Pleomorphic Adenoma and Trauma: a Case Report With Rare Clinical Presentation

Basma Morsy (basmasaad94@gmail.com)
Alexandria University Faculty of Dentistry https://orcid.org/0000-0002-8029-957X
Eglal Moussa
Alexandria University Faculty of Dentistry
Nourhan Aly
Alexandria University Faculty of Dentistry
Enas Omar
Alexandria University Faculty of Dentistry
Samar El Achy
Alexandria University Faculty of Medicine

Case report

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Abstract

Background

Pleomorphic adenoma (PA) is the most common benign salivary gland tumor. Many factors have been implicated in the etiology of PA, one of which is genetic alteration in PLAG1 and HMGA2 genes. Few cases were reported about PAs appearing in patients with history of trauma or denture wear.

Case presentation

A 73-year-old female patient presented to the clinic with a gradually increasing mass that appeared two months ago in the upper left labial vestibule. The patient reported wearing a maxillary complete denture for 15 years. Clinical examination revealed a typical denture fissuratum, so surgical excision was the treatment of choice. Upon excision, a fully encapsulated mass was exposed and sent for histological and immunohistochemical analyses that confirmed a final diagnosis of PA.

Conclusion

This case suggests a contributory role for trauma in the development of PA, following DNA alterations or through oxidative stress resulting from Chronic Mechanical Irritation (CMI).

Background

Salivary gland tumors are a group of rare heterogeneous lesions with complex clinical and histological features accounting for about 3–5% of all head and neck neoplasms. [1] Pleomorphic adenoma (PA), a benign mixed tumor, is considered the most prevalent salivary gland neoplasm constituting about 60% of all benign salivary gland tumors. [2, 3]

The most common locations for PAs are the parotid glands (60–73%), followed by submandibular and minor salivary glands (40–60%). [4] Among minor salivary glands, the most frequently affected site is the palate (42.8–68.8%) and upper lip (10%) with other rare intraoral locations reported such as the oropharynx (2.5%) and retromolar trigone (0.7 %). [5]

PAs have a female predilection with an average age ranging from 43 to 46-years-old. [6, 7] It is considered one of the few benign lesions that can undergo malignant transformation; changing into carcinoma (CXPA-Carcinoma ex pleomorphic adenoma) with 6% aggressive progression rate, [8] following multiple genetic alterations that are still not fully clear. [9, 10] The risk increases as the age of the patient, duration and size of the lesion increase. [3, 6]

Little is known about the etiology of PAs in terms of onset, progression, chromosomal alterations, and gene mutations detected. Some alterations were suggested by previous cytogenetic studies that revealed characteristic processes of recurrent translocations and intrachromosomal rearrangement that consequently lead to specific gene fusion that involves certain transcription factor genes namely: PLAG1

and HMGA2. [11, 12] However, some other factors have been implicated such as exposure to head and neck irradiation, oncogenic simian virus (SV40) and excessive use of tobacco and their products. [3, 6]

To date, very few case reports have recorded intraoral PA associated with a previous history of trauma, injuries, or ill-fitting dentures. The following case-report is an oral PA located in the upper left labial vestibule, clinically resembling a typical denture fissuratum.

Case Presentation

A 73-year-old female presented to the Oral Medicine Department complaining of a painless exophytic mass located on the upper left labial vestibule, which started two months ago and increased in size over time. The patient reported wearing a maxillary complete denture all day and during sleep for 15 years. The denture was not professionally modified or relined all over this period.

Upon medical history taking, the patient reported being on oral hypertensive drugs for years. No specific findings were noted on extra oral examination, while intraoral examination revealed a firm, pink, leaf-like exophytic mass measuring 1 by 1 cm in the upper left labial vestibule (upper lateral/ canine region). (Fig. 1, 2) The mass had normal consistency, smooth surface texture and was surrounded by normal oral mucosa. No other abnormal findings were found elsewhere in the oral cavity.

The initial differential diagnosis included denture fissuratum (because of the long-term use of the denture and the typical leaf-like clinical appearance) and irritational fibroma (that could be due to irritation from the denture upper flange). An excisional biopsy was performed, and it revealed a capsulated submucosal mass (Fig. 3) that was taken for histopathological examination to help in reaching a conclusive final diagnosis. Two independent pathologists reviewed the hematoxylin and eosin stained specimens (Fig. 4), and to confirm the diagnosis, immunohistochemical staining was performed (Fig. 5)

Histopathology and Immunohistochemistry

Microscopic examination (Fig. 4, 5) revealed an encapsulated tumor growth composed of a mixture of epithelial and myoepithelial/stromal components. Epithelial elements are disposed in ducts lined by a layer of cuboidal cells (as evidence by CK7 immunohistochemistry staining) lying on a flattened myoepithelial cell layer (as evidenced by p63 and SMA immunohistochemistry staining). Spindled myoepithelial cells stream from the ductal elements into the stroma. Few ducts contain eosinophilic secretion within their lumina. The stromal elements are composed of hyalinized stroma with few myxomatous areas. Mitotic figures were scarce.

