EXTRA-PAROTID PLEOMORPHIC ADENOMA: CLINICAL FEATURES AND THERAPEUTIC DIFFICULTIES

ADÉNOME PLÉOMORPHE EXTRA-PAROTIDIEN: PARTICULARITÉS CLINIQUES ET DIFFICULTÉS THÉRAPEUTIQUES

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ABSTRACT

Background: Salivary gland tumors are rare pathologies, accounting for around 6% of all head and neck tumors. They are located in the accessory salivary glands in 10 to 15%. Pleomorphic adenoma (PA) is the most common histological type. Our aim is to assess the particularities of extra-parotid PA localization and analyze its therapeutic results.
Methods: A retrospective study was conducted in the ENT department of Mohamed Taher Maâmouri Hospital in Tunisia between 2010 and 2023, collating all patients presenting with PA of extra-parotid location.
Results: All patients (14 cases) had a slow-growing, firm, painless swelling on examination. The submandibular gland and the hard palate were the most attractive sites (four and three cases respectively), followed by the nasal septum (two cases). MRI was suggestive of pleomorphic adenoma in five cases. Treatment was surgical, depending on location, submandibulectomy or total excision of the tumour with a healthy margin. Pathology showed AP in all cases. No malignant degeneration or recurrence was observed. Postoperative follow-up was uneventful.
Conclusions: Extraparotid PAs are rare and present a high risk of malignant degeneration and recurrence. They should be considered in the presence of various chronic indolent swellings of the head and neck. Long-term follow-up after treatment is essential to detect recurrence.
Keywords: pleomorphic adenoma, palate, parapharyngeal space, surgical, rare diseases

RÉSUMÉ

Introduction: Les tumeurs des glandes salivaires sont des pathologies rares, représentant environ 6 % des tumeurs de la tête et du cou. Ils se localisent dans les glandes salivaires accessoires dans 10 à 15 %. L'adénome pléomorphe (AP) constitue le type histologique le plus fréquent. Notre objectif est d'évaluer les particularités des localisations de l'AP extra-parotidien et d'analyser ses résultats thérapeutiques.
Méthodes: Une étude retrospective a été menée au service d'ORL de l'hôpital Mohamed Taher Maâmouri en Tunisie entre 2010 et 2023, colligeant tous les patients présentant un adénome pléomorphe (AP) de localisation extra-parotidienne.
Résultats: Tous les patients colligés (14 cas), présentaient une tuméfaction à croissance lente, ferme, indolore à l'examen. La glande submandibulaire et le palais dur étaient le siège le plus atteint (quatre et trois cas respectivement) suivi de la cloison nasale (deux cas). L'IRM était suggestive d'adénome pléomorphe dans cinq cas. Le traitement était chirurgical, selon la localisation, une submandibulectomie ou une excision totale de la tumeur avec une marge saine. L'anatomopathologie a conclu à un (AP) dans tous les cas. Aucune dégénérescence maligne ou récidive n'a été constatée. Le suivi postopératoire était sans incident.
Conclusion: Les AP extraparotidiens sont rares et présentent un risque élevé de dégénérescence maligne et de récidive. Ils doivent être évoqués devant les diverses tuméfactions chroniques indolentes de la tête et du cou. Le suivi à long terme après le traitement est essentiel pour détecter une récidive.
Mots clés: adénome pléomorphe, palais, espace parapharyngé, chirurgical, pathologie rare

BACKGROUND:

Salivary gland tumors are relatively uncommon, accounting for only 6% of head and neck tumors [1]. Pleomorphic adenoma is the salivary glands' most common benign neoplasm [2] preferentially affects the parotid glands in 80% of all cases [3] Rare localizations in the other main salivary glands have been described. According to the location of the accessory salivary glands along the aerodigestive tracts, other localizations have been described.

Though a benign lesion, early diagnosis and management of this process are needed to avoid a

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mass-increasing, malignant degeneration risk and recurrence after surgical resection.
This article aims to present rare locations of extra-parotid pleomorphic adenoma and its treatment outcomes

METHODS:

This is a retrospective study conducted in the ENT department of Mohamed Taher Maâmouri Hospital in Tunisia. The study period spanned over 14 years (January 2010- December 2023). All data were collected based on the ENT department's medical observations including pathology reports. We collected all relevant information concerning patients with extra-parotid pleomorphic adenomas, including demographics, clinicopathological features, treatments and post-operative results.

