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PLEOMORPHIC ADENOMA OF THE SALIVARY GLAND: FROM DIAGNOSIS TO TREATMENT, A LITERATURE REVIEW

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ABSTRACT

Pleomorphic adenoma (PA) is the most common benign tumor of the salivary glands, accounting for approximately 60% of cases, and may rarely evolve into malignancy due to genetic alterations. Although slow-growing and painless, it requires accurate differential diagnosis, especially with other tumors such as mucoepidermoid carcinoma. PA mainly affects adults between 30 and 60 years of age, being more common in women and the parotid gland, but it can also affect other areas such as the palate and upper lip. Its etiology is controversial, and risk factors include smoking, radiation, and genetic predisposition. Diagnosis is confirmed by biopsy, and malignant transformation, although rare, may lead to carcinoma ex-pleomorphic adenoma, with a risk of metastasis. OBJECTIVE: to compile and critically analyze the research already conducted, offering a comprehensive overview of advances in diagnosis, surgical management, prognosis, and possible complications, such as malignant transformation. METHODOLOGY: This is a literature review on pleomorphic adenoma of the salivary gland. The research used the Virtual Health Library (VHL) as a data source and applied specific terms such as "pleomorphic adenoma", "salivary gland", "diagnosis" and "treatment", with language filters (Portuguese, English, and Spanish) and publication period (2019-2024). Thirty-two studies were selected after applying the inclusion and exclusion criteria. Although it does not require ethical approval, the review follows good scientific practices. RESULTS AND DISCUSSION: RESULTS AND DISCUSSION: The analysis of the studies reveals that pleomorphic adenoma (PA) has varied clinical and histopathological characteristics, making effective diagnostic methods and appropriate therapeutic approaches essential. Ultrasonography and computed tomography are useful in the initial evaluation, but fine needle aspiration biopsy (FNAB) remains the standard method for diagnostic confirmation. Surgical treatment, with complete resection and safety margins, is essential to prevent recurrences, which can occur in up to 45% of cases, depending on the technique used. Malignant transformation, although rare, can lead to carcinoma ex pleomorphic adenoma, an aggressive condition that requires extensive surgical interventions and, in some cases, radiotherapy. Recent studies highlight the promising role of molecular markers such as PLAG1 and HMGA2 in diagnosis and prognosis, especially in cases of malignant transformation. CONCLUSION: The management of pleomorphic adenoma of the salivary gland requires an accurate diagnosis, using imaging methods and FNAB, in addition to appropriate surgical treatment to minimize recurrences and avoid malignant transformation. Advances in molecular markers offer new possibilities for early

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diagnosis and prognosis, reinforcing the importance of rigorous postoperative follow-up to monitor complications.

Keywords: Pleomorphic Adenoma. Salivary Gland. Diagnosis and Treatment.

INTRODUCTION

Pleomorphic adenoma (PA) is a common benign tumor of the salivary glands, accounting for approximately 60% of tumors that affect both the minor and major salivary glands. In some cases, it can evolve into malignancy due to alterations in tumor suppressor genes and oncogenes1. Although these lesions are generally benign and have an indolent evolution, in some rare cases, other lesions may be underlying, requiring an accurate differential diagnosis to ensure adequate treatment and reduce recurrence rates2. It presents epithelial and myoepithelial cells, which join together in the mesenchymal stroma. Epidemiologically, it is more common in adults aged 30 to 60 years and in females.3

Among the salivary glands, pleomorphic adenoma occurs mainly in the parotid gland, although it can also affect other minor salivary glands and extra glandular locations, a rarer event.4 Another possible location of these lesions is in the oral cavity, especially in the palate, upper lip, and buccal mucosa. Clinically, it presents as a nodular mass, which generally presents slow growth, is painless, and has a surface with or without ulceration.5

The etiology of pleomorphic adenoma is controversial, but it is believed to be linked to ductal elements and myoepithelial cells.5 From a histopathological perspective, pleomorphic adenoma presents a varied morphology, which can be divided into myxoid (80% stroma), cellular (80% cells), and mixed, which is the most classic.6

