Case Report

Polymorphous adenocarcinoma: a review of the literature and presentation of a case in an uncommon anatomical area

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Abstract

Background. Polymorphous adenocarcinoma (PAC) is a type of salivary gland tumor that is rare and diverse in morphology. It is typically found in the minor salivary glands, with the palate being the most common location. However, this tumor is often misunderstood, underdiagnosed, and controversial in nomenclature. Its low-grade behavior may be unpredictable, making it challenging to manage.

Case report. In this paper, we detail a case of PAC that developed in the buccal mucosa, which is a less common anatomical location. We discuss the patient's clinical presentation, imaging findings, histological examination results, as well as the surgical treatment and follow-up outcomes. We also examine relevant literature related to the topic to provide a comprehensive understanding of this rare case.

Conclusions. Although complete surgical excision is the primary management for PAC, there is no gold standard treatment for it. It is crucial to follow up on patients with PAC in the long term, as recurrences, lymph nodes, and distant metastasis, even rare, may impair the prognosis in certain patients.

Keywords: polymorphous adenocarcinoma, salivary gland tumor, treatment, prognosis.

Introduction

Previously named polymorphous low-grade adenocarcinoma (PLGA), polymorphous adenocarcinoma (PAC) is a rare and morphologically diverse type of salivary gland tumor that occurs almost exclusively in the region of the minor salivary glands. The polymorphic nature of PAC refers to the variety of growth patterns that may be identified within the same lesion and among different lesions, including solid, glandular, cribriform, ductal, tubular, trabecular, or cystic lesions. In 1983, Batsakis et al. described polymorphous adenocarcinoma as terminal duct carcinoma originating from the terminal intercalary ducts [1]. Freedman and Lumerman also described it as lobular carcinoma, due to its resemblance to lobular breast carcinoma [2]. One year later, the term "polymorphous low-grade adenocarcinoma" was introduced by Evans and Batsakis to describe an infiltrative salivary tumor with a variety of growth patterns, but bland nuclei [3]. Finally, in 2017, the World Health Organization's classification of salivary gland tumors replaced the term polymorphous low-grade adenocarcinoma (PLGA) with polymorphous adenocarcinoma (PAC) [4]. PAC is often misunderstood, underdiagnosed, and controversial in terminology, and its apparent low-grade behavior may be unpredictable. This tumor is most commonly found in minor salivary glands of the palate, but it can also affect the buccal mucosa, upper lip, retromolar region, floor of

DOI: 10.15386/mpr-2882

Manuscript received: 14.03.2025
Received in revised form: 08.04.2025
Accepted: 28.04.2025

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the mouth, posterior tongue, and nasal cavity. It is rare in major salivary glands where it has been reported as a primary lesion or, more commonly, as the carcinomatous component of carcinoma ex pleomorphic adenoma [5]. Regarding minor salivary glands, PAC is the third most common malignancy, after mucoepidermoid carcinoma and adenoid cystic carcinoma (ACC) [6]. PAC rates have varied over the period studied, and the frequency of reported PAC cases also varied across countries and continents, with an increasing trend as knowledge about this tumor is gained [7]. The tumor mostly affects adults, in their fifth and sixth decade of life, and the male-to-female ratio is 1:2 [5]. The accurate etiology of this malignant tumor is still unknown, and its clinical presentation is a slow-growing solid mass with non-aggressive behavior in most cases. Whenever there is doubt regarding the diagnosis, immunohistochemistry might be considered [8]. There is no gold standard treatment for PAC, although complete surgical excision is its primary management [9-11].

Case report

On January 18th, 2021, a 67-year-old woman was referred to the Emergency County Hospital Bihor, specifically the Department of Oral and Maxillofacial Surgery. She had a lesion in the right buccal mucosa that had not healed in over six months. Although she had not experienced any pain, the lesion had been gradually increasing in size. The patient had no history of family-related cancer, smoking, or drinking alcohol. There was no chronic mechanical trauma or local irritation. Upon inspection, a 2.5 cm diameter polilobulated mass was discovered approximately 1 cm under the right Stensen's duct (Figure 1). The lesion was hard on palpation and somewhat movable.

