

Chronic Swelling of the Submandibular Glands and Sicca Syndrome: An Unusual ENT Presentation of AL Amyloidosis

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Abstract

Amyloidosis is a systemic disease characterized by accumulation in the extracellular and perivascular spaces of insoluble fibrillar proteins (amyloid), which determines the impairment of the function of the affected tissues. Clinically it can mimic conditions. In the case report we reported the case of a clinical overlap with Sjögren's syndrome.

Keywords: Amyloidosis • Sjögren's syndrome • Congo red staining

Introduction

Amyloidosis is a group of pathologies characterized by the accumulation of insoluble fibrillar proteins (amyloid) in extracellular spaces; the amyloid deposits that follow can affect any organ and tissue of the body, compromising its functionality [1]. There are about 3 types of amyloidosis in humans, differentiable by clinical aspects and biochemical characteristics of the amyloid, and subdivided into localized and systemic forms [2]:

- Primitive amyloidosis is not associated with other diseases (with the exception of multiple myeloma). This condition involves more often heart, lungs, skin, tongue, thyroid and intestinal tract. The typical amyloid of this form of amyloidosis is called AL and has an N-terminal sequence homologous to a portion of the variable region of the light chains of the immunoglobulins.
- Secondary amyloidosis is associated with chronic diseases, both infectious (tuberculosis, bronchiectasis, osteomyelitis, leprosy) and inflammatory (rheumatoid arthritis, granulomatous ileitis). This form is characterized by frequent involvement of spleen, liver, kidneys, adrenals glands and lymph nodes. However, no system is spared and vascular involvement can be widespread, even if cardiac involvement is rare. Liver and spleen are often increased in volume, hard and elastic. The kidneys are usually enlarged. Amyloid has a N-terminal sequence characteristic of a non-immunoglobulin protein.
- Transthyretin (TTR) amyloidosis is a systemic disorder characterized by the extracellular deposition of amyloid fibrils composed of TTR, a plasma transport protein for thyroxine and vitamin A that is produced predominantly by the liver. TTR can dissociate from its native tetramer form, then misfold and aggregate into amyloid fibrils that accumulate in various organs and tissues, causing progressive dysfunction. TTR amyloidosis is the most common form of hereditary (familial) amyloidosis, and is caused by mutations that destabilize the TTR protein. TTR amyloidosis can present as a progressive, axonal sensory autonomic and motor neuropathy (familial amyloidotic polyneuropathy; TTR-FAP, also known as FAP or ATTR-PN) or as an infiltrative cardiomyopathy (familial amyloid cardiomyopathy).

Amyloid Light-chain (AL) amyloidosis, which is the most common type in

industrialized countries, is caused by misfolded light chains produced by a small and dangerous B-cell clone. The estimated incidence is 9 cases/million people/year and affects men more frequently, with an average age of 65 years.

Case Report

In May 2016 a 57-year-old woman, P.D. has noticed the appearance of a swelling at the submandibular level (Figure 