The incidence of AP in the Western world is 2.5 to 3.0 cases per 100,000 inhabitants per year, which represents 3% to 10% of all head and neck neoplasms. The transformation of AP into malignancy accounts for 1% of all malignant neoplasms of the salivary gland and can lead to the emergence of carcinoma ex-pleomorphic adenoma (3% to 4%), which can generate distant metastasis, especially in cases of long evolution and recurrence.6

As risk factors for pleomorphic adenoma, lifestyle habits, such as smoking and exposure to ionizing radiation are predisposing factors.7 In addition, other risk factors are related, such as genetic predisposition, viruses, such as Epstein-Barr and Acquired Immunodeficiency Syndrome in advanced stages, and industrial chemical agents.

Pleomorphic adenoma (PA) is a benign neoplasm of salivary gland origin that can present insidiously and mimic other skin lesions, such as sebaceous cysts. Therefore, a biopsy should always be performed.7 Sebaceous cysts are common skin lesions resulting from obstruction of the sebaceous gland ducts, characterized by the formation of a cavity lined by an epithelium with an accumulation of sebaceous material.2

Also regarding differential diagnoses, mucoepidermoid carcinoma, a type of salivary gland cancer, can mimic pleomorphic adenoma, requiring precise histopathological differentiation for appropriate management.8 PA also makes a differential diagnosis with

benign salivary gland nodules and other common tumors of the maxillofacial complex, as well as neoplasms with malignant potential such as neurofibroma and rhabdomyosarcoma. Lipoma, Kaposi's sarcoma, condyloma acuminata, squamous cell carcinoma, oral papilloma, and syphilitic gumma are also considered differential diagnoses.9

Accurate identification and differential diagnosis of skin lesions are frequent challenges in the field of medicine, especially about conditions that may present similar clinical and histopathological characteristics.6

Therefore, the literature review study is of great importance, since this is the most common type of benign tumor of the salivary glands, representing a diagnostic and therapeutic challenge due to its histological heterogeneity and potential for recurrence. By compiling and critically analyzing the research already carried out, the review provides a comprehensive overview of advances in diagnosis, surgical management, prognosis, and possible complications, such as malignant transformation. This also helps health professionals to update their knowledge, contributing to safer and more effective clinical practices.

METHODOLOGY

This study is a literature review on pleomorphic adenoma of the salivary gland, with the aim of exploring and synthesizing information on best diagnostic practices, which may include clinical examinations, imaging tests, and biopsies, in addition to the most effective therapeutic options, such as surgical techniques and postoperative management. To achieve this objective, rigorous procedures were followed to search for and select relevant scientific articles, using the Virtual Health Library (VHL) as the main source of data.

The search strategy involved the use of specific terms and appropriate filters to ensure the relevance and quality of the selected studies. The keywords used in the search were “pleomorphic adenoma”, “salivary gland”, “diagnosis” and “treatment” and their equivalents in English. These terms were combined in order to optimize the results and applied with specific filters.

Initially, the filter “full text available” was applied to ensure that all selected articles were accessible in their entirety, enabling detailed analysis and the complete extraction of relevant information. Next, the language filter was used, covering publications in Portuguese and English, ensuring a broad review of the available literature. In addition, filters were activated so that the main theme of the articles was "Pleomorphic Adenoma" and that the selected studies included prognostic, risk factor, diagnostic, and systematic review research. Finally, the publication range was restricted to the years 2019 to 2024, to

incorporate the most recent and significant findings on the topic.

The inclusion criteria for selecting studies included those published in English, Portuguese, and Spanish; indexed in the period 2019 to 2024; with free and complete publication; and that addressed the mentioned descriptors in the abstract or title. On the other hand, the exclusion criteria were: articles that were not in English, Portuguese, or Spanish; published before 2019; that did not have free or complete dissemination; and that did not address the descriptors in the title or abstract.

The study selection process resulted in an initial collection of articles. After applying the inclusion and exclusion criteria, 32 articles were selected. These studies were analyzed and their findings were summarized to provide an analysis of pleomorphic adenoma of the salivary gland.