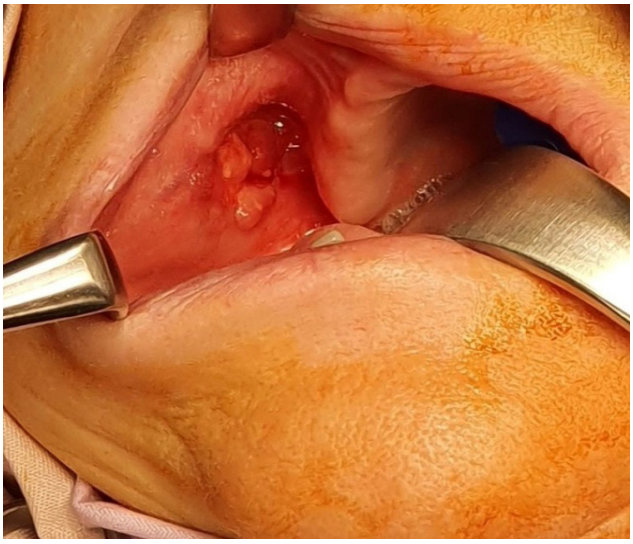

Figure 1. Preoperative clinical aspect.

The contrast-enhanced CT scan assessed the presence of a tumor infiltrating the masseter and buccinator muscles, in contact with the lateral wall of the right maxillary sinus, but without any signs of bone osteolysis. This expansive, lobed growth was isodense before contrast administration and iodophilic after, and measured approximatively 25/30/30 mm (Figure 2).

An incisional biopsy was performed, which confirmed the malignant diagnosis after histopathological examination: polymorphic adenocarcinoma. Three weeks later, the patient was informed about the diagnosis and the treatment options. She agreed to undergo surgical intervention under general anesthesia with oro-tracheal intubation. The excision was performed with an oncological safety margin, and the defect was reconstructed with Bichat's fat pad (Figure 3, Figure 4).

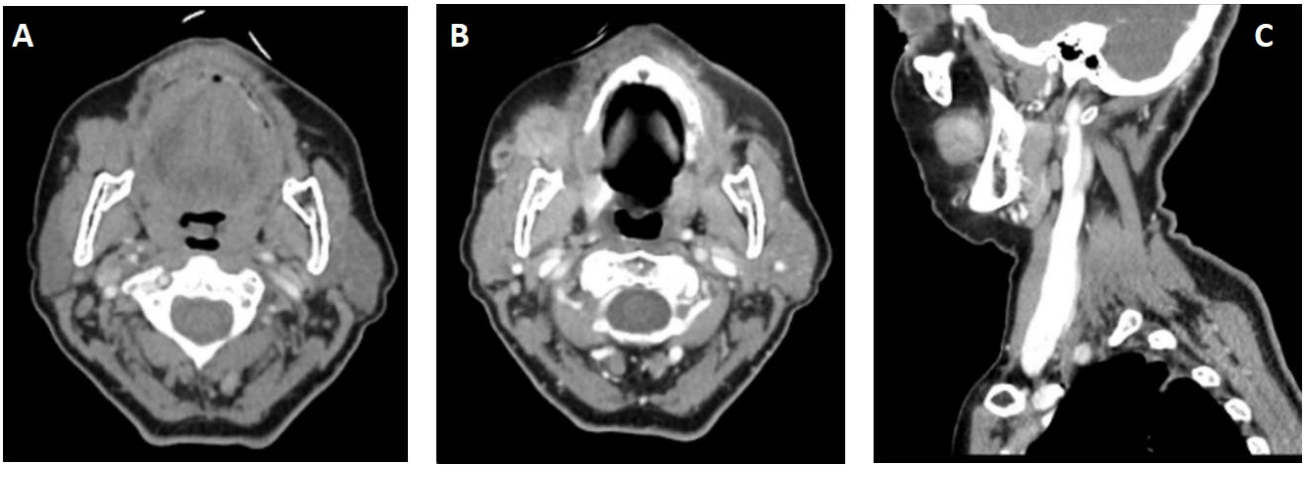

Figure 2. A. Axial native CT scan section; B. post-contrast CT scan section; C. Sagittal post-contrast CT scan section.

