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ORAL MANIFESTATIONS OF AMYLOIDOSIS AS AN EARLY INDICATOR OF THE DISEASE - A LITERATURE REVIEW

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ABSTRACT

Introduction and Purpose: Amyloidosis is a rare group of diseases characterized by the irreversible extracellular deposition of insoluble amyloid fibrils in various organs and tissues. Treatment should begin as early as possible, immediately following diagnosis. Therefore, clinicians should be aware of the disease's characteristic features, including those visible in the oral cavity- which will be the focus of this article. While systemic manifestations are often emphasized, changes in the oral cavity can serve as early- and sometimes the first- indicators of the disease.

The aim of this article is to present the most relevant and recent scientific reports from the past ten years regarding oral manifestations of amyloidosis, highlight their diagnostic value, and emphasize the role of the dental professionals in the multidisciplinary approach to early detection and patient care.

Description of the State of Knowledge: Recent literature highlights a broad range of oral manifestations in amyloidosis, including macroglossia, nodular lesions, hemorrhagic changes, and chronic ulcers- some of which may appear without systemic symptoms. Histopathological biopsy with Congo red staining remains the gold standard for confirming amyloid deposits. Case reports increasingly show that oral findings can prompt systemic evaluation, leading to earlier diagnosis and management. This underscores the importance of dental professionals in recognizing subtle signs and initiating appropriate referrals.

Conclusions: Oral signs of amyloidosis can be the first clue to a systemic disease. Recognizing the type and location of lesions helps assess whether the disease is localized or systemic. Early diagnosis may improve outcomes- and in some cases, even save the patient's life.

KEYWORDS

Amyloidosis, Oral Manifestations, Oral Cavity Symptoms, Oral Health, Oral Cavity Mucosa

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1. Introduction

Amyloidosis is a rare group of diseases characterized by the irreversible extracellular deposition of insoluble amyloid fibrils in various organs and tissues. Depending on the type of amyloid and its distribution, the condition may affect multiple organ systems, leading to significant clinical consequences, or remain localised, presenting as a solitary lesion without systemic manifestations [1]. More than 15 types of systemic amyloidosis have been identified and extensively discussed in numerous publications [2-7]. Diagnosis may be confirmed through biopsy, genetic testing, or technetium-based cardiac scintigraphy. Treatment should begin as early as possible, immediately following diagnosis [8]. Therefore, it is crucial not to overlook the initial signs of amyloidosis. Clinicians should be aware of the disease's characteristic features, including those visible in the oral cavity- which will be the focus of this article. While systemic manifestations are often emphasized, changes in the oral cavity can serve as early- and sometimes the first- indicators of the disease.

The aim of this article is to present the most relevant and recent scientific reports from the past ten years regarding oral manifestations of amyloidosis, highlight their diagnostic value, and emphasize the role of the dental professionals in the multidisciplinary approach to early detection and patient care.

2. Research Materials and Methods

A literature search was performed using the Pubmed and Google Scholar databases to gather publications related to amyloidosis. We have been focusing on articles mentioning that amyloidosis can manifest itself in the oral cavity. Both databases were searched through independently using a consistent line by line application of key words to maintain uniformity. The search strategy included combinations such as „amyloidosis and oral cavity symptoms” alongside terms like „oral health”, „oral cavity mucosa”, „oral manifestations”.

Inclusion criteria prioritized articles published from 2015 onward, which made up over 75% of the referenced literature. The gathered data were then summarized based on studies posted in medical literature databases.

3. Discussion

Diagnosis of Amyloid Lesions

To determine whether a lesion is related to amyloidosis, various tests can be performed. Confirmation is typically achieved through histopathological biopsy of oral tissue, with Congo red staining still considered the gold standard. For a positive result, Congo red staining under polarized light should reveal the characteristic apple-green birefringence, confirming the presence of amyloid. Immunohistochemistry (IHC), and Hematoxylin & Eosin (H&E) staining can also be used, although they have their limitations. IHC helps identify the specific type of amyloid protein, while H&E is not specific and requires additional confirmation [1, 9-11].

Oral Manifestations of Amyloidosis

Amyloid deposits. Tavares, T. S. et al. analysed amyloid deposition in the oral cavity in Brazilian population, using biopsy as the main diagnostic tool. Their observations in 23 individuals showed that in 67% of cases, oral involvement was the first manifestation of the systemic disease. Amyloid was deposited in various sites listed in the article, including intramuscular, subepithelial, perivascular, perimuscular, periductal, and perineurial areas [12]. In some cases, deposits were even found histologically without any coexisting clinical symptoms. Since oral tissue biopsy is much easier and less invasive than internal organ biopsy, this approach could become a helpful diagnostic tool- making the diagnosis simpler, less invasive, and less stressful for the patient [9].

Asymptomatic, soft amyloid deposit was also observed on the right palatopharyngeal arch, and the dorsal surface of the tongue in the form of a yellow patch [1].

