Pomeranian J Life Sci 2021;67(2):27-32 doi: 10.21164/pomjlifesci.777

Pleomorphic adenoma of the lip – a case report

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ABSTRACT
This case report describes a pleomorphic adenoma in an unusual location. A 47-year-old man presented with a painless, slow growing tumor in his upper lip. An interview and physical examination were the basis for an initial diagnosis of a benign tumor. The lesion was removed entirely under local anesthesia using the trans-mucosal route. Histopathological examination revealed pleomorphic adenoma. The patient remains under constant outpatient control.
Keywords: minor salivary glands; pleomorphic adenoma; mixed salivary gland tumor; chondroid syringoma.

INTRODUCTION

Pleomorphic adenoma (PA) is a tumor of epithelial origin [1, 2]. It is classified as a benign neoplasm, although its clinical course often differs from that of benign lesions [3, 4]. The main part of the tumor mass is surrounded by a pseudocapsule [3]. Pleomorphic adenoma has a pronounced tendency to recur due to the fact that pseudocapsule defects are found in most cases [3, 4, 5, 6, 7]. Numerous studies also demonstrate the incidence of malignant PA [8, 9, 10, 11, 12, 13, 14, 15]. The risk of transformation of recurrent PA into a malignant neoplasm is more than 3% [5, 6].

Pleomorphic adenoma originates from the parenchymal cells of the salivary and lacrimal glands [16, 17]. A pleomorphic skin tumor with identical morphology to PA develops from the sweat glands [18, 19]. Pleomorphic adenoma has a particular predilection for the parotid glands where it is the most common benign tumor. It is approx. 2 times more common in women than in men. In addition to the major salivary glands, it is also found in the palate [20, 21, 22]. Minor labial salivary glands are considered to be a rare location for PA and individual cases are described in the professional literature [23, 24, 25, 26]. For this reason, the authors of this study decided to present the rare case of a patient with PA of the upper lip.

CASE DESCRIPTION

A 47-year-old man reported to the Maxillo-Facial Surgery Clinic in Kielce in April 2018. He was referred for surgical consultation by a dentist during a routine dental examination. As his chief complaint, the patient reported the presence of a tumor of the mucosa of the upper lip on the left side. The patient described a slow growth of the lesion lasting for more than 6 months. The patient did not report the presence of pain or functional disturbances accompanying the tumor growth. He also reported no trauma or surgical procedures involving the lips. He denied taking any medication or exposure to ionizing radiation.

Extraoral examination showed no enlarged cervical lymph nodes of groups I–IV on either side. An elastic hard tumor approx. 10 mm in diameter was found in the area indicated by the patient. The tumor was located above the border of the vermilion and upper lip mucosa, submucosally on the left side, at the level of tooth 23. The tumor did not cause any pain or bleeding on palpation. The tumor was mobile with respect to the overlying mucosa and slightly mobile with respect to the substratum. No skin lesions or redness of the lip were found in the area of the described lesion.

Orthopantomography did not reveal any pathology regarding the teeth or alveolar bone of the maxillary second quadrant. Also, X-ray imaging showed no foreign bodies within the examined region.

Due to the lack of clinical features of a malignant lesion and due to its small size, an excisional biopsy was performed. The procedure was performed on an outpatient basis under local anesthesia. Articaine 4% with adrenaline (1:100,000) was administered as infiltration anesthesia. The lesion was excised transmucosally with a margin of about 2 mm of macroscopically unchanged tissue. The wound was closed by simple suturing with single 5-0 non-absorbable knotted sutures. There were no complications during the operation. There was no need for additional hemostatic techniques other than wound suturing.

The postoperative wound healed normally. On postoperative day 14, the sutures were removed. The result of the histopathological examination was then obtained and given to the patient. The histopathological examination showed a completely removed PA. The patient was informed about the specifics of the diagnosed neoplasm and told about the necessity of further observation. At the next follow-up, performed after 18 days, the

wound was found to be fully healed. Instructions for self-examination were given and initial follow-up visits were scheduled at 3 and 6 months after the surgery. After this, the patient remained under regular outpatient follow-up every 6 months. No features of PA recurrence were observed during the 2.5-year follow-up. The linear scar of the lip mucosa did not cause discomfort to the patient. The complete removal of the lesion and absence of clinical signs of recurrence are good prognostic factors.