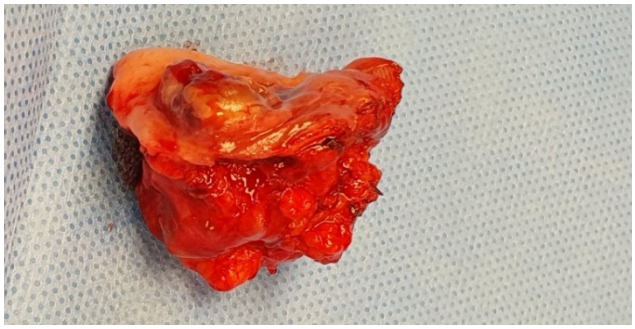

Figure 3. The excised specimen .

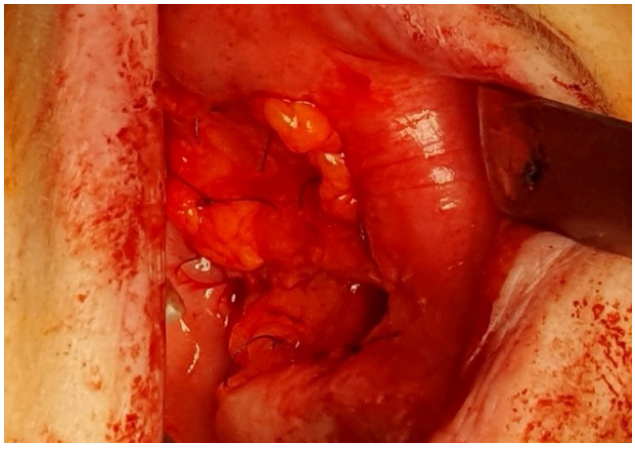

Figure 4. Reconstruction of the post-excisional defect with Bichat's fat pad.

The examination of the tissue sample revealed a well-defined tumor growth that was partially encapsulated. The tumor was made up of relatively uniform tumor cells with slightly hyperchromic, round or oval-shaped nuclei. The tumor showed a variety of architectural patterns, mostly solid, but also trabecular, tubular areas, and cribriform secretory microfoci. The surrounding stroma was intensely hyalinized, with numerous congested blood vessels and occasional bleeding within the tumor. There was minimal inflammation around the tumor, and the overlying buccal mucosa was ulcerated. There was no evidence of the tumor invading nearby blood or nerve vessels. The surgical margins were clear of any remaining tumor cells. The histological classification was pT1NxMxL0V0PN0R0 (Figure 5 AB).

The patient entered the follow-up program for oncological patients, and the last examination, on May 2024, revealed no local recurrence nor regional nodal spreading (Figure 6).

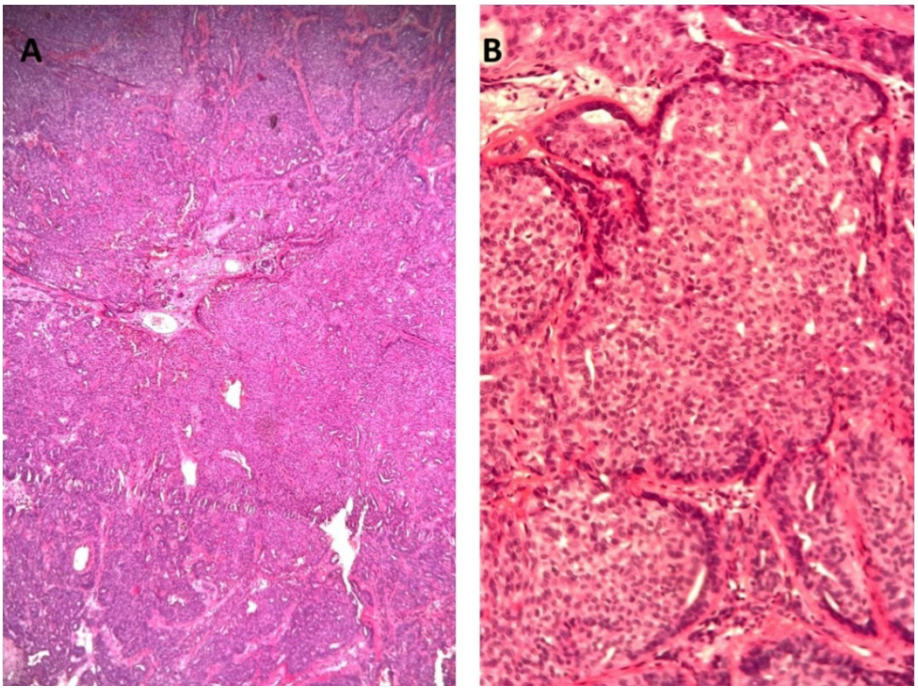

Figure 5. A. Tumor proliferation composed of multiple lobules separated by fibrous septa, with a predominantly solid architectural pattern, and focal areas of peripheral palisading; **B.** Relatively uniform tumor cells with monotonous nuclei, mildly clarified chromatin, low mitotic activity, and no nuclear or cellular pleomorphism.