As this is a literature review, there is no need for approval by an ethics committee; however, the review complies with the principles of good scientific practice, such as correct citation of sources and non-plagiarism.

In this way, the article allows a comprehensive understanding of pleomorphic adenoma of the salivary gland, providing a solid basis for future research and clinical advances.

RESULTS AND DISCUSSION

Pleomorphic Adenoma (PA) is the most common tumor of the salivary glands (SG), accounting for 60 to 80% of benign tumors in these glands and approximately 60 to 70% of cases located in the parotid gland. Its incidence ranges from 4.2 to 4.9 cases per 100,000 people per year.

This type of tumor primarily affects young and middle-aged adults, with higher frequency between the ages of 30 and 60, and the average age at diagnosis is 44 years. Literature also points to a slight predominance of women, with a ratio of 1.43 women for each man diagnosed.

The clinical characteristics of this tumor are a solid, solitary, and lobulated nodular lesion with firm consistency upon palpation. It usually has a long and progressive growth history, as growth is slow in most cases. Symptoms can vary depending on the affected location; for example, if the lesion is near innervated regions, symptoms may become painful. In rare cases, there may be changes in the function of the affected salivary gland, such as dry mouth or difficulty chewing, but it is mostly asymptomatic and discovered during routine clinical exams.

One of the most commonly affected areas is the parotid gland, which represents approximately 10% of cases, followed by the minor salivary glands and the submandibular gland (ratio of 12:2:1). Additionally, another frequently affected region is the intraoral area, especially between the hard palate and the soft palate.

Regarding imaging diagnosis of salivary gland tumors, the gold standard examination for evaluation is ultrasound, which is very useful for guiding fine-needle aspiration (FNA), helping correctly identify the facial nerve, thus reducing the risk of injury. CT scans are important for diagnosis and staging, particularly contributing to surgical planning, as they define the anatomical relationships of the lesion with other structures, as well as visualize necrotic foci and calcifications.

In this context, imaging diagnostic methods, fine-needle aspiration (FNA) biopsy, and advances in molecular markers play a crucial role in both identifying and managing the disease.

Imaging diagnostic methods are essential tools for the initial evaluation of salivary gland lesions. Ultrasound (USG) is often the first test requested and widely used due to its availability, low cost, and lack of ionizing radiation. In pleomorphic adenoma, ultrasound reveals a homogeneous, hypoechoic, well-defined mass, with occasional internal vascularization, characteristics that suggest benignity. While ultrasound is an excellent tool for initial evaluation, CT and MRI also play important roles in more complex cases.

CT, particularly useful in larger and deeper tumors, allows detailed visualization of tumor margins and involvement of adjacent structures. Through CT, calcifications and other morphological details that might not be detected in ultrasound can be identified. MRI, considered the gold standard in the diagnosis of salivary gland tumors, offers superiority in defining soft tissues. Pleomorphic adenomas typically present hyperintense signals in T2-weighted sequences and isointense in T1, characteristics that aid in the differentiation between benign and malignant tumors. Thus, the combined use of these imaging modalities provides crucial information for diagnosis and therapeutic planning.

In addition to imaging exams, FNA is widely used as a minimally invasive method for the cytological diagnosis of salivary gland lesions. Although effective in differentiating between benign and malignant lesions, FNA can be challenging in pleomorphic adenomas due to their histological variability. The presence of a mixture of epithelial and mesenchymal components can result in insufficient or unrepresentative cytological samples. Therefore, in many cases, the definitive diagnosis depends on surgical excision and histopathological examination of the tissue.

In recent years, the development of molecular markers has offered new perspectives for both the diagnosis and prognosis of pleomorphic adenoma. Among these, PLAG1 (Pleomorphic Adenoma Gene 1) and HMGA2 (High Mobility Group AT-Hook 2) stand out as the most studied. PLAG1 is involved in chromosomal rearrangements specific to pleomorphic adenoma, and its elevated expression has been associated with uncontrolled cell proliferation. Similarly, HMGA2 participates in chromatin rearrangement and is frequently rearranged in pleomorphic adenomas, indicative of tumor growth.