DISCUSSION

A PA is also known as *tumor mixtus* due to its heterogeneous microscopic image, i.e., it is composed of myoepithelial and epithelial cells. According to Nezhad et al., a microscopic examination of PA most commonly identifies spindle, plasmocytoid and cubic cells. Spaces between PA cells are filled with stroma, dominated by mucoid, myxoid and chondroid components [1]. The classification of PA into a histological subtype depends on the proportion of cells and the extracellular matrix. The first division was presented by Seifert et al. as 4-grades; currently, 3 subtypes of PA are distinguished: myxoid, classical and hypercellular [1, 2].

According to the current 2017 classification of the WHO, PA is considered a benign neoplasm [27]. According to generally accepted criteria, such tumors are characterized by slow expanding growth, clear-cut lines of demarcation from surrounding tissue, and a lack of ability to recur and metastasize. However, studies demonstrate that PA often deviates from this description [3, 4]. Zbären and Stauffer performed a histological analysis of pseudocapsules surrounding PA. Their examination of this neoplasm in 218 patients showed that in almost 3 out of 4 cases, PA cells extended beyond the macroscopically defined boundary [3]. Researchers also described other features of PA that were non-characteristic for benign lesions, namely the presence of tumor pseudopodia, incomplete encapsulation, penetration of cells into the pseudocapsule structure, and the presence of satellite tumors [3, 28]. An analysis by Dulguerov et al. of previous publications on PA recurrence mentioned pseudocapsule defects, a mucoid histological subtype and a large tumor size as the main risk factors for PA recurrence [4].

The recurrence of PA has been best studied for tumors located in the parotid gland [5, 6]. According to Andreasen et al. in an analysis of a group of nearly 5,500 patients from Denmark, the recurrence rate of PA originating from the parotid gland is just under 3%. However, this study did not take into account a very important criterion, namely the length of postoperative follow-up [5]. Valstar et al. subsequently took the criterion of the duration of postoperative follow-up into account, evaluating a group of approx. 3,500 patients with diagnosed PA in the Netherlands. By analyzing the postoperative 20-year follow-up of these patients, they calculated a recurrence rate at over 6.5%. The median time calculated from the removal of the primary tumor to the time of the first recurrence was approx. 7 years in the study group [6]. Both Andreasen et al. and Valstar et al. pointed out the risk of PA malignancy after recurrence. This percentage was slightly over 3% according to both groups of researchers [5, 6].

A special case of PA recurrence is metastasizing pleomorphic adenoma (MPA). This neoplasm cannot be distinguished histologically from PA, but its clinical course differs significantly as it may metastasize to distant organs, most frequently to the lungs and bones [27, 29]. Santaliz-Ruiz et al. described a case of this rare tumor, confronting their report with available publications [29]. Santaliz-Ruiz et al. argued that in about 4 out of 5 patients, the occurrence of MPA is associated with a previous recurrence or multiple recurrences of PA [29]. As reported by Seethala and Stenman regarding the update of the WHO division of head and neck cancers, MPA has been removed from the malignant category in the latest 4th edition of the classification. It is now classified as a PA subtype, i.e., a benign neoplasm of the salivary glands. At the same time, the same authors emphasize that MPA can give both regional and distant metastases. The latter are usually localized in the lungs or bones [27].

The exact etiology of PA is unknown. However, as reported by Warfield and Smallman, a link can be made between prior irradiation of the area in question and the development of the tumor described [30]. Similar conclusions were reached by Bokhari and Greene in their article on PA [31]. In addition to the gradual increase in radiation as an environmental factor, they point, following Martinelli et al., to SV40 polyomavirus infection as a possible risk factor [31, 32]. The study by Martinelli et al. showed the presence of virus DNA in 28 of the 45 PA cases analyzed, compared to an absence of the SV40 virus in the 11 control samples [32]. In the search for the etiology of PA, another route is in the analysis of genetic material collected from the tumor itself [8]. Martins et al. and Kandasamy et al. performed molecular studies of 16 and 7 tumor cases respectively. Both groups of authors independently demonstrated abnormalities of the *8q12 locus* responsible for encoding the *PLAG1* protooncogene [8, 33]. Yet another possible cause of PA development is phenytoin intake, according to Maharshi and Nagar. In their report they refer to the body of evidence of the induction of various cancers due to a chronic intake of this and other antiepileptic drugs [34]. In contrast, Tzermpos et al., in their study on PA detected in the upper lip, note that the patient had a trauma to the area where the tumor developed 8 years later [35].