Immunohistochemistry staining was performed on 4 um thick formalin-fixed paraffin embedded sections of tumor samples using a standard streptavidin-biotin-peroxidase method (LSAB). We used cytokeratin polyclonal antibody (Catalog # PA5-290337), Alpha-Smooth Muscle Actin Monoclonal Antibody (1A4), eBioscience (Catalog # 14-9760-82), Phospho-c-Kit (CD117) Polyclonal Antibody (Catalog # 44-496G) and Monoclonal Mouse Anti-Human p63 Protein (Catalog # M7317). Tissue sections were obtained and

mounted on slides 3800083 - Apex Adhesive Microscope Slides - Surgipath Apex Adhesive Microscope Slides, Leica. Sections were deparaffinized using xylene and rehydrated in graded ethanol. To block the endogenous peroxidase activity, the slides were incubated in 3% hydrogen peroxidase in absolute methanol for 10 minutes and then rinsed with phosphate-buffered saline (PBS). They were incubated with primary antibodies against (cytokeratin 7, SMA, P63, CD117) at 4C° overnight. A negative control for each reaction was obtained by omitting the primary antibody. The immunoreactivity analysis showed membranous reaction to cytokeratin 7 in the epithelial elements of the tumour. While Smooth muscle actin revealed cytoplasmic staining in the myoepithelial cells. Furthermore, p63 immunohistochemistry staining highlighted the myoepithelial cell component by positive nuclear staining. CD117/c-KIT immunohistochemistry staining revealed a weak positive cytoplasmic staining in very few ductal epithelial cells.

Management

Histopathological results suggested the diagnosis of PA and since the recommended approach for managing intraoral minor salivary gland neoplasms that lack malignant features is conservative complete surgical excision with tumor-free margins, [13] and as excisional biopsy was already performed, no further interventions were needed. However, since previous studies concluded general difficulty in complete surgical removal of salivary gland PA, which leads to a 4.6% first recurrence rate, [10] the patient was called for follow up after three months. (Fig. 6) In addition, the patient was advised to stop wearing the denture for two weeks and was instructed about proper denture-hygiene measures. After one year, the patient reported that the lesion healed completely with no evidence of recurrence.

Discussion And Conclusion

PAs usually present as painless, well delimited masses frequently arising in major salivary glands with uncommon occurrence in minor salivary glands primarily involving the palate followed by upper lip and buccal mucosa. [14–17] When occurring in the upper lip, they usually manifest as mobile, submucosal nodular masses with partial or no capsules. [14]

The presented case shows a PA that resembles a denture fissuratum, with a typical leaf-like appearance, in the upper labial mucosa. Clinical examination suggested a differential diagnosis of denture fissuratum followed by irritational fibroma that would classically be surgically excised to allow proper fit of the denture. To reach a definitive diagnosis, an excisional biopsy was performed that revealed a well-encapsulated nodular mass making the diagnosis of both denture fissuratum and irritational fibroma less probable. Histopathological examination revealed a well encapsulated mass showing proliferating glandular epithelial cells exhibiting architectural diversity which is a characteristic feature for PA. The proliferating glandular cells were formed mainly of ductal and myoepithelial cells. Numerous duct-like structures showing pinked eosinophilic stroma were detected, confirming a final diagnosis of PA. Since PAs are benign epithelial neoplasms demonstrating both epithelial and modified myoepithelial differentiation with diversified histologic features, immunoexpression of different immunomarkers (CK7,

P63, SMA, CD117) were investigated. Our results were consistent with other data reported in literature. [18, 19] The tumor cells showed positive immunosignals to Ck7,SMA. Furthermore, p63 immunohistochemistry staining was detected and it was evident as nuclear expression. On the other hand, CD117 immunohistochemistry staining revealed weak positive cytoplasmic staining in very few ductal epithelial cells, excluding the diagnosis of adenoid cystic carcinoma, which is consistent with other studies showing similar results regarding CD117 expression in Pas. [20, 21] Since excisional biopsy was already performed, no further invasive interventions were intended.

