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AMYLOIDOSIS OF ORAL CAVITY- A REVIEW

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ABSTRACT

Oral amyloidosis is a rare and debilitating disease that, whether primary or secondary, may severely impact the quality of a patient's life. Amyloidosis represents a group of conditions in which there is extracellular deposition of amorphous fibrillar proteins, termed amyloid. There are many biochemically distinct forms of amyloid proteins that have been identified. Two of the most common forms are AL type, derived from immunocytes and containing immunoglobulin light chains, and AA type, a unique non-immunoglobulin protein. The current classification of amyloidosis is based on the biochemical composition of amyloid. One-third of the patients with either the AA or AL amyloidosis are reported to have oral amyloid deposits. Deposition of amyloid fibrils derived from circulating acute-phase reactant serum amyloid A protein causes systemic amyloidosis, a serious inflammatory disorder. Amyloidosis may manifest as periodontal destruction that leads to severe chronic periodontitis. Proper periodontal treatment may alleviate systemic inflammatory mediators caused by the amyloidosis.

KEY WORDS

Amyloidosis, immunoglobulin light chains, AL type, AA type

INTRODUCTION

The term *amyloid*, meaning starch or cellulose, was introduced by Virchow in the mid-19th century to describe abnormal extracellular material seen in the liver at autopsy. At present, the term amyloidosis is used to describe a group of diseases characterized by extracellular deposition of fibrillar proteins in organs and tissues. The classification is based on the nature of the precursor plasma proteins that form the fibril deposits and is divided into primary and secondary amyloidosis. The pathogenesis is multifactorial. Nonetheless, the common final pathway is identical in all forms of the disease: the production of amyloid fibrils in the extracellular matrix. All amyloid deposits have a common fibrillar structure consisting of linear, aggregated fibrils with an approximate diameter of 7.5-10 nm and a cross ß-pleated sheet conformation, evidenced by x-ray diffraction.

The commonest types of primary amyloidosis are immunoglobulin/light-chain related (AL) and familial transthyretin-associated (ATTR). Secondary amyloidosis due to chronic diseases (*e.g.* rheumatoid arthritis and chronic infections) is caused by amyloid derived from serum amyloid A, an acute-phase protein produced in response to inflammation. In the past, tuberculosis was one of the commonest causes of amyloidosis associated with inflammatory conditions (*i.e.* AA amyloidosis). In a small percentage of AL amyloidosis cases, the bone marrow plasma cells show the clonal dominance of a light chain isotype, and the light-chain variable region of the immunoglobulin represents the main constituent of AL amyloid deposits. These patients commonly produce urinary free monoclonal light chains, referred to as *Bence Jones proteins*, of the κ or λ isotype. Unlike multiple myeloma and monoclonal gammopathies, in which κ chains are more frequent, in AL amyloidosis the ratio of κ to λ light chains has been found to be 1:3. The familial transthyretin associated (ATTR) type of

amyloidosis is derived from a group of autosomal dominant diseases in which, beginning in midlife, a mutant protein forms amyloid fibril.

Reactive systemic AA amyloidosis, with a sustained acute phase response (APR), can complicate chronic inflammatory disorders. AA amyloid fibrils are derived from the acute-phase reactant serum amyloid A protein (SAA) through a process of cleavage, misholding, and aggregation [1]. Renal disease is a frequent manifestation of the systemic amyloidosis and a major cause of morbidity [1].

SAA is an apolipoprotein constituent of high density lipoprotein that is synthesized by hepatocytes under the transcriptional regulation of pro inflammatory cytokines [2]. Sustained overproduction of SAA is a prerequisite for the development of AA amyloidosis. Amyloidosis affects a small proportion of patients that present with chronic inflammatory disorders [3,4]. The etiologies for this disease remain unknown. The activation pattern of SAA protein in the presence of inflammation is similar to that of C-reactive protein (CRP) [5]. The level of SAA increases during acute and chronic infections [6,7]. It has been shown that patients with chronic periodontitis display signs of a sub-clinical systemic inflammatory condition [8]. Furthermore, treatment of advanced periodontitis by full-mouth tooth extraction reduced systemic levels of cardiovascular risk and inflammatory reaction [9].

Cross-sectional studies have demonstrated that plasma levels of inflammatory markers such as CRP, fibrinogen, IL-6 and leukocyte counts increase in periodontitis patients when compared to periodontally healthy patients [9,10]. Some studies have shown that effective periodontal therapy reduced levels of CRP [11]. This implies that inflammatory reaction triggered by periodontitis con- tributes to the whole-body inflammatory burden.

Secondary amyloidosis, representing approximately 45% of all cases of systemic amyloidosis, has been associated with various chronic inflammatory conditions such as rheumatoid arthritis, sarcoidosis, Crohn's disease, ulcerative colitis and tuberculosis [12]. Secondary amyloidosis has also been linked to malignant diseases such as Hodgkin's disease and mesothelioma [12]. In addition, familial Mediterranean fever (FMF), an autosomal recessive disease, primarily affects the population in the Mediterranean basin [13]. FMF is characterized by recurrent episodes of fever and serosal inflammation along with a very intense APR. The most important complication of FMF is secondary amyloidosis [13]. Mutation analysis of Mediterranean fever gene (MEFV) can be helpful in con- firming the diagnosis for patients with an atypical presentation. Infection or inflammatory diseases may cause AA amyloidosis even without obvious infection or inflammation [14,15]. The progression of secondary amyloidosis depends on the nature and status of the underlying chronic inflammatory disease. For example, secondary amyloidosis-associated tuberculosis has been shown to undergo remission when the chronic infection has been eliminated [16].