Primary neoplasms of PA histological type most often originate in the parotid glands [20, 21]. Mejía-Velázquez et al. conducted a retrospective epidemiological analysis of the incidence of salivary gland tumors in the Mexican population. Approximately 66% of the 360 patients with salivary gland neoplasms had PA. This publication identified the following descending order of incidence depending on the location: the parotid gland, submandibular gland, and minor salivary glands of the palate, labium, and others. Primary neoplasms of the lips accounted for approx. 4% of cases. Using the same data, the female to male incidence ratio was calculated to be approx. 2:1 [20]. Similar results were obtained by Araya et al. analyzing patient data from Chile. Of the 279 cases of salivary gland tumors, approx. 54% were PA [21]. The percentage of PA cases localizing in the lips was similar to the study by Mejía-Velázquez et al. of

about 4%. The authors of both publications concurrently found a higher incidence of PA in women [20, 21]. In the study by Araya et al. the female to male incidence ratio was approx. 1.5:1 [21]. Gontarz et al. studied 776 patients from Poland diagnosed with salivary gland tumors. Among the entire group of 776 patients, PA accounted for approx. 39% of cases whereas in 19 patients aged 18 years or younger, PA accounted for about a half of salivary gland tumors. The authors noted that 2 of the 10 cases of PA in patients under 18 years of age were located in the minor salivary glands of the palate and buccal mucosa. No cases of PA in the lips were found in the younger patients [22]. An epidemiological analysis of the incidence of minor salivary gland tumors was also conducted by Venkata and Irulandy. The researchers compiled data of patients from India, and out of 185 cases of minor salivary gland neoplasms, mucinous carcinoma was predominant (34%). The next most common was PA (22%). In other words, PA was identified as the most common benign neoplasm of the minor salivary glands [36].

Although PA occurs mainly in the major and minor salivary glands, other locations of this tumor have also been described in the literature [16, 17]. Yeşiltaş et al. analyzed nearly 100 cases of lesions originating from the lacrimal glands. Based on their study, they concluded that PA is the most common benign tumor of the lacrimal glands in the Turkish population, accounting for more than 80% of all cases [16]. This percentage was consistent with a study conducted by Andrew et al., in which the results of an analysis of 268 biopsies performed in Australia were described. The data collected by the authors put the frequency of PA among benign lacrimal gland neoplasms at over 70% [17].

Chondroid syringoma, originating from the sweat glands, shows a histological picture identical to PA [18, 19]. Another summary of reports on this tumor determined the incidence of chondroid syringoma to be between 1:1,000 and 1:10,000 of all skin neoplasms, with the female-to-male incidence ratio at 1:2. The authors identified the areas of the nose, cheeks and upper lip among the most common sites of incidence [18]. A report of 5 cases of chondroid syringoma of the upper lip can be found in an article by Min et al. The descriptions in the publication differ only slightly from those for PA [19]. This neoplasm is characterized by a subcutaneous location, unlike the submucosal location of PA [18, 19].

Approximately half of neoplasms originating from the minor salivary glands are located on the palate. This was confirmed by an analysis conducted by Wyszyńska-Pawelec et al., in which the percentage was approx. 46% [37]. According to the studies by Mejía-Velázquez et al. and Araya et al., the palate is the most common region of intraoral PA occurrence [20, 21]. As reported by Singh et al., PA originating from the palatal salivary glands is usually located at the border of the hard and soft palate [38]. Moore et al. explain this by pointing out that the highest concentration of minor salivary glands are in this area [39]. The lips represent the second most common intraoral location, although it is difficult to assess upper to lower lip incidence ratio. Most authors report that the neoplasm is much more common in the upper lip but there is no hypothesis of why this is so [20, 21, 37, 40]. Al-Khateeb conducted an analysis of 818 cases of proliferative and inflammatory lesions detected within the oral cavity in the Jordanian population. Among them, 36 cases were benign neoplasms. Based on the data compiled, the author found 3 cases of PA of the upper lip and 1 case of this neoplasm in the tissues of the lower lip [40]. Indeed, there are more descriptions of PA of the upper lip in the literature, whereas case reports of PA of the lower lip are infrequent. Sengul and Sengul analyzed literature in English concerning PA localization in the lower lip. On that basis, the authors confirm the uniqueness of PA occurrence in the lower lip [41]. To confirm their thesis, they refer among others to the publication of Kuo et al., a review of 37 cases of PA of the minor salivary glands, which did not show a single case concerning the lower lip [9].