To date, very few cases of PAs arising intraorally in different places were associated with a history of trauma or denture-wear. Fatahzadeh [15] reported a case of upper lip PA with an onset related to a lip trauma that occurred 25 years ago. This is in addition to a case reported by Singh et al.[22] of a male patient having an upper labial PA with a history of trauma 7 years earlier in the same location, and another case of a female patient reporting a history of trauma 8 years ago before developing a PA on the upper right side of the lip. [23]

Only two case reports were recorded by Jiménez [24] and Dyalram et al. [25] for patients wearing maxillary dentures where PAs developed on the hard palate and upper labial sulcus, respectively. However, the denture status in terms of fitting, stability, and duration of wearing the dentures were not stated.

Several previous studies already suggested that Chronic Mechanical Irritation (CMI) caused by intraoral injury-causing agents such as ill-fitting dentures (including those with sharp surfaces, defective retention or stability and overextended flanges) can trigger changes in healthy oral mucosa, intensify an existing oral disease and even play a role as a tumor promotor. [26, 27]

In a recent study conducted on oral mucosal epithelial cells and fibroblasts, mechanical stress was found to influence a significant increase in inflammatory cytokines Interleukin 6 and Interleukin 8 (IL-6 and IL-8) production. It also demonstrated that high stress levels induced production of Fibroblast Growth Factor (FGF-2) and Epidermal Growth Factor (EGF) as means of cellular defense mechanism. [28]

A meta-analysis showed that chronic trauma was linked to carcinogenesis in several mechanisms including increased mitosis, DNA alteration and chemical mediators/oxidative stress release; which contributes to further DNA damage. [29] Additionally, there was an increased risk of cancer development in denture users, with an elevated likelihood for ill-fitting dentures, which could suggest a similar correlation between denture wearing and tumor development (including salivary gland tumors). [30] Nevertheless, to date, there is not enough evidence that links denture use or CMI to development of Salivary gland tumors including PAs.

Limitations of the presented case include improper testing of the denture stability/fit, denture hygiene and inability to recall the patient for a clinical follow-up due to the total lockdown measures during the COVID-19 pandemic.

To conclude, this case suggests a relation between trauma and development of salivary gland tumors including PAs. Based on the role of CMI in tumorigenesis, DNA alteration and oxidative stress release which advocates a contribution to genetic alterations responsible for PA formation. Further studies are needed to establish an association with much closer focus to dental prosthesis role in development of such tumors with proper assessment of the denture status in terms of stability and hygiene. More studies are also needed to examine PLAG1 and HMGA2 genes in patients with PAs with a history of trauma, for any genetic mutation/fusion.

Abbreviations

PA: Pleomorphic Adenoma

CMI: Chronic Mechanical Irritation

IL-6: Interleukin 6

IL-8: Interleukin 8

FGF-2: Fibroblast Growth Factor

EGF: Epidermal Growth Factor

Declarations

Ethical approval and consent to participate

Not applicable

Consent for publication

A written informed consent was obtained from the patient for publication of this case report and a copy is available for review by the editor of this journal.

Availability of supporting data

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

BMM performed the initial examination, diagnosis, photography and followed up with the patient. BMM and NMA drafted the initial version of the manuscript. EMO and SEA performed the histological analysis. EM supervised the clinical work and critically revised the manuscript. All authors read and approved the final version of the manuscript.

