

## Hiperplasia adenomatoide de glândulas salivares menores: uma revisão sistemática.

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### 1. INTRODUÇÃO

Adenomatoid hyperplasia of minor salivary glands (AHMSG) is a uncommon benign lesion, accounting for less than 2% of biopsied specimens (Gunhan *et al*, 2019). The precise etiology of AHMSG remains uncertain, though it is theorized to occur as a reactive process to chronic local trauma (Barret *et al*, 1995). Clinically, AHMSG usually presents as a single, asymptomatic, hardened nodule covered by normal mucosa, most commonly located on the palate. Studies report a predilection for males, and those in their fifth decade of life (Buchner *et al*, 1991). Differential diagnosis includes salivary benign or malignant gland neoplasms. The final diagnosis of AHMSG is made through microscopic examination of biopsied specimens which reveal an increased number of normal-appearing mucous acini surrounded by fibrous connective tissue, along with hypertrophy and/or hyperplasia of minor salivary glands.(Buchner *et al*, 1991)

AHMSG is particularly significant due to its resemblance to a malignant salivary gland neoplasm, which has led to its description as "a sheep in wolf's clothing" (Scully *et al*, 1992). However, most documented cases of AHMSG come from isolated case reports or a limited number of larger case-series, making it difficult to fully understand the main features of this condition. Therefore, the goal of this study was to review the existing literature on AHMSG cases and to integrate the data into a systematic review to address the question: "What are the clinical, demographic, histopathological and immunohistochemical characteristics of AHMSG?"

### 2. METODOLOGIA

Inclusion criteria were based on the PECOS acronym, as follows: P: patients of any age; E: patients diagnosed with AHMSG; C: not applicable; O: clinical, demographic, histopathological and immunohistochemical characteristics of patients with diagnosis of AHMSG; S: observational and intervention studies. Exclusion criteria were as follows: 1. Pathology reported is not AHMSG; 2. Reviews, book chapters, letters to the editor, personal or expert opinions, conference abstracts; experimental or in vitro studies; 3. Studies for which full texts were not available; 4. Duplicated samples.

Electronic searches, with no restrictions on publication date or language, were performed on July 9, 2024, in six databases and gray literature. Personalized search strategies were developed for each bibliographic database. Additionally, a

manual search of bibliographies and reference lists of selected studies was performed. The references found were imported into Rayyan software (Qatar Foundation, State of Qatar), where duplicates were removed after identification.

The titles and abstracts of all articles identified through the searches were reviewed independently by two previously calibrated authors (G.L.B. and A.C.S.). If the title and abstract met the inclusion criteria, or lacked sufficient information, the article was selected for a comprehensive review of the full text. After evaluation of the full texts, articles that satisfied the eligibility criteria were selected.

The data were extracted from each article included, when available, as follows: author's name; year, continent and country of publication; study design; individual's sex and age; clinical presentation; anatomical location; number of lesions; symptoms; color; size; time of evolution; history of trauma (presence/absence); clinical diagnosis; intervention; histopathological characteristics; staining markers; recurrence and follow-up. The Joanna Briggs Institute – University of Adelaide tool for case reports was used to evaluate the included articles (Moola *et al*, 2015). Each parameter was answered as “yes” (low risk of bias), “no” (high risk of bias) or “not applicable”.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 25.0 (IBM Corporation, Armonk, NY). Descriptive statistics included the mean, standard deviation (SD), and percentages. This systematic review was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and MetaAnalyses (PRISMA) Statement (Page *et al*, 2021).

### 3. RESULTADOS E DISCUSSÃO

The search strategy for this systematic review identified 96 articles in the five main databases and additional 174 records through other methods, totalizing 270 studies. After automatic and manual removal of the duplicates, 219 references remained. Screening by titles and abstracts resulted in a total of 55 studies selected for full text evaluation. Ultimately, 40 studies comprising 30 case reports and 10 case series were included.