Uvula amyloidosis. Enlarged uvula with confirmed amyloid deposits and coexisting oropharyngeal dysphagia was also noted [13].

Salivary glands amyloidosis. A detailed article by Chiu, A. et al. shows that both major and minor salivary glands can present amyloid deposits. These may coexist with other diseases such as plasma cell neoplasm or pleomorphic adenoma, or appear alone. Deposits may be periductal, perivascular, or take other forms as described in the referenced article [12].

Nodular lesions. Multiple soft nodules are typically characteristic of localised oral amyloidosis. They can appear in various sites- for example, the dorsal surface of the tongue, labial commissures, and the labial or buccal mucosa. These lesions are chronic, sometimes painful, and may appear yellowish, as described in the article by Bezerra, H. K. F. et al. [14-16].

Macroglossia. Painful tongue enlargement can be an oral manifestation of amyloidosis and is usually secondary to the systemic form of the disease, as confirmed by multiple publications. Tongue lesions have been estimated to be associated with systemic amyloidosis in 92.3% of cases [17]. It can appear as early as the first month after systemic onset, making it a very important diagnostic sign. Macroglossia may be accompanied by more prominent lingual margins, nodular protrusions, purpura, or colored papules [15, 18-21]. It often occurs in association with multiple myeloma and can lead to restricted tongue movement [19, 22]. In some cases, amyloid may also be deposited in muscle tissue, leading to bilateral submucosal thickening of the cheeks [10, 23].

Scalloped tongue. This symptom is typically a consequence of macroglossia, as it appears following tongue enlargement. However, if the patient has never had this tongue shape before, pathological enlargement should be suspected. Scalloping results from amyloid deposition in the tongue, its enlargement, and subsequent pressure against the teeth. Although usually harmless, this sign can often be one of the earliest indicators of changes occurring in the oral cavity [24].

Ulcers. In case of oral ulcers, especially long-lasting, resistant to treatment, clinicians should always consider systemic disease as a potential underlying cause [19].

Hemorrhagic lesions. Recent publications describe rare cases of ecchymoses, blood blisters, hemorrhagic bullae, and petechiae of the oral mucosa, without any other signs of localised or systemic amyloidosis. This highlights that systemic amyloidosis may sometimes present in the oral cavity as hemorrhagic lesions [15, 25, 26].

The importance of Early Recognition

Maturana-Ramírez, A. et al. in their case report describe a situation where macroglossia, initially overlooked by other clinicians, turned out to be the first sign of amyloidosis- diagnosed only thanks to an oral pathologist. Unfortunately, the patient died due to poor general condition, organ dysfunction, and eventual failure [18].

Zhang, Y. Et al. also emphasize the importance of always suspecting systemic disease when a patient presents with a chronic, treatment-resistant ulcer, as it may- as in their case- be the first manifestation of a broader systemic issue.

A case report from 2025 describes a painless and asymptomatic lump on the palatopharyngeal arch, where biopsy and Congo red staining confirmed amyloid deposits. This finding initiated further investigation to determine whether the amyloidosis was localised or systemic and to potentially begin treatment. In this case, the disease turned out to be localized, but this should not discourage dental professionals from referring patients for broader diagnostics to rule out systemic involvement [1].

Xue, N. et al. and Gonzalez-Ramos, J. et al. highlight that amyloidosis can also manifest without any other signs- in the form of oral mucosal hemorrhagic lesions. This is an important observation, as it can change the diagnostic pathway for such patients, even leading to systemic amyloidosis diagnosis, as it did in these cases [25, 26].

There are many more reports showing that oral manifestations led clinicians to initiate diagnostics and confirm systemic amyloidosis [15].

4. Conclusions

There are many different manifestations of amyloidosis and numerous possible sites of amyloid protein deposition. It is important to understand and recognize the correlation between the location and type of these lesions and the likelihood of the disease being systemic or localised. Numerous case reports describe oral manifestations as the first sign that led to the diagnosis of amyloidosis, which underlines the importance of clinicians being familiar with these correlations. Early recognition- especially in the oral cavity- can significantly influence the further diagnostic process and overall patient outcome.

Author's Contributions:

Conceptualization, Kinga Popielarska; Methodology: Michał Borowski, Monika Augustyn; Software: Anna Maria Zakrzewska, Klaudia Elżbieta Niwińska; Check: Julia Agnieszka Michalak, Aleksander Midera; Formal analysis: Natalia Maria Leśniak, Klaudia Martyna Patrzyka; Investigation: Julia Aleksandra Leśniak, Monika Augustyn; Resources: Anna Maria Zakrzewska, Aleksander Midera; Data curation: Klaudia Elżbieta Niwińska, Julia Agnieszka Michalak, Klaudia Martyna Patrzyka; Writing-rough preparation: Kinga Popielarska, Julia Aleksandra Leśniak, Natalia Maria Leśniak; Writing-review and editing: Kinga Popielarska, Michał Borowski; Supervision: Kinga Popielarska; All authors have read and agreed with the published version of the manuscript.

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