In a 10-year retrospective study, Kuo et al. found 3 recurrences and 1 case of PA malignancy [9]. According to Zbären et al., *carcinoma ex pleomorphic adenoma* (CXPA) accounted for up to 14% of all parotid malignancies in the Swiss population [10]. Antony et al. in a study on CXPA demonstrate the convergence of the results of Zbären et al. with 2 studies conducted in the United States of America [10, 11]. Antony et al. highlight the difficulty of clinical and histological diagnosis of this neoplasm [11].

We compared our own case of PA with the descriptions of other authors, especially with the high-quality reports of Tzermpos et al., Singh et al., Lotufo et al., Debnath and Adhyapok, Ali et al., and Ahmedi et al. All the reports involve a tumor located in the upper lip. Primary neoplasms initially grows asymptomatically, only palpation of the tumor or dysfunction leads to a suspicion that the disease is present. The authors unanimously describe this tumor as non-painful, elastic-hard, ellipsoid, and with a slow growth [35, 38, 42, 43, 44, 45].

Ahmedi et al. point out that a benefit of lip physiology is the ease with which pathologies originating from the lip can be identified by the patient themselves. According to these authors, this localization results in a markedly better detection rate than is the case for parotid tumors of the same histologic complex. This is due in part to the functional activity of the lips, which are involved in activities such as speaking and eating [45]. However, the path from detecting the presence of a lesion to making a definitive diagnosis is difficult, e.g. due to the anatomical complexity of the lips. Both the upper and lower lips consist of skin, muscle, submucosal tissue, and mucosa. The skin is made up of 3 layers: the epidermis, dermis and subcutaneous tissue and contains hair follicles and sweat glands. Minor salivary glands are located within the submucosa. In addition, as in other locations, blood and lymphatic vessels and nerve branches are present. Given the complexity of lip tissue, multiple conditions must be considered in a differential diagnosis. Bhandarkar and Shetty, in an article on the differential pathology of the upper lip, divides lesions of this location into salivary gland tumors, mesenchymal tumors, and sequelae of infection. According to these authors, lesions that can mimic PA include oral mucosal fibromas, lipomas, other tumors originating from mucosal glands, stagnant and true salivary cysts, and carcinomas, among others [46].

Because there are many pathologies that can localize in the lips, it is always advisable to extend the diagnosis of suspicious

lesions with methods other than visual inspection and palpation. One simple and accessible technique is an exploratory puncture to allow collection of a sample that can be immediately evaluated macroscopically. In ambiguous cases, the initial exploratory puncture can easily be converted to a fine-needle aspiration (FNA) biopsy; the obtained material is then sent for cytological examination [47].

Rajendra Santosh et al. performed a comparative analysis of research papers on an FNA biopsy of salivary glands. The researchers considered 414 publications from 1980 to 2016, from which they selected 29 articles containing an analysis of 5,274 FNA biopsies. Based on the analyzed data presented by many authors, they proved that the sensitivity of this diagnostic method is no less than 87% in terms of the differentiation of malignant from non-malignant neoplasms [48]. The ratio of malignant to non-malignant neoplasms of the minor salivary glands was given by Venkata and Irulandy as 3:1 [36]. On this basis, the percentage of false negative results is about 11%. Therefore, it can be assumed that more than 1 in 10 people who developed a malignant neoplasm of a minor salivary gland may be incorrectly classified on the basis of FNA as having a benign lesion and, consequently, incorrectly treated [36, 48]. Rajendra Santosh et al. determined the specificity of FNA to be at least 90% [48]. For minor salivary glands, this results in approx. 2.8% of tests being false positives. This means that nearly 3 out of 100 patients diagnosed with benign cancer by FNA alone would be scheduled for excessively mutilating surgery [36, 48]. Not covered by the aforementioned review, a newer study by Singh et al. on the FNA of 64 small salivary gland tumors showed a sensitivity of 81% and a specificity of 95% for the detection of malignancy [47].

Other tests which can be useful in diagnosing PA in various locations are X-ray imaging, computed tomography scanning, magnetic resonance imaging, and ultrasonography (USG) [49, 50]. Ultrasonography can also be used as guidance while performing FNA. A study of the effectiveness of this method was performed by Huang et al. by performing biopsies in 137 patients. The specificity of FNA was thus improved to over 98% [49]. When calculating the sensitivity of FNA under ultrasound guidance, Huang et al. was more stringent on this method than Rajendra Santosh et al. [48, 49]. Instead of only looking for features of malignancy, the sensitivity of indicating the exact type of tumor was evaluated. Despite such stringent criteria, the sensitivity of USG-guided FNA was just about 69% [49].