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Figures

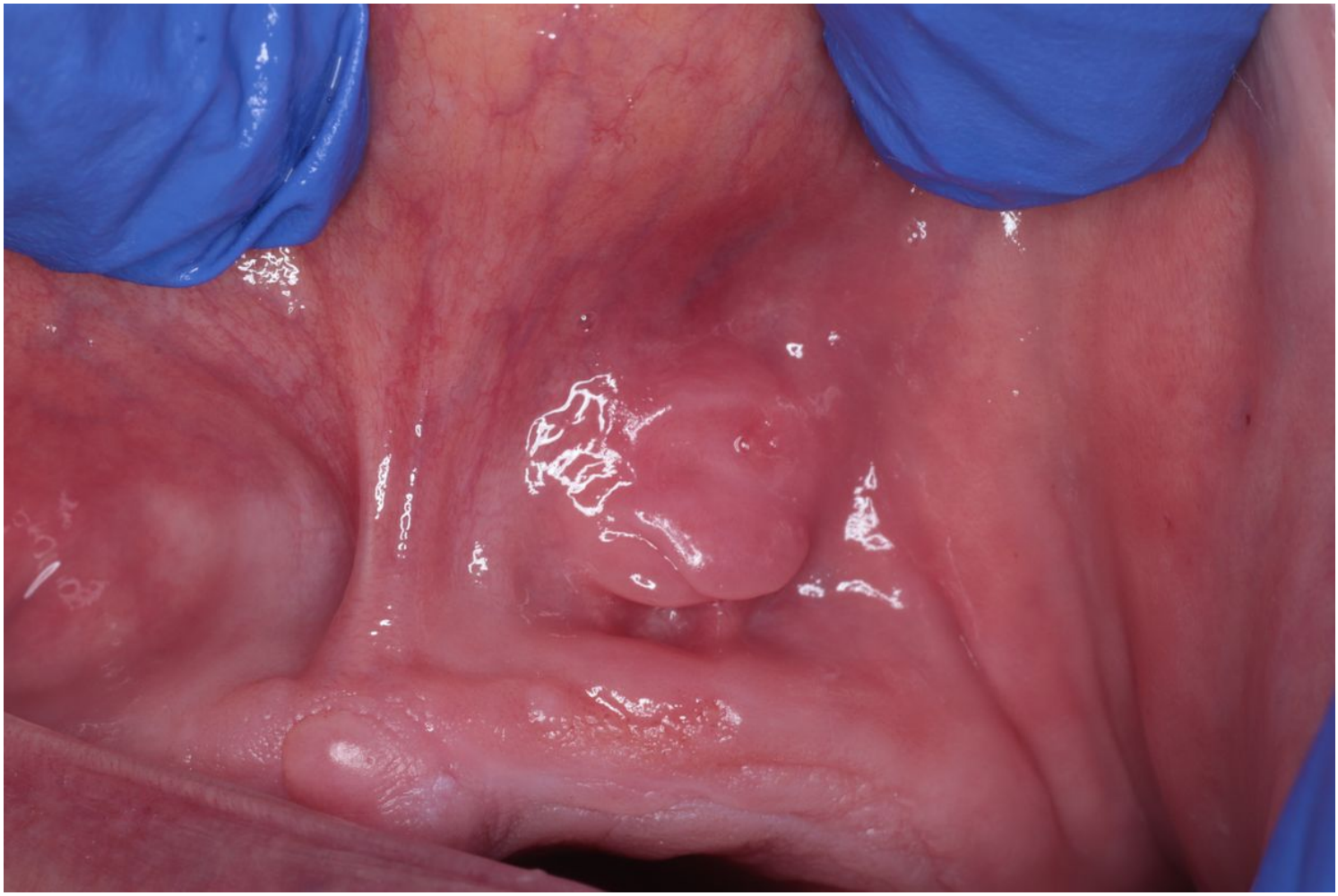

Figure 1

A photograph of the upper left vestibule showing the exophytic mass

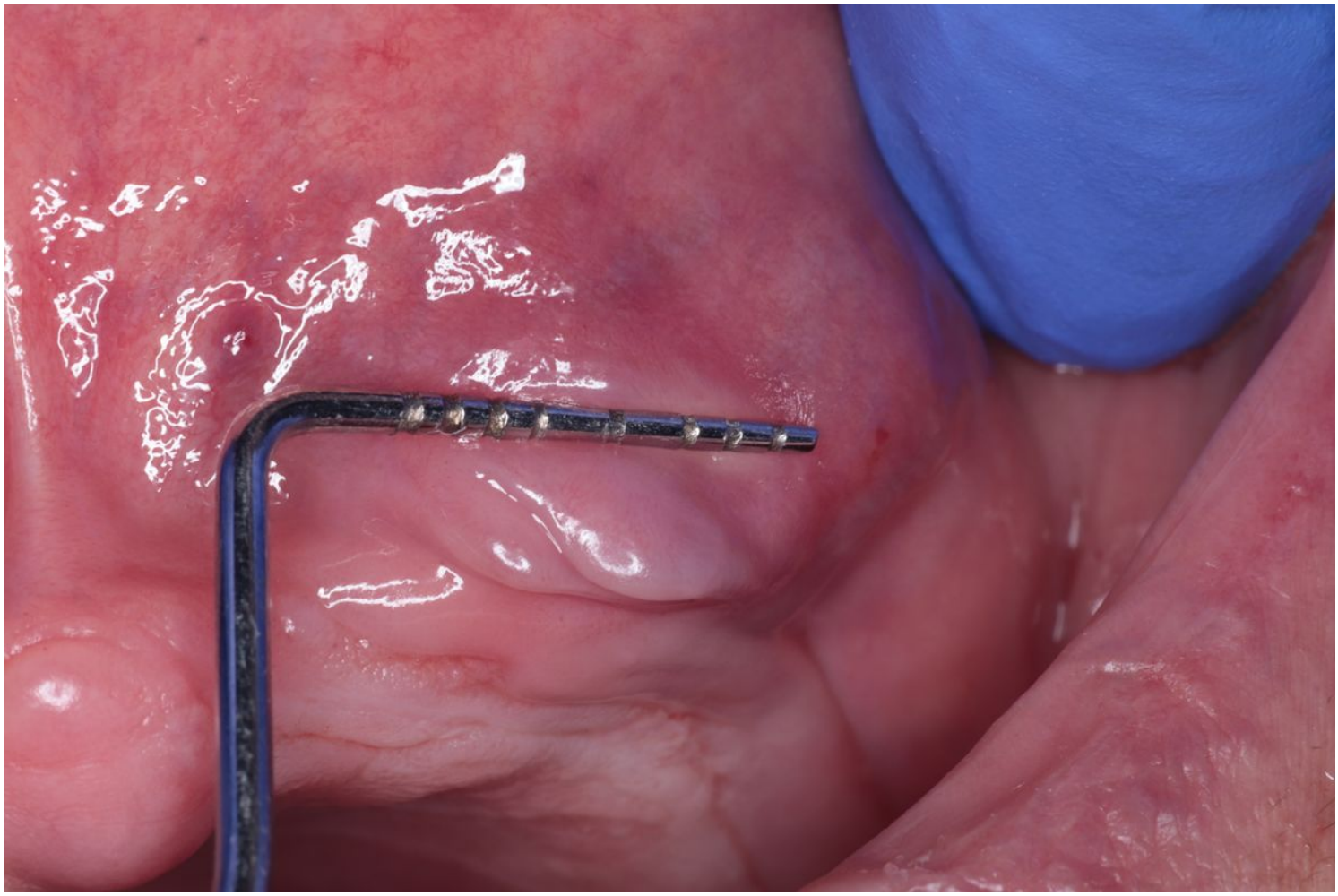

Figure 2

A photograph of the mass with approximate dimensions measured using Michigan “O” probe with William’s markings.