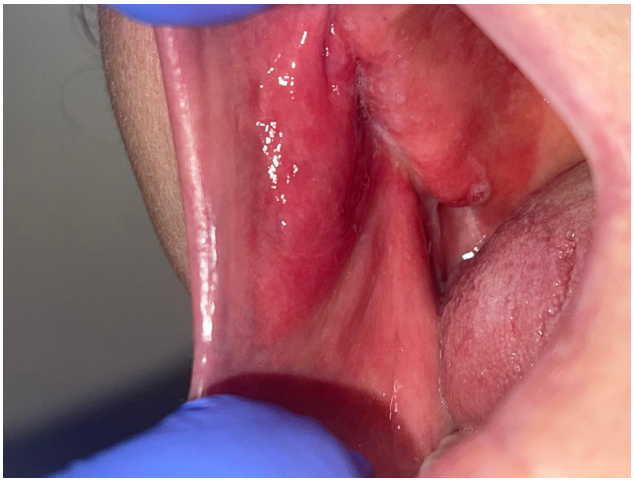

Figure 6. Clinical aspect at 3 years postoperatively.

Discussion

Oral Squamous Cell Carcinoma (OSCC) is the most commonly occurring tumor in the oral cavity. Although malignant salivary gland tumors are a rare form of head and neck cancers, they constitute 1-6% of all cases [12,13]. However, it is important to note that minor salivary gland tumors are estimated to make up 9-23% of all salivary gland neoplasms [14]. These tumors should not be underestimated, as up to 80% of them are malignant. Polymorphous adenocarcinoma (PAC) is a malignant epithelial tumor that is rare and develops from the intercalated (terminal) duct cells of the salivary gland. This tumor has a low metastatic potential, infiltrative growth, morphological diversity, and cytological uniformity. Previously, this tumor was known as lobular carcinoma or terminal duct carcinoma, but specific histopathological criteria have established it as a distinct tumor. Pleomorphic Adenocarcinoma (PAC) is a type of tumor that typically affects the minor salivary glands of the palate, but it can also occur in the buccal mucosa, upper lip, and base and lateral borders of the tongue, alveolar ridge, maxillary sinus, and mucosal sites, not otherwise specified (NOS) [15]. The frequency of reported PAC cases varies by the country in which the malignant minor salivary glands studies were performed and also varies significantly by continent, with frequencies ranging from 3.9 to 20.0% [7]. None of the risk factors for salivary gland carcinoma such as tobacco and alcohol consumption, history of radiotherapy, HIV infection could be identified in our patient. Few recent studies also investigated the role that salivary microbiota could play in the onset of salivary gland malignancies [16,17]. Even if this association has not yet been completely demonstrated, microbiota could promote chronic inflammatory processes, direct antiapoptotic effects, activation of cell proliferation, promotion of cellular invasion, and production of carcinogenic metabolites, all these increasing the susceptibility for malignant growth [16,17]. PAC affects patients of ages, ranging from 16 to 94 years, with a peak incidence in the fifth and sixth decades of life [5,7]. Although PAC is more prevalent in elderly patients, it can also affect adolescents and children, making it essential to remain vigilant across all age groups. Furthermore, some studies suggest that PAC can be more aggressive when it presents early in life, particularly during adolescence [18, 19]. PAC is more frequent in women, with a female: male ratio of 2:1. Interestingly, studies have shown that this condition tends to manifest at a slightly younger age in women than men [5]. The case presented in this paper fits these data. Typically, the clinical presentation of PCA reveals circumscribed firm to solid masses, that range from a few mm up to 6 cm (average = 2 cm) [20]. They are indolent, slow growing and the overlaying mucosa is generally intact, making the clinical diagnosis challenging. In our case, after a history of a couple of years, the tumor began to increase in size and caused persistent non-healing ulceration of the buccal mucosa, which was the trigger event for the patient to seek medical consultation. Although in our case the diagnosis was established upon the incisional biopsy, there are studies that show that cytology or small tissue samples can lead to misdiagnoses [21]. Therefore, a thorough examination of the whole specimen is mandatory, since preoperative diagnosis may not succeed in identifying all the features of salivary gland tumors, which are known for their polymorphism. Even if PAC was previously named PLGA and was considered a low-grade malignancy, the course of the disease may prove fatal for some individuals. Local recurrence, regional lymph node as well as distant metastasis have been reported [10,22], and therefore the tumor should be treated as a true malignancy, including long-term follow-up. The treatment of Polymorphous Adenocarcinoma (PAC) is complex and requires a comprehensive approach to ensure its completeness. Currently, there is no gold standard treatment for PAC, as the roles of radiotherapy and chemotherapy are still controversial [23]. However, complete surgical excision is the primary management for PAC, regardless of its location [5]. In our case, a local wide excision with tumor-free borders was performed. The defect was reconstructed with the Bichat fad pad, allowing for proper healing. Bichat's fat pad, also known as Bichat's fat ball, is an underused option for oral mucosal reconstruction, despite its close proximity, easy availability, plasticity, and simple use as a flap. Even in cases of significant weight loss, Bichat's fat pad remains resistant to lipolysis [24]. The flap's rich vascularization is often cited as its most significant advantage. The buccal fat pad can serve as either a pedicled flap or a free graft. One of the primary benefits of this flap is that it can become keratinized over time when used for oral cavity reconstruction. The fat cells in the flap have stem cell