The alternative to FNA in regard to PA within lips is conventional biopsy [51]. It should be noted that a conventional biopsy is not the method of choice in cases of major salivary gland tumors [47, 48, 49]. A percutaneous incision in such cases would risk the formation of a salivary fistula [52]. Therefore, biopsies from lip tumors are taken transmucosally; this also applies to excisional biopsy. This does not contradict the cases of the percutaneous removal of chondroic syringoma described by Min et al., where chondroic syringoma is characterized by subcutaneous localization, which differs from submucosally located PA [19].

Numerous authors indicate that complete excision is the only appropriate treatment for PA. This issue is most fully elaborated on in the systematic review by Dulguerov et al., emphasizing that the risk of recurrence is not only reduced by a small tumor size, but also by preserving more than a 1 mm margin of macroscopically unchanged tissue and avoiding intraoperative pseudocapsule damage [4]. Kiciński et al. additionally emphasized the importance of surgical technique for minimizing the risk of recurrence. They point to a more than threefold reduction in the recurrence rate by using magnifying optical devices during tumor resection [53]. As reported by Achauer et al., lip tissue defects no larger than a third of the length of the lip can be closed by simple wound suturing or musculomucosal V-Y plasty [54]. Ebrahimi et al. suggest considering additional methods such as W-shaped excision or laterally pedicled advancement flap [55]. Kister et al. confirm the usefulness of W-Y plasty for small defects [56].

Most of the available literature does not clearly define the follow-up protocol after surgical treatment of PA. Lotufo et al., Debnath and Adhyapok, and Ali et al. observed patients with PA of the lip for 1 year before preparing their manuscripts [42, 43, 44]. Tzermpos et al. prolonged the pre-publication follow-up period up to 3 years [35]. However, these authors do not report the frequency and extent of the follow-up visits [35, 42, 43, 44]. Ahmedi et al. scheduled their treated patients for follow-up at 12-month intervals for 3 years after surgery [45]. Debnath and Adhyapok [43] and Ali et al. [44] scheduled post-publication follow-up visits for their treated patients for at least 5 years.

The growth rate of PA is quite low. The tumor described by Tzermpos et al. had been growing for about 3 years before reaching 1 cm in the longest dimension [35]. Lotufo et al. report 2 cm as the largest tumor dimension, determined after a 1-year observation of a child with PA by his parents [42]. The patient described by Debnath and Adhyapok reported a 1-year growth of a tumor that was 2 cm in diameter at the time of examination [43]. The case reported by Ali et al. involves a 3 cm tumor removed approx. 1.5 years after the first symptoms [44]. A boy diagnosed with a 2 cm PA was reported by Ahmedi et al. after 3 years of growth observation [45]. However, the slow enlargement of PA should not be a limiting factor for patient follow-up visits after the removal of this tumor.

In a study of 2,719 PA patients by Valstar et al., recurrence occurred in 125 cases, or about 4.5%. The authors noted an increasing probability of recurrence over time based on a 20-year follow-up, increasing by about a third of a percentage point each year, yielding more than 2% at 5 years, and nearly 7% at 20 years after surgery. The median time from resection to first recurrence calculated in this study was 7 years [6]. Redaelli de Zinis et al. followed Italian patients diagnosed with a recurrent form of PA. The authors routinely performed USG and in certain cases additionally used FNA, magnetic resonance imaging, computed tomography and sialography. Despite the high likelihood of subsequent recurrence, tumor malignancy, or the development of a metastatic form of PA, only 4 of 33 patients had regular annual follow-up visits [50]. Ayoub et al. suggested that special attention should be paid to educating patients and emphasized the importance of self-examination to minimize the time between recurrence and treatment [57].

CONCLUSIONS

Localized in the upper lip, PA originate from both the salivary and sweat glands. Pleomorphic adenoma should be treated by clinicians with oncological caution and vigilance, both at the diagnostic and surgical removal stages and during follow-up visits, in view of its recurrence rates, metastasis, and propensity to grow beyond the pseudocapsule. Tumor chromosomes show a defect in the *PLAG1* gene *locus*; however, this information does not currently have any clinical implications. There is some evidence of an association between PA development and exposure to ionizing radiation and the SV40 virus infection. For unknown reasons, the tumor is more frequently found in the upper lip than in the lower lip. The treatment of PA consists of complete excision with a margin of unchanged tissue. In all cases, it is advisable to instruct the patient on self-examination techniques and the necessity of periodic checking, at least once a year.

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