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CASE REPORT

Polymorphous adenocarcinoma of the upper lip: challenges in diagnosing a malignant lesion presenting benign clinical appearance

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Abstract:

Polymorphous Adenocarcinoma (PAC) is a distinctive malignancy that primarily affects the minor salivary glands. A defiant diagnosis of this lesion is related to its pathological findings, including architectural diversity, and its clinical aspect that usually mimics benign lesions. A 72-year-old male presented a slow-growing painless nodule in the upper lip with two years of evolution. An excisional biopsy was performed, and despite the first clinical impression of a benign condition, the histopathological analysis confirmed PAC. The immunohistochemical analysis showed positive expression for CKAE1/AE3, CK7, S100 and p63, and negative for SMA, CK20 and p40 distinguishing this case from other salivary gland tumors. In addition, the lesion usually affects the palate, revealing an atypical site of occurrence for this case. The patient was referred to a Head and Neck surgeon to ensure a second surgical intervention to include margin extension. One year follow-up reveals no signs of recurrence. This case highlights the need for clinicians to consider malignancies in lesions with a clinical aspect usually common to benign conditions. In addition, the unexpected PAC occurrence in the upper lip was emphasized. This case report reinforces the PAC clinical appearance diversity and its microscopic features, accompanied by a unique immunohistochemical profile.

Keywords: Salivary gland; Neoplasm; Diagnosis; Pathology, Immunohistochemistry.

INTRODUCTION

Polymorphous adenocarcinoma (PAC) is an uncommon malignant neoplasm of the salivary glands, previously known as polymorphous low-grade adenocarcinoma. It primarily affects the minor salivary glands, with a propensity for the palate, and manifests in individuals around fifth decade, showing a higher incidence among females[1].

PAC is characterized by architectural diversity, cytologic uniformity, and an infiltrative growth pattern[1,2]. The World Health Organization's reclassification in 2017 acknowledged the contentious nature of PAC, removing the term "low-grade" to better reflect its variable clinical behavior[3].

Due to the histologic diversity and molecular heterogeneity of PAC, immunohistochemistry plays a crucial role in confirming the diagnosis, differentiating it from other salivary tumors, and assessing the severity of the lesion. The complexity of the diagnostic process underscores the need for a comprehensive approach[4].

Statement of Clinical Significance
A case of a 72-year-old patient diagnosed with Polymorphous adenocarcinoma (PAC) is presented to underscore the importance of considering malignant neoplasms, particularly salivary gland tumors, in the differential diagnosis of benign oral lesions, mainly when affecting uncommon sites.

Treatment modalities for PAC typically involve wide surgical excision, tailored according to the clinical TNM stage, subtype, grade, and stage of the malignancy. Despite its potential for local recurrence and cervical lymph node metastasis, PAC generally exhibits a favorable prognosis[2,5].

This study aimed to report a case of PAC affecting the upper lip, an intraoral site uncommonly associated with this neoplasm. Also, discuss this condition's demographic and clinical profile, emphasizing the importance of considering malignant neoplasms in the differential diagnosis of benign oral lesions.

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CASE REPORT

A 72-year-old man was referred to a Public Center of Dental Specialties for excision of a slow-growing painless nodule in the upper lip before installing a new upper total prosthesis.

Upon intraoral examination, a submucosal nodule in the central region of the upper labial mucosa was noted, approximately 1.5 cm, with a firm consistency and mobility during palpation (Figure 1A). The underlying mucosa revealed normal condition and a pinkish coloration with focal areas of a yellowish color (Figure 1B). The patient denied an event of local trauma. No facial asymmetry or cervical/submandibular lymphadenopathy was observed. There was no pain symptoms related to the region, and the patient reported having the lesion for more than 2 years.

Due to clinical appearance the diagnostic hypotheses included benign lesions, such as benign reactive lesions, neural lesions, and other common benign salivary gland lesions. An excisional biopsy was then performed under local anesthesia, without intercurrences.