RESULTS:

Our study included fourteen patients with tumors in extra-parotid sites diagnosed as pleomorphic adenoma by histopathological examination. Among them, eight were male and five were female, with a median age of 44 years [7-77].
The various sites of involvement were as follows: oral region (seven cases), submandibular gland (four cases), parapharyngeal space (one case) and nasal septum (two cases). (Table 1)

Table 1: Summary table of case characteristics

Characteristics				Case	Total
Localizations	Oral locations	Hard palate		3	7
		Inner cheek mucosa		2	
		Upper lip		1	
		Retromolar trigone		1	
	Submandibular gland				4
	Parapharyngeal space				1
	Nasal septum				2
Radiological findings	Ultrasound	Hypoechoic		4	4
		Heterogeneous		2	
		Homogenous		2	
	CT	Tissue density		5	5
		Enhancement after injection : late		5	
		Bone lysis : none		5	
	MRI	T1-weighted	Low signal	6	6
			High signal	0	
		T2-weighted	Low signal	5	
			Iso signal	1	
		Enhancement	Heterogeneous	6	
		ADC	>1	5	
			=1	1	
		Dynamic contrast	Type A curve	6	
		Capsule	Low signal	6	
Treatment	Surgery	Transorally excision performed with one centimeter of healthy margins			7
		Submandibulectomy			4
		Cervical resection with a right lazy S incision extending forward with a total parotidectomy.			1
		Endoscopic surgery			2
Histopathology	Pleomorphic adenoma	Typical form		13	14
		Cellular form		1	

ORAL LOCATIONS:

The sex ratio for lesions in the oral region was 0.4, with an average age of 51 years [37-77]. The hard palate was the most common site (three cases) (Figure 1), followed by inner cheek mucosa (two cases), upper lip (one case), and retromolar trigone (one case).

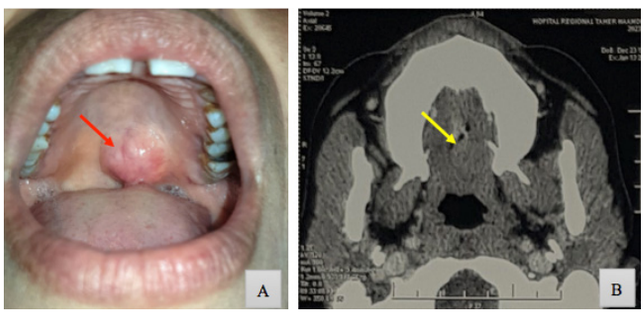

Figure 1:
(A) Left hard palate bosselated three-centimeter swelling (red arrow)
(B) An axial section of an injected cervical CT scan showing a well-limited bosselated hard palate mass (yellow arrow)

All patients complained of slow-growing and painless masses. No other obvious symptoms were reported. The mean consultation time was 29 months [1-72]. Masses were hard in only one case and firm in the other cases. They were lateralized to the left side in five cases. The average size was 2.28 cm [2-4].
Computed Tomography (CT) was conducted in four cases (hard palate localization, retromolar trigone localization). In all cases, it showed a well-defined, lobulated, or rounded mass with moderate homogeneous enhancement, causing displacement but not invasion of adjacent structures.
Magnetic Resonance Imaging (MRI) examinations were conducted in four cases. In three cases, facial MRI revealed a well-defined bosselated mass that exhibited low signal intensity on T1-weighted images and high signal intensity on T2-weighted images, with a hypo signal capsule and heterogeneous enhancement (Figure 3). On Diffusion-Weighted Images (DWI), it showed a high signal with a high Apparent Diffusion Coefficient (ADC) (> 1.1), except for one case that had an ADC = 1. The Dynamic Contrast-Enhanced (DCE) images were classified as type A. These characteristics argued in favor of a pleomorphic adenoma, except in the case with an ADC = 1, where a tumor of intermediate malignancy was also suspected.

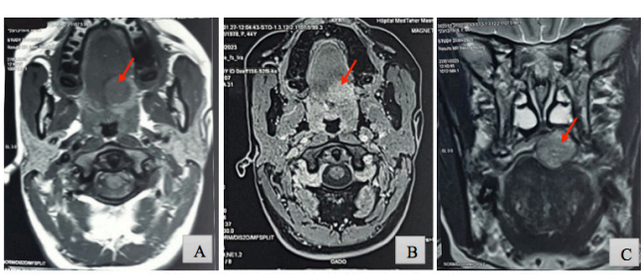

Figure 3: Facial MRI showing a left well-limited two-centimeter soft palate tumor with low signal T1 (A), intermediate signal T1 FAT SAT gadolinium-enhanced (B) and T2 moderate enhancement (C) (red arrows).