Histopathologic examination of amyloid is essential for the diagnosis and classification of amyloidosis [17,18]. The sensitivity and specificity of the histopathologic diagnosis depend on the biopsy site and the adequacy of the tissue sample [19,20]

Amyloidosis affecting the oral cavity tends to involve the buccal mucosa, tongue and gingiva. Involvement of the palate is rare.

DISCUSSION

A diagnosis of amyloidosis is usually made on the basis of clinical presentation; a tissue biopsy is used subsequently to establish a definitive diagnosis. Bennhold introduced the Congo red stain in 1922 and showed the characteristic red staining of amyloid in normal light. Apple-green birefringence with polarized light microscopy, however, is the gold standard for diagnosis. The nature of amyloid deposition in the oral cavity has long been the subject of controversy. In the absence of clinical symptoms of amyloidosis, biopsy of oral tissues has been advocated to confirm amyloid deposition. The tongue is the most frequently reported intraoral location of amyloid deposition. If the deposition is extensive, macroglossia may develop, which may cause difficulty in speaking and chewing.

It has been shown that chronic infection or inflammatory diseases may cause secondary amyloidosis even without obvious infection or inflammation [14,15]. Patients with chronic periodontal diseases had higher levels of SAA, the precursor protein of amyloid fiber in secondary amyloidosis, than patients with- out periodontal disease [22]. To date, only a few reports address the interaction between periodontal disease and secondary amyloidosis [20,23]. One study showed the prevalence of moderate to severe

periodontitis was greater in FMF patients with amyloidosis than without amyloidosis [20].

The other study was a case report that illustrated an interaction between systemic amyloidosis and severe periodontitis in a patient with rheumatoid arthritis [23].

The definitive method of diagnosing amyloidosis is tissue biopsy. Although biopsies can be obtained from compromised organs, blood vessel fragility associated with amyloid deposition carries a risk of bleeding. Biopsy of oral tissues has been advocated as an adjunctive or alternate method of detecting amyloid deposition. Gingival, tongue, buccal mucosa and minor salivary gland tissue have all been reported as potential sites for biopsy; however, there are inconsistent results with regard to the sensitivity of amyloid detection in each of these tissues [24].

As a result, it has been reported that the anatomic location of the amyloid deposition within the tissue was consistent regardless of the location of the biopsy. This may have important implications for the biopsy technique used for the detection of amyloid [24]. If intra-oral biopsies are used more commonly for patients with chronic periodontal disease, amyloid may be found more frequently than expected.

Secondary amyloidosis is also associated with malignant diseases such as Hodgkin's disease and mesothelioma. Clinical examination, abdominal and chest computed tomography were negative for any malignant disorders or airflow obstruction. With the decline of tuberculosis in the developed countries, rheumatoid arthritis and inflammatory bowel disease remain the leading cause of secondary amyloidosis [12]. However, in the developing countries, chronic infectious diseases such as tuberculosis and leprosy are major causes [12].

Indeed, patients with chronic periodontal diseases have higher levels of SAA protein in secondary amyloidosis than patients without periodontal disease [22]. Chronic periodontal disease could exaggerate secondary amyloidosis via increased levels of systemic inflammatory mediators. In addition, our report highlights the possibility that amyloid deposition in patients with systemic amyloidosis causes accelerated periodontal destruction and bone loss of affected teeth. Amyloid deposition within the periodontium elicited an inflammatory reaction similar to that of foreign body material. Accelerated destruction of periodontium and associated supporting bone apparently is caused by this foreign-body-type giant cell reaction. Therefore, elimination of local infection associated with periodontal diseases will aid in the reduction of levels of systemic inflammatory mediators, which may slow the progression of secondary amyloidosis.

Sustained overproduction of SAA is a prerequisite for the development of AA amyloidosis, although the reasons for these remain unknown. Robbins [27] proposed two possible explanations for this. First, SAA-protein is normally degraded to soluble end products via monocyte derived enzymes. Conceivably, individuals who develop amyloid have an enzyme defect that cannot breakdown SAA-protein completely hence insoluble AA molecules were produced. Second, a genetically determined structural abnormality in the SAA-protein molecule itself renders it resistant to degradation by monocytes. Evidence has suggested that individual genetic susceptibility to amyloidosis may influence the host's response to infection. Nibali et al. [28] have found the link between polymorphisms of genes encoding for neutrophils receptors and pro-inflammatory cytokines and the presence of pathogenic bacteria in patients with aggressive periodontitis.

The authors then speculated that complex interactions between the microbiota and host genome may be at the basis of a patient's susceptibility to aggressive periodontitis. Currently many investigators are trying to define the genotype- phenotype correlations and risk factors for the development of secondary amyloidosis.

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