Histopathological analysis revealed to be a salivary-gland neoplasm. The different organization of the neoplastic epithelial cells was the primary finding, which was composed of small nests and forming ductal structures (Figure 2A and B). In addition, cords of neoplastic cells presented in a myxomatous stroma with pseudocystic spaces were also found. Immunohistochemistry was conducted and showed positive expression for

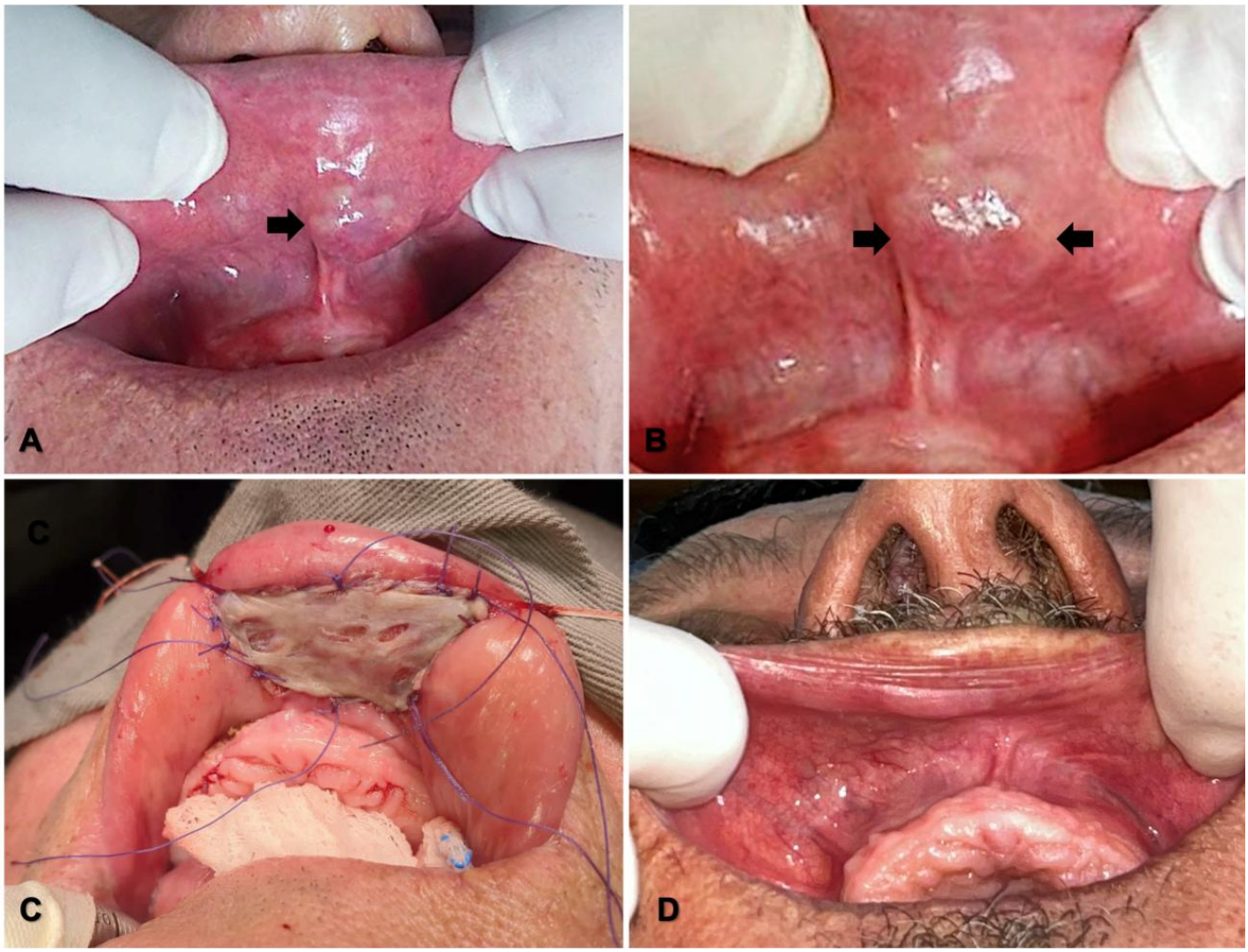

Figure 1. Clinical presentation evidencing a submucosal nodule in the upper labial mucosa. **(A)** A volumetric augmentation covered by a normal mucosa and **(B)** in a higher approximation it was possible to identify a few yellowish lobules within the lesion (black arrow). **(C)** Microsurgical flap in position during the surgical resection. **(D)** Follow-up examination revealed the absence of alterations at one year after the treatment.