Surgical excision was transorally performed with one centimeter of healthy margins. Pathological examination confirmed a pleomorphic adenoma in all cases. In the case of ADC = 1, pathological examination confirmed the nature of a pleomorphic adenoma in its cellular form.

SUBMANDIBULAR LOCATIONS:

For submandibular locations (four cases), the average age was 34 years [7-58]. Two patients were smokers. The mean consultation time was 27 months [12 - 60]. The chief complaint was painless submandibular swelling in all cases. On examination, it was a firm mobile submandibular swelling with no inflammatory signs. The average size was 2,25 cm [2-3].

All patients had a cervical ultrasound, which confirmed the mass's submandibular location and suggested its histological nature as a pleomorphic adenoma. In fact, on imaging, pleomorphic adenoma typically appears as a well-defined, hypoechoic or mildly heterogeneous lesion, with posterior acoustic enhancement and no evidence of invasive characteristics.

The patients underwent submandibulectomy under general anesthesia. In all cases, pathology confirmed the diagnosis of pleomorphic adenoma, with no evidence of malignancy. There was no recurrence during the follow-up period, ranging from 6 to 72 months.

PARAPHARYNGEAL SPACE LOCATIONS:

In the case of the parapharyngeal space, it was a 57-year-old man who presented with one-year trigeminal neuralgia (V2) and dysphagia. He was generally in good condition, with no abnormalities in the cervical examination. His right parapharyngeal wall was slightly raised, but the aerodigestive tract was normal in nasofibroscopy. The neurological examination revealed an ipsilateral paretic palate.

The MRI revealed a well-defined tissue mass in the right prestylian space, measuring 46 × 37 mm. On T1-weighted images, the mass exhibited a low signal intensity with heterogeneous enhancement after gadolinium injection. On T2-weighted images, it demonstrated a high heterogeneous signal. The mass was encapsulated by a low-signal peripheral capsule on T2-weighted images. The diffusion coefficient was measured at 1.9, and the dynamic contrast-enhancement pattern corresponded to a "Type A" curve. These characteristics suggest a well-encapsulated tumor with variable internal composition.

The patient underwent a cervical resection with a right lazy S incision extending forward, which required a total parotidectomy. The procedure involved a total parotidectomy with careful identification of the facial nerve (Figure 4).

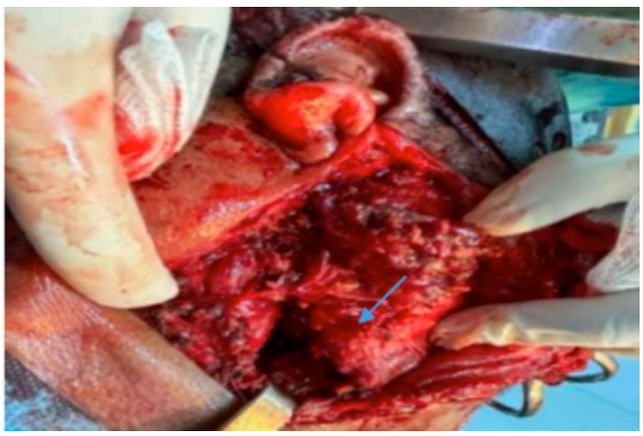

Figure 4: Perioperative view of the parapharyngeal tumor (blue arrow)

The surgery concluded with a meticulous dissection of the parapharyngeal tumor, which was completely independent of the parotid gland. Histopathological analysis confirmed the diagnosis of pleomorphic adenoma without evidence of malignant transformation (Figure 5). The trigeminal neuralgia (V2) was spontaneously regressive one month after surgery. During two years of follow-up, no signs of recurrence or malignant transformation were observed.

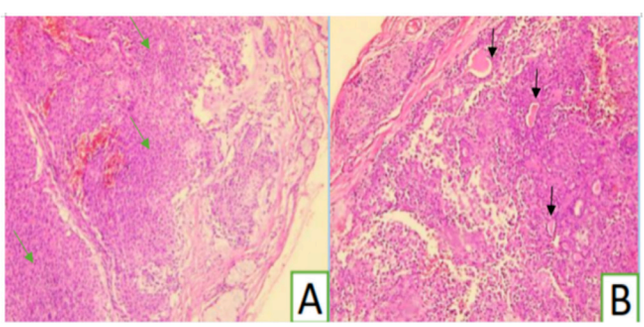

Figure 5: histopathological **examination** of a parapharyngeal pleomorphic adenoma
(A: HE x40): Benign tumour proliferation, surrounded by mucinous salivary glands, with a double contingent myoepithelial (green arrows) and epithelial embedded in a myxoid stroma. (B: HE x100): The epithelial component is made of tubular and glandular structures fulfilled by eosinophilic material (black arrows).

