018; 124(1): 118-24.
39. Aro K, Valle J, Tarkkanen J, Måkitie A, Atula A. Repeatedly recurring pleomorphic adenoma: A therapeutic challenge. Acta Otorhinolaryngol Ital. 2019; 39(3): 156–61.
40. Witt RL, Eisele DW, Morton RP, Nicolai P, Poorten VV, et al. Etiology and management of recurrent parotid pleomorphic adenoma. Laryngoscope. 2014; 125(4): 888-93.
41. Suh MW, Hah JH, Kwon SK, Jung YH, Kwon TK, et al. Clinical manifestations of recurrent parotid pleomorphic adenoma. Clin Exp Otorhinolaryngol. 2009; 2(4): 193-7.
42. Israel Y, Rachmiel A, Ziv G, Nagler R. Benign and malignant salivary gland tumors – clinical and demographic characteristics. Anticancer Res. 2016; 36(8): 4151-4.