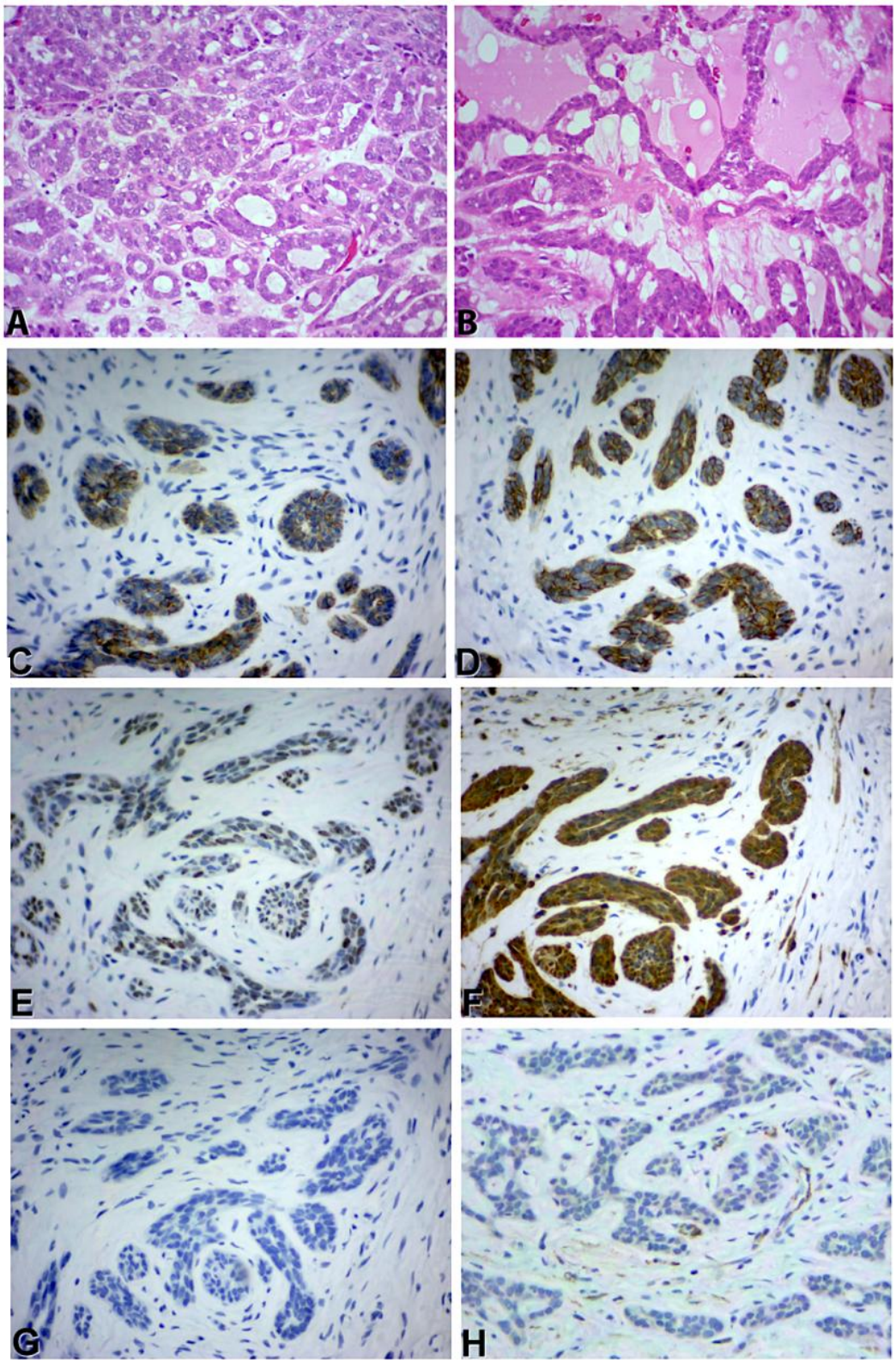

Figure 2. Microscopic features of the lesion. **(A)** Neoplastic epithelial cells organized in small nests and forming ductal structures (hematoxylin and eosin [H&E], 400x). **(B)** Cords of neoplastic cells in a myxomatous stroma with the presence of pseudocystic spaces (H&E, 400x). **(C)** Cytoplasmic immunohistochemical positivity for cytokeratin AE1/AE3 (400×). **(D)** Cytoplasmic immunohistochemical positivity for cytokeratin 7 (400×). **(E)** Nuclear staining for p63 (400×). **(F)** Cytoplasmic immunohistochemical positivity for S100 (400×). **(G)** Negative staining for cytokeratin 20 and **(H)** SMA in neoplastic cells (400×).

Cytokeratin (CK) AE1/AE3, CK7, S100, and p53, and no expression for CK20, SMA, and p40 (Figure 2C–H). The diagnosis of Polymorphous Adenocarcinoma was confirmed with a T2N0M0 clinical stage.

The patient was referred to a head and neck surgeon to a second surgical intervention including margins. A skin graft obtained from the neck was excised and repositioned (Figure 1C). The surgically resected specimen evidenced that the margins were disease-free. The patient was under regular follow-up for 12 months, with no sign of recurrence or metastasis (Figure 1D).

This case report was approved by the Institutional Ethics Committee of *CEPON* (CAAE: 75136423.2.0000.5355, Approval number 6.514.433).

DISCUSSION

The present report emphasizes a case of a nodule in the upper lip which clinically appeared to be a benign lesion, however revealed to be a PAC, which is a malignant neoplasia. This case of a submucosal nodule in the upper lip presented various diagnostic possibilities, including reactive, cystic, and neoplastic lesions. Given its limited size and slow growth, the lesion was initially presumed to be benign, guiding the differential diagnosis towards more common non-malignant entities.

An mucocele was one clinical hypothesis, considering its high prevalence in the labial mucosa and typically presenting as asymptomatic nodules, although not common in the upper lip[6,7]. Nevertheless, the patient in this case did not report any history of local trauma, it is conceivable that the absence of lip support in edentulous patients could lead to abnormal mastication, resulting in chronic irritation and potential injury. A traumatic fibroma was also considered in the differential diagnosis, as it is the