NASAL SEPTUM LOCATIONS:

For nasal septum location, the first patient was a nine-year-old child with no prior pathological history. He presented with a 5-month history of unilateral left nasal chronic obstruction and occasional homolateral rhinorrhea. The second patient was a 57-year-old male with a history of obstructive sleep apnea syndrome, complaining of chronic left-side nasal obstruction with recurrent homolateral epistaxis for one year. In both cases, physical examination revealed a soft tumor, originating in the anterior third of the septum, covered by normal mucosa, filling the left nasal cavity without extension to the nasopharynx (Figure 6).

A facial CT scan showed in both cases an expansive process in the left nasal cavity, with tissue density, no bone lysis and late enhancement after injection (Figures 7).

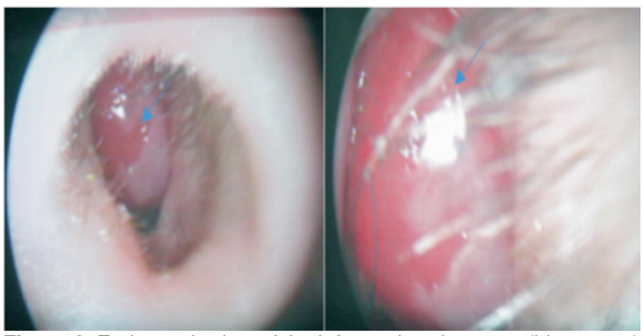

Figure 6: Endoscopic view of the left nasal cavity tumor (blue arrow)

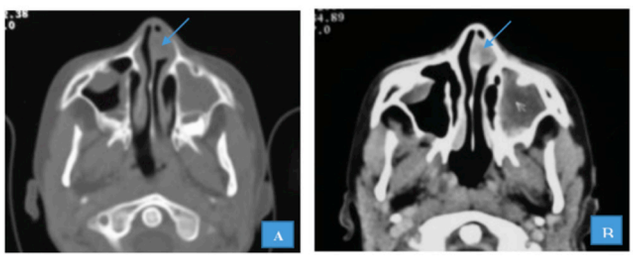

Figure 7: Facial CT axial section showing an expansive process in the left nasal cavity (A) enhancing after injection (B) (blue arrow) (nine-year-old child)

In both cases, the tumor was removed under endoscopic surgery, first controlling the hemorrhagic state with bipolar coagulation and then removing the mass with a cartilage collar.

The pathological examination revealed a well-defined but non-encapsulated proliferation of polygonal epithelial cells; some showed epidermoid differentiation with keratin production. These cells were arranged in trabeculae and small clusters, often forming gland-like cavities. Cellular growth areas were interspersed with regions of loose, sclerohyaline tissue, as well as edematous and cartilaginous patches.

Based on these findings, the diagnosis of nasal septal pleomorphic adenoma was established. During respectively five and seven years of follow-up, no signs of recurrence were observed in our patients.

DISCUSSION:

Pleomorphic adenoma most commonly arises in the parotid gland. Still, it can also occur in extra-parotid locations, including the palate, lips, buccal mucosa, tongue, tonsils, throat, retromolar region, parapharyngeal space, nasal cavity and larynx.

Regarding gender distribution at extra-parotid sites, our data revealed a slight male predominance, contrasting with findings from previous studies [5,6]. For instance, a nationwide observational study published in 2017 of 3506 pleomorphic salivary gland adenoma cases reported a female predominance (male-to-female ratio of 1/1.43)[7]

According to the literature, females are predisposed to benign salivary tumors [8]. In addition, as noted by Nagao et al. [9], malignant salivary gland tumors are more common in males over 50 years of age. In our study, males were more frequently affected than females, though no malignant cases were observed. However, given the limited size of our sample, our findings do not allow for statistically significant conclusions.

This pathology can occur at any age, but it is particularly prevalent among middle-aged individuals and has a peak incidence between 40 and 60 years [10-12].

The pathophysiology of pleomorphic adenomas is thought to be related to the chromosomal activation of the pleomorphic adenoma proto-oncogene 1 (PLAG1), which is driven by various chromosomal aberrations[13].