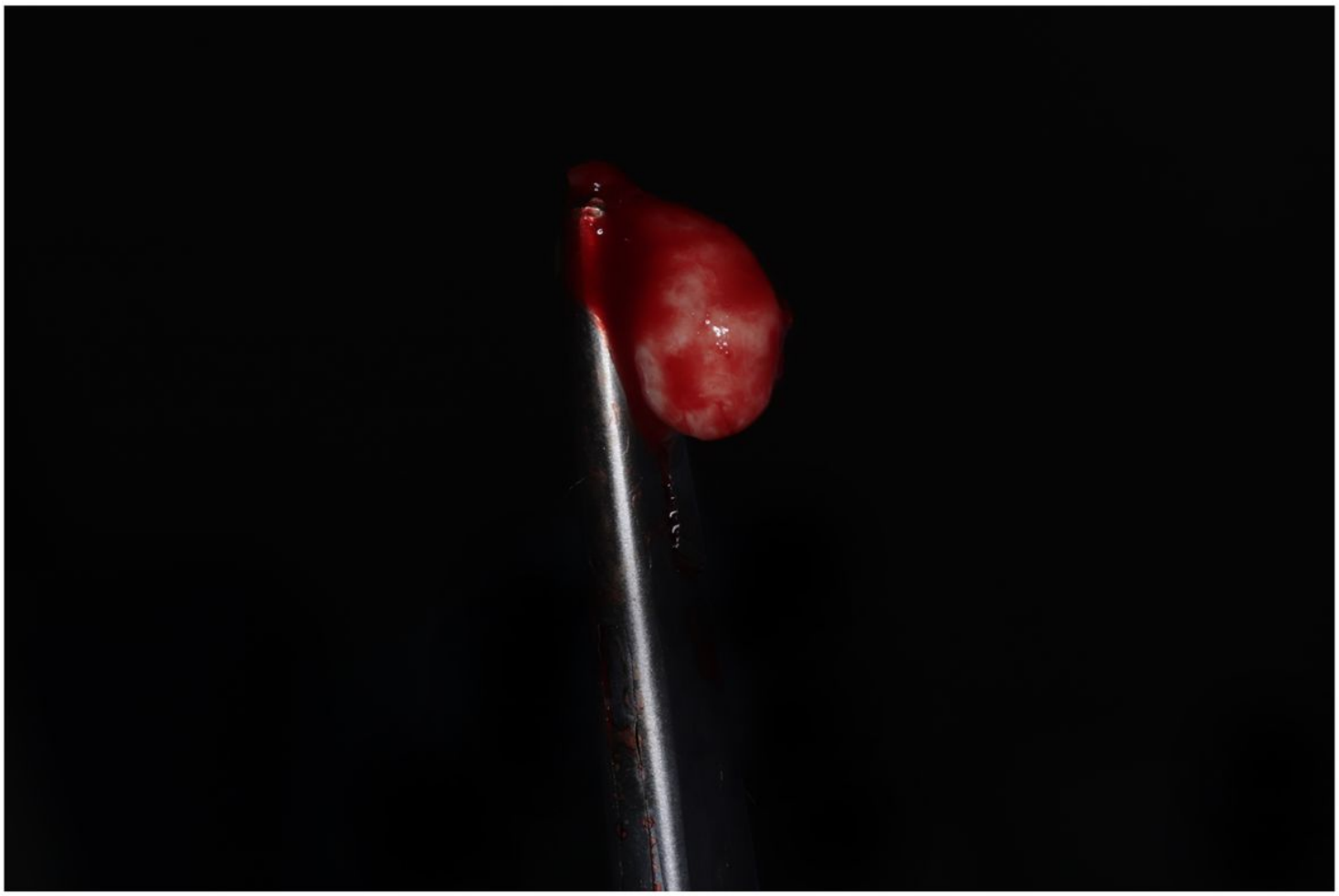

Figure 3

A photograph of the sub epithelial excised mass immediately post-op showing a full capsule