most frequent benign lesion of the oral mucosa, commonly found in trauma areas such as the lips. Clinically, it presents as a firm, sessile, asymptomatic nodule with a smooth surface and pale pink coloration, closely resembling the lesion in this case[8]. Benign neoplasms were also considered. Lipoma was considered due to its similar clinical characteristics; however, the absence of a predominant yellowish hue reduced its likelihood[9]. Although less common, an epidermoid cyst was also included in the differential diagnosis, as it is a benign developmental cyst originating from ectodermal tissue and can present as an asymptomatic nodule on the lip[10]. Despite these benign clinical features, histopathological analysis revealed a malignant neoplasm. This finding underscores the necessity of considering malignancies in the differential diagnosis, particularly in anatomical sites containing salivary glands. The case highlights the importance of histopathological examination for definitive diagnosis and the potential for malignant neoplasms to mimic benign lesions in their early clinical presentation.

Considering the clinical appearance, PAC can occur in a wide age range, with the literature revealing to vary from 16 to 94 years old, and more frequent in females[1]. The lesions may present as a submucosal painless firm nodule, with or without surface ulceration. This aspect is similar to a variety of benign nodules in the oral mucosa[11,12]. Interestingly, our case occurred in a male patient, and the fact that it was a painless lesion non-related to any trauma was the finding that did not contribute to including a malignant salivary gland at first.

PAC is a malignant salivary gland tumor characterized by architectural diversity, cytologic uniformity, and infiltrative growth pattern[5]. It was first described by Evans and Batsakis in 1984 as a distinct entity named "polymorphous low-grade adenocarcinoma". The World Health Organization (WHO) Classification of Head and Neck Tumors removed in 2017, the term "low-grade" to better reflect the wide spectrum and the presence of rare, aggressive cases[3]. Since then, PAC has been the most contentious entity for the iteration of WHO's reclassification due to its clinical-pathologic characteristics. PAC remained with the same nomenclature in the last classification (5th Edition), including classic and cribriform subtypes[14].