Pleomorphic adenomas at uncommon sites often lack characteristic clinical features, making their differentiation from other lesions particularly challenging [12]. The clinical presentation largely depends on the tumor's size and location [13]. Regardless of location, pleomorphic adenomas typically demonstrate slow and asymptomatic growth [14, 15].

However, giant forms can cause compressive symptoms, such as obstructive syndromes of the upper aerodigestive tract, leading to dysphagia, dyspnea, snoring, and rhinolalia. In rare instances, pleomorphic adenomas can produce misleading or even life-threatening symptoms. For instance, a case documented in the literature reported syncope as a result of a pleomorphic adenoma in the parapharyngeal space, causing compression of the carotid sinus [16].

The literature identifies certain risk factors for malignant transformation, including changes in consistency, rapid growth, pain, tenderness and regional lymphadenopathy [17]. These factors were carefully evaluated during our clinical assessments, yet none were observed in our cases.

On CT and MRI, pleomorphic adenomas typically show moderate heterogeneity due to their mixed content, with lobulated contours and well-defined margins indicating encapsulation. On T2-weighted MRI, they usually show marked hyperintensity due to abundant myxoid chondroid stroma, surrounded by a hypointense fibrous capsule. These features are commonly seen in typical pleomorphic adenomas, as described by Kato et al. [18]. On dynamic sequences, they exhibit a high ADC (usually >1,2 10-3 mm2/s) and a Type A curve, both characteristic of benign tumors. Malignant transformation may be suspected if the tumor presents irregular margins. This transformation is often associated with heterogeneous hyperintensity on T2-weighted images, hypointensity on T1-weighted images, low ADC values on diffusion-weighted imaging, and a Type C enhancement curve on dynamic contrast imaging, indicating a more aggressive tumor with altered vascular characteristics [19].

Fine-needle aspiration cytology combined with MRI has a 95% positive predictive value for characterizing salivary gland tumors [20].

Considering the risks of malignant transformation and recurrence, achieving complete surgical excision with healthy margins is crucial [21-23]. Enucleation,

while less invasive, is not advisable due to its high recurrence rates. Therefore, excision of the tumor with one-centimeter margins of healthy tissue is strongly recommended [24-27]. However, this approach carries potential risks, including aesthetic deformities and damage to nearby neurovascular structures.

Histopathologically, pleomorphic adenoma is a complex mixed lesion comprising epithelial and myoepithelial components arranged within a mucopolysaccharide-rich stroma. The tumor is typically separated from the surrounding tissue by a fibrous capsule [11, 28]. Three main histological subtypes are differentiated: myxoid (with 80% stroma), cellular (with a predominance of myoepithelial cells) and mixed (classic). In minor glands, lesions are more cellular than in major glands [29-31]. In our study, the myxoid subtype was the most common, with only one case presenting as the cellular type.

It is important to highlight the role of immunohistochemistry and molecular biology techniques in the diagnosis and management of pleomorphic adenoma. These techniques not only help distinguish pleomorphic adenoma from other salivary gland neoplasms, such as adenoid cystic carcinoma or mucoepidermoid carcinoma, but also assist in evaluating tumor progression and determining prognosis. Commonly utilized markers include CD9, p63, and S-100, which are valuable in confirming the diagnosis [32].

Although pleomorphic adenomas are benign tumors, there is a risk of recurrence and malignant transformation into aggressive cancers such as adenoid cystic carcinoma or mucoepidermoid carcinoma. Therefore, we recommend long-term, regular follow-up for our patients.

Based on multivariate analysis in the Netherlands national study, the overall 20-year recurrence rate for pleomorphic adenomas was 6.7%, with a median time to first recurrence of 7 years. Risk factors for recurrence included positive or uncertain resection margins and younger age at diagnosis, with odds ratios decreasing accordingly [7].

It is also important to highlight the advancements in molecular analysis for detecting malignant transformations of pleomorphic adenomas, as well as in recurrent cases, which may indicate the need for more aggressive treatment strategies [33].

Conclusion:

The diverse clinical presentations of extra-parotid pleomorphic adenoma can make diagnosis challenging. However, early identification is essential, as timely treatment initiation significantly enhances patient prognosis.

Our reported cases highlight the importance of considering this entity in the differential diagnosis for persistent slow-growing swellings in the head and neck region. Wide local surgical excision remains the treatment of choice. Regular follow-up ensures early detection of potential late recurrences.

Conflicts of interest

The authors declare no conflict of interest in preparing this article

Ethics Approval and Consent to participate

Since our study is retrospective, our institution does not require the approval of the Ethnic Committee.

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