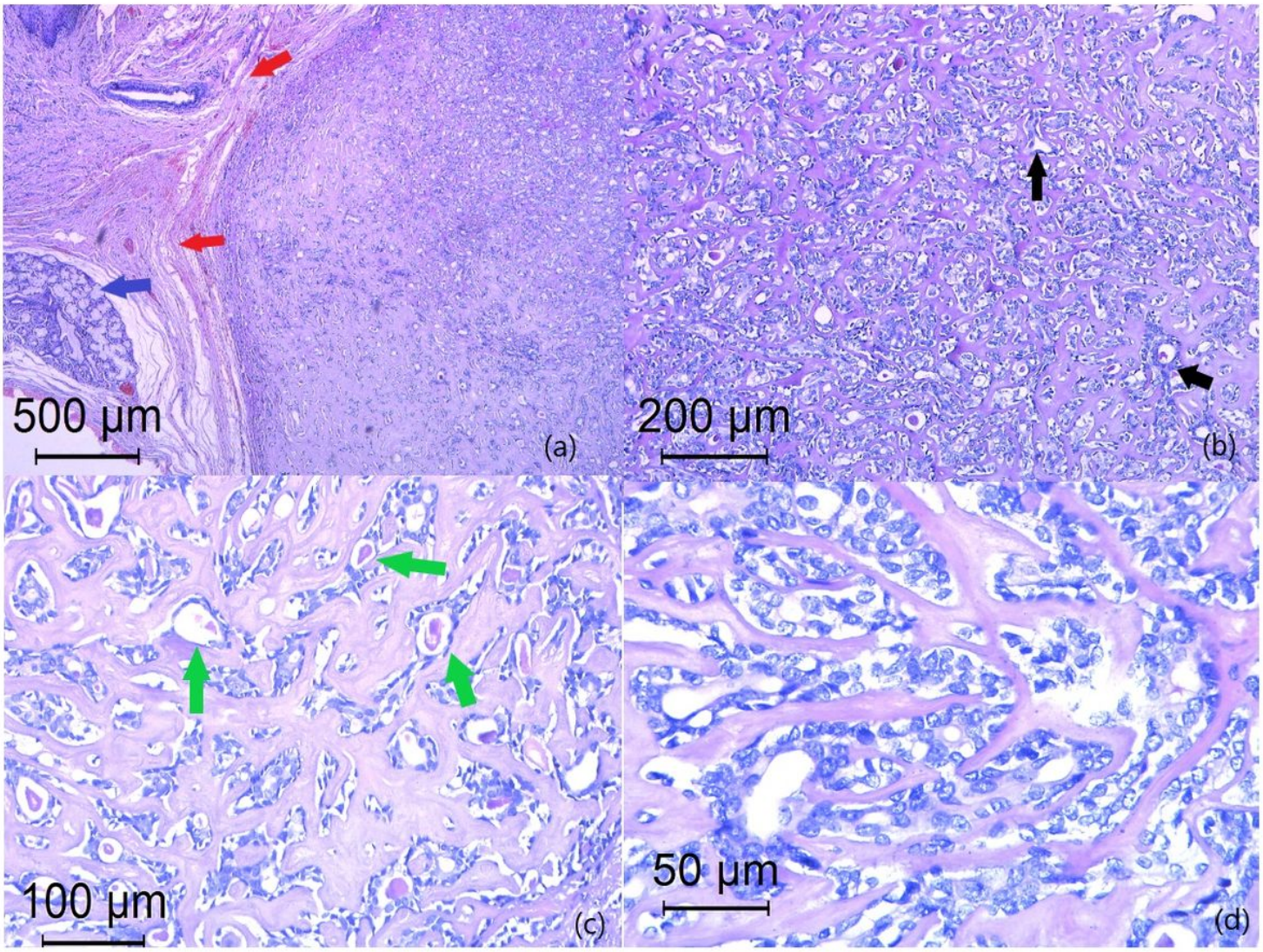

Figure 4

(a) A photomicrograph showing the encapsulated tumor (red arrow) and minor salivary glands in the surrounding tissue (blue arrows) (H&E x40). (b) A cellular neoplastic growth composed of epithelial elements; ducts and trabeculae (black arrows), and mesenchymal elements; hyalinized stroma. (H&Ex100). (c) The glandular epithelial elements disposed in ducts, trabeculae and cords. Ducts are lined by two cell layers with empty lumina. (H&Ex200) (d) higher magnification of the previous photomicrograph showing Ducts are lined by two cell layers with empty lumina (H&E x400)