Currently, there is no evidence suggesting a geographic preference for this pathology, race was an insignificant factor (Bryant *et al*, 1996). Regarding demographic data, this survey observed a preference for males (n=72/64.29%) and a higher occurrence in the fourth and fifth decades of life, with a mean age of 42.57 years. Some studies show that men are commonly associated with greater needs for dental prosthesis repair due to exposure to traumatic events and more associated with traumatic mucosal lesions in prosthesis use (Etinger *et al*, 2019), supporting the theory that local trauma is closely related with AHMSG (MacEntee *et al*, 1998).

Minor salivary glands (MSGs), are distributed throughout the oral cavity, except for the gingiva, midline and anterior hard palate, and anterior dorsal tongue. Although AHMSG can occur at any site where MSGs are present, the strong preference for the palate observed in this survey can be attributed to the high concentration of mucous acini in this region (Shimoyama *et al*, 2001), which agrees with the present survey having 89 (73.55%) cases presented in the palate. Most of the included cases in the present survey presented as slow-growing, solitary (n=67/91.8%), asymptomatic (n=47/81.03%), normochromic (n=14/ 58.3%) nodules (n=37/92.5%). Several past epidemiologic studies indicates that

pleomorphic adenoma (PA) and fibroma are the most common intraoral minor salivary gland tumors (MSGTs) and mesenchymal lesions found in oral cavity, respectively (Kokubun *et al*, 2023). These were also the two most frequent clinical diagnoses observed in our review (n=62/86.1%). Both conditions present as slow-growing normochromic nodules, and typically occur in the sixth decade of life (Rivera *et al*, 2017; Bruzinga *et al*, 2023). Fibromas usually occur in the buccal mucosa, which is also the second most frequent anatomical location for AHMSG observed in this survey.

Kokubun and colleagues (2023) conducted a retrospective a clinicopathologic evaluation of 432 cases of intraoral MSGTs, and compared the most frequent features of benign and malignant lesions (Kokubun *et al*, 2023). The authors demonstrated that MSGTs are more common in women, but malignant tumors more reported in men (Fuoco *et al*, 2023). The authors also observed a significant difference in mean age of benign (48.4 years) and malignant tumors (53.2 years), with palate being the most frequent anatomical location in both types. These findings align with the results of the present survey, demonstrating that the lack of distinctive clinical signs between benign and malignant intraoral MSGTs makes differentiation challenging for clinicians.

Histopathologically, AHMSG is characterized by the abundant proliferation of glandular acini, predominantly mucous, arranged in a lobular pattern and separated by delicate fibrous septae (Raju *et al*, 2023). Myoepithelial cells surrounding the acini are evident, and mild chronic inflammatory infiltration is usually present, as observed in the present cases. Excisional biopsy was the most frequent initial intervention observed in this review being executed in 33 of 40 cases (82.5%), aligning with the high frequency of benign clinical suspicion. Thus, the current literature suggests that recurrence of AHMSG is not considered a likely event, and the recommended treatment is surgical excision (Brannon *et al*, 1985).

The present study has some limitations that should be acknowledged. Firstly, given the classical histological features and benign course, it is likely that the frequency of AHMSG has been underestimated. Second, the lack of detailed information in several datasets limits a more thorough analysis, such as meta-analysis, highlighting the importance of utilizing tools like the CARE guidelines (CAsE REports) and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines to ensure more standardized and comprehensive reporting.

#### 4. CONCLUSÕES

AHMSG is an uncommon hyperplastic lesion, primarily located on the palate. It predominantly affects men in their fourth and fifth decades of life, and usually presents as solitary normochromic nodules on the palate. Histologically, AHMSG is characterized by an abundant proliferation of glandular acini, with occasional ductal dilation and inflammatory infiltrate. Recurrence is not expected and surgical excision is considered curative. It is crucial to pathologists and clinicians to recognize AHMSG, as it can clinically resemble both benign and malignant mesenchymal and salivary gland lesions, which has important therapeutic and prognostic implications.

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