properties, so it can transform into any type of tissue under the right conditions [24]. The process of epithelialization typically begins 8 to 10 days after surgery and is typically completed within the second or third week. In our case, the fat volume was sufficient to fill the defect. However, different authors suggest that the fat pad is only suitable for areas with a loss of matter lesser than 6 cm [25]. Lymph node metastases are rarely reported in PAC cases, which is why neck dissection should usually be performed when there are positive lymph nodes. According to different authors, radiotherapy is most often used postoperatively when treating patients with extensive primary tumors or when section margins are not clear, when there is perivascular or perineural spread ahead of the main front in the resected specimen, and/or when cervical nodal metastases have been found. However, in patients without lymph node metastases, postoperative radiotherapy does not seem to influence their prognosis [5,11]. Although there is no specific evidence supporting its use in PAC treatment, some authors reported the use of chemotherapy restricted to palliative cases. It may be used concomitantly with radiotherapy for unresectable PAC, when the patient refuses surgery, is inoperable, or in the postoperative setting. After complete surgical excision, PAC generally has a good prognosis, with a recurrence rate of about 10-15%, usually occurring within 5 to 7 years of treatment of the primary tumor [26]. However, recurrences are more common in women than in men. Cases of recurrence have also been observed after 14 years, highlighting the importance of long-term follow-ups for up to 15 to 20 years [27]. PAC can behave aggressively when it presents early in life, especially during adolescence. Local recurrence and lymph node metastases were observed in several cases of PAC localized in the palate [18,28]. Although it may appear that localization in the palate may correlate with a poor prognosis, cancer originating from the base of the tongue frequently metastasizes toward cervical lymph nodes, suggesting the importance of preventing neck dissection for these patients. The greater tendency of tumors located at the base of the tongue to metastasize could be related to their anatomical characteristics, such as their vascularization and proximity to the cervical lymph nodes [29,30]. PAC has an excellent overall prognosis, with a 10-year disease-specific survival rate of 94%–99% and a 10-year recurrence-free survival rate of 83–88% [31,32]. Distant metastasis is rare in PAC but may occur in up to 3% of cases. Histologic architecture with ≥10% papillary pattern or ≥30% cribriform pattern has been shown to be an independent adverse prognostic factor associated with decreased disease-free survival [22]. Another prognostic factor is the depth of invasion (Mauceri). CASG and PRKD1/2/3 fusion are associated with an increased risk of lymph node metastasis [33].

Conclusions

This study presents polymorphous adenocarcinoma (PAC), which is a less common pathology of the minor salivary glands that can be misdiagnosed, misunderstood, and mistreated. The localization of the PAC on the buccal mucosa is not usual, yet a systematic clinical examination is crucial to facilitate early diagnosis and appropriate treatment. Although it is a mildly aggressive tumor, the possibility of recurrence post-surgical excision should not be neglected, as well as the occurrence of lymph node involvement and distant metastases. Long-term patient follow-up should be a rule.

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