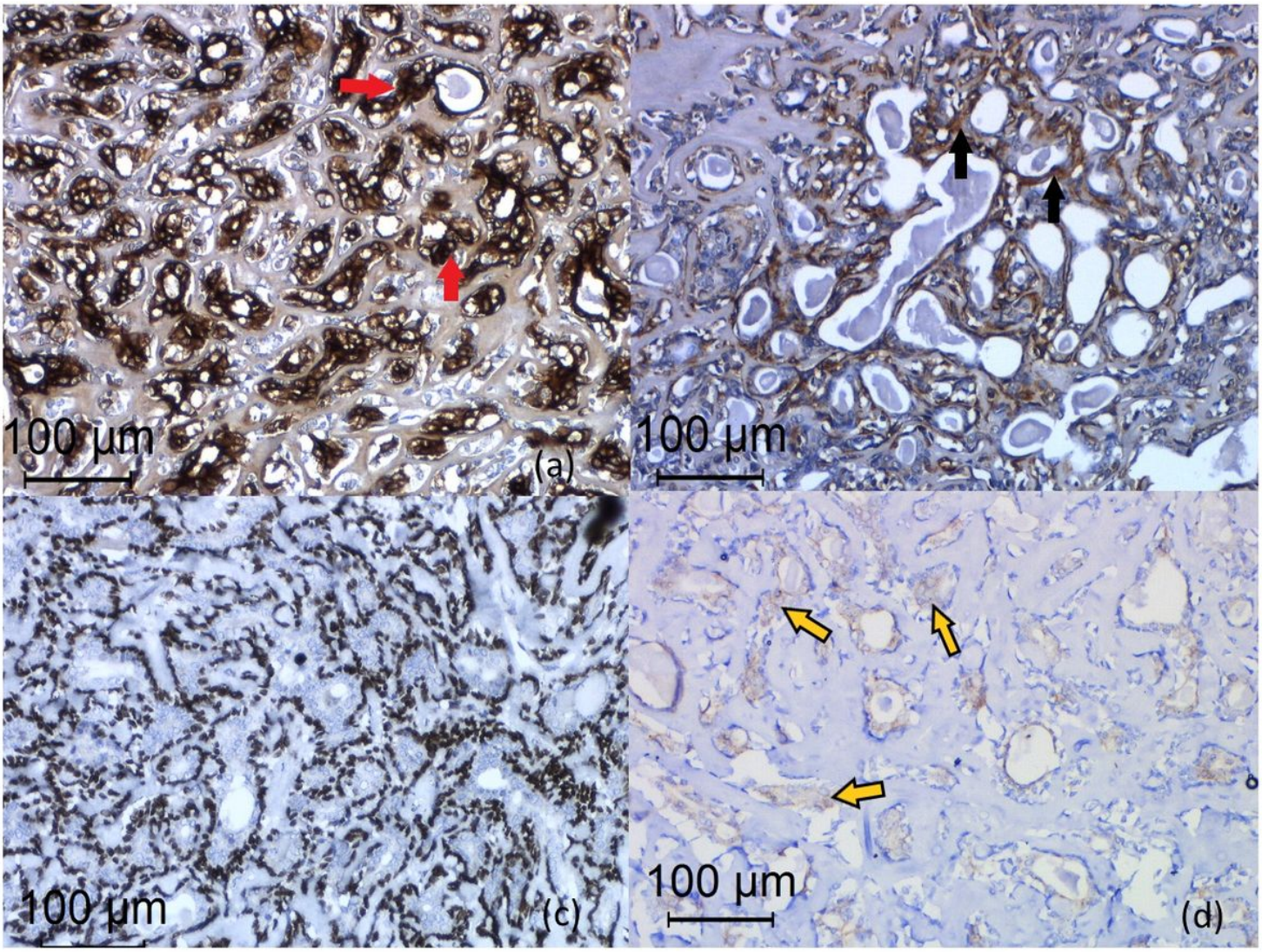

Figure 5

(a)An anti-CK7 stain showing strong positive membranous and cytoplasmic staining in the epithelial elements (cytokeratin 7 x100). (b) An anti-SMA immunostaining showing cytoplasmic positive signals in the myoepithelial cells surrounding the ducts and merging into the stroma (SMA x200) (c) An anti-p63 immunostaining showing positive nuclear staining in the myoepithelial cells surrounding the ducts and merging into the stroma (P63 x100). (d) An anti-CD117 immunostain showing weak cytoplasmic signals in the epithelial cells (CD117x100)