Therefore, we report this case of PAC of the minor salivary gland due to its uncommon features and its clinical resemblance to a benign lesion. The tumor has a strong predilection to the minor salivary glands, most commonly the palate (in approximately 60% of cases)[11], yet in our case, it presents on the upper lip.

Microscopically, PAC presents as an infiltrative non-encapsulated mass primarily visualized in lower magnification, characterized by cytology uniformity and architectural diversity. The neoplasm occasionally represents a diagnostic challenge because of its high morphological and histological heterogeneity and similarity with other salivary tumors such as adenoid cystic carcinoma (ACC) and pleomorphic adenoma (PA). Immunohistochemistry is of significant help when extra analysis is needed[4,5]. Architectural patterns may present

as lobular, trabecular, solid, microcystic, papillary projection with or without fibrovascular cores; and cribriform[13,15]. Typically, PAC comprises one type of tumor cells characterized by open chromatin, small to medium size and uniform shape, minimally hyperchromatic, oval nuclei, and occasional nucleoli. Perineural invasion is frequent[5]. In addition, immunohistochemistry in PAC has been extensively investigated, although it is not commonly employed in routine diagnostic practice[4,5]. In our case, although the histopathology of the tumor is compatible with PAC, immunohistochemistry was performed to confirm the diagnosis, to exclude other entities, and assess other features related to the severity of the lesion, helping choose an appropriate treatment. Interestingly, our case revealed some areas of cribriform like areas, although not interfering with our final diagnosis which was indeed the PAC condition.

PAC immunoreactivity shows several epithelial and myoepithelial markers considered valuable as diagnostic markers[4,15]. As a salivary glandular neoplasm, the neoplastic cells show high epithelial and relatively low myoepithelial characteristics. A systematic review by Nonaka & Takei[5] shows a summary of immunohistochemical profiles indicating nearly 100% expression status for Cytokeratin (CK) AE1/AE3, CK7, Vimentin, and S100, and always negative for CK20. In our case, CK20, SMA had a negative expression, being in accordance with the literature. Another myoepithelial marker, p63, is often expressed as a transcriptional factor expressed in salivary glands and can be related to PAC prognosis. However, p40 shows a distinct expression profile. Studies have suggested the utility of a combined p63/p40 immunophenotype in differentiating PAC (p63+/p40−) from adenoid cystic carcinoma (p63+/p40+)[4,15,16]. In the current case, p63 and S100 were also expressed. As S100 is positively expressed in 97–100% of PAC cases and SMA was negative, these findings help differentiate this case from adenoid cystic carcinoma.

Wide surgical excision is usually the treatment of choice for PAC. The extent of surgery and the need for neck dissection or adjuvant radiotherapy will depend on the malignance's subtype, grade, and stage[3]. The case reported revealed to be a PAC, requiring a less aggressive surgical treatment. However, despite the prognosis being usually excellent, and distant metastasis is rare, it may recur locally and metastasize to cervical lymph nodes, requiring careful and long-term clinical monitoring[3,11]. In our patient's case, a one-year follow-up revealed no signs of recurrence; however, a longer and more comprehensive clinical follow-up is warranted.

CONCLUSION

PAC is a malignant neoplasm with diverse clinical and pathological characteristics. Malignant salivary gland neoplasms should be considered in the differential diagnosis, particularly for lesions with a benign clinical appearance in oral sites containing minor salivary glands. Although PACs have good prognosis, they must be treated correctly to avoid an adverse outcome.

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AUTHORS' CONTRIBUTIONS

KBT: conceptualization, methodology, writing – original draft. BCB: methodology, supervision, writing – original draft. KCO: investigation, methodology, supervision. FBCS: data curation, visualization. ERCR: formal analysis, investigation, writing – review & editing. GDR: supervision, validation, writing – review & editing. LJG: Supervision, Writing – review & editing.