Other markers, such as BCL2, an anti-apoptotic protein, and c-kit (CD117), a transmembrane protein involved in cell growth, have also been investigated. Increased expression of BCL2 may be related to the tumor's ability to evade programmed cell death, contributing to its persistence and growth. On the other hand, c-kit has been suggested as a potential indicator of malignant transformation in pleomorphic adenomas, although its exact role is not yet fully understood.

Thus, advances in the identification of molecular markers such as PLAG1, HMGA2, and BCL2 have improved diagnostic accuracy and understanding of the biological behavior of these tumors, contributing to the personalization of therapeutic strategies and consequently, a better prognosis.

The standard treatment for pleomorphic adenoma is surgical excision, with the choice of modality depending on the affected gland, including total or superficial parotidectomy, depending on the case evaluated. In large tumors located in the parotid region, parotidectomy, with or without radiotherapy, may be employed, as it reduces postoperative sequelae, including facial nerve paresis or paresthesia, as well as Frey's syndrome, which is characterized by sweating and flushing in the face when eating due to abnormal regeneration of nerve fibers. It also aims to reduce the risk of recurrence.

Pleomorphic adenoma, although considered a benign tumor, has a significant recurrence rate, especially when surgical treatment is not performed adequately. Incomplete removal of the tumor and excessive manipulation of the capsule during surgery are the main factors associated with recurrence. The recurrence rate ranges from 5% to 45%, depending on the surgical technique used and the extent of the tumor, with recurrence being most common in tumors located in the parotid gland.

The recurrence rate of pleomorphic adenoma is directly related to the surgical approach used. Tumors excised with insufficient surgical margins or those with capsule rupture during removal are more likely to recur. On the other hand, superficial or total parotidectomy, which removes the tumor with a safety margin, reduces this rate to less than 5%.

Several factors contribute to the recurrence of pleomorphic adenoma, with inadequate surgical technique being the most common. Rupture of the tumor capsule during removal favors the spread of residual neoplastic cells, leading to the formation of multiple recurrent nodules with a multinodular growth pattern. In addition, the tumor's location, with a higher prevalence of recurrences in parotid tumors, and the size of the primary lesion are also determining factors for recurrence. Larger tumors and those located in areas of difficult surgical access have a higher risk of incomplete removal.

Management of recurrent tumors requires a more complex surgical approach, as the lesions tend to be multiple and dispersed. Reintervention surgery is the treatment of choice, with superficial or total parotidectomy being recommended in most cases. In patients with multiple recurrences or when recurrence occurs in areas of difficult access, postoperative radiotherapy may be indicated as adjuvant treatment.

Although radiotherapy is not the primary treatment for pleomorphic adenoma, its use in recurrent cases has been shown to reduce the recurrence rate. Additionally, in more complex cases, molecular markers such as PLAG1 and HMGA2 have been studied as potential therapeutic targets for recurrent tumors. Research indicates that the overexpression of these genes may be related to the aggressive biological behavior of recurrent tumors, opening possibilities for targeted therapies in the future.

The recurrence rate of pleomorphic adenoma of the parotid gland ranges from 2% to 45%, depending on the type of treatment and surgical margin. Recurrences are more common when excision is incomplete, there is a rupture of the tumor capsule during surgery, or the safety margin is inadequate.

CONCLUSION

It is concluded that pleomorphic adenoma of the salivary gland, despite being a benign neoplasm, requires an accurate diagnosis and a careful therapeutic approach to avoid recurrence. The combined use of imaging methods, such as ultrasound, computed tomography, and magnetic resonance imaging, together with fine needle aspiration biopsy (FNA), is essential for an accurate diagnosis.

Therefore, surgical treatment, especially when performed with adequate margins, significantly minimizes the risk of recurrence. In recurrent cases, more complex interventions, including reoperations and, in some cases, radiotherapy, are indicated. The identification of new molecular markers also appears as a promising tool to improve prognosis and guide future therapeutic approaches. Thus, the adequate management of this condition requires multidisciplinary planning and rigorous follow-up to ensure the best

results for patients.

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