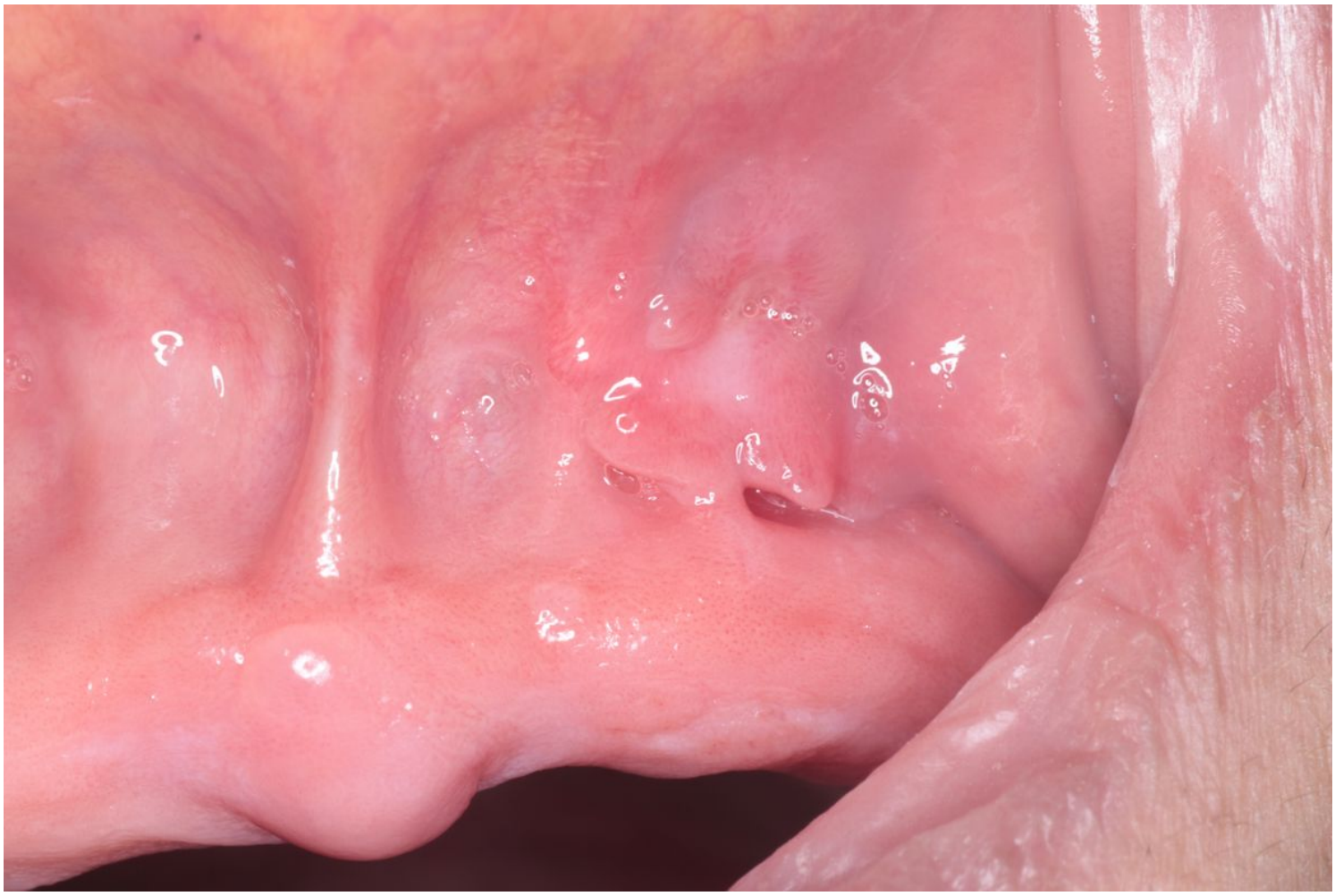

Figure 6

A 3 month follow up photograph for the original site of the mass

Supplementary Files

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- CAREchecklistEnglish20138.1.pdf