CONFLICT OF INTEREST STATEMENT

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REFERENCES

1. Mauceri R, Coppini M, Alecci G, Cordova A, Florena AM, Magro G, et al. Polymorphous adenocarcinoma: a systematic review of the literature and presentation of two cases in a less-considered anatomical site. Cancers (Basel). 2024;16(1):220. https://doi.org/10.3390/cancers16010220
2. Mimica X, Katabi N, McGill MR, Hay A, Zanoni DK, Shah JP, et al. Polymorphous adenocarcinoma of salivary glands. Oral Oncol. 2019;95:52-8. https://doi.org/10.1016/j.oraloncology.2019.06.002
3. Fonseca I, Assaad A, Katabi N, et al. Polymorphous adenocarcinoma. In: El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ,

eds. WHO classification of head and neck tumours. 4th ed. Lyon: IARC; 2017. p. 163-87.
4. Fukumura M, Ishibashi K, Nakaguro M, Nagao T, Saida K, Urano M, et al. Salivary gland polymorphous adenocarcinoma: clinicopathological features and gene alterations in 36 Japanese patients. J Oral Pathol Med. 2022;51(8):710-20. https://doi.org/10.1111/jop.13336
5. Nonaka T, Takei H. Immunohistochemical profile of polymorphous adenocarcinoma of minor salivary gland: a systematic review and meta-analysis. Head Neck Pathol. 2022;16(4):980-90. https://doi.org/10.1007/s12105-022-01453-6
6. Baurmash HD. Mucoceles and ranulas. J Oral Maxillofac Surg. 2003;61(3):369-78. https://doi.org/10.1053/joms.2003.50074
7. Bowers EMR, Schaitkin B. Management of mucoceles, sialoceles, and ranulas. Otolaryngol Clin North Am. 2021;54(3):543-51. https://doi.org/10.1016/j.otc.2021.03.002
8. Bukhari AF, Farag AM, Treister NS. Chronic oral lesions. Dermatol Clin. 2020;38(4):451-66. https://doi.org/10.1016/j.det.2020.05.006
9. Dehghani N, Razmara F, Padeganeh T, Mahmoudi X. Oral lipoma: case report and review of literature. Clin Case Rep. 2019;7(4):809-15. https://doi.org/10.1002/ccr3.2099
10. Mahalakshmi S, Reddy S, Ramamurthy TK, Shilpa B. Rare locations of epidermoid cyst: case reports and review. Ethiop J Health Sci. 2016;26(6):595-601. https://doi.org/10.4314/ejhs.v26i6.14
11. Katabi N, Xu B. Polymorphous adenocarcinoma. Surg Pathol Clin. 2021;14(1):127-36. https://doi.org/10.1016/j.path.2020.09.011
12. Fonseca FP, Brierley D, Wright JM, Santos-Silva AR, Almeida OP, Rocha AC, et al. Polymorphous low-grade adenocarcinoma of the upper lip: 11 cases of an uncommon diagnosis. Oral Surg Oral Med Oral Pathol Oral Radiol. 2015;119(5):566-71. https://doi.org/10.1016/j.oooo.2015.01.001
13. Bradley PJ. Frequency and histopathology by site, major pathologies, symptoms and signs of salivary gland neoplasms. Adv Otorhinolaryngol. 2016;78:9-16. https://doi.org/10.1159/000442120
14. Salivary gland tumours. In: WHO Classification of Tumours Editorial Board. Head and neck tumours. 5th ed. Lyon: International Agency for Research on Cancer; 2024. p. 159-252.
15. Skalova A, Hyrcza MD. Proceedings of the North American Society of Head and Neck Pathology Companion Meeting, New Orleans, LA, March 12, 2023: classification of salivary gland tumors: remaining controversial issues? Head Neck Pathol. 2023;17(2):285-91. https://doi.org/10.1007/s12105-023-01541-1
16. Sivakumar N, Narwal A, Pandiar D, Devi A, Anand R, Bansal D, et al. Diagnostic utility of p63/p40 in the histologic differentiation of salivary gland tumors: a systematic review. Oral Surg Oral Med Oral Pathol Oral Radiol. 2022;133(2):189-98. https://doi.org/10.1016/j.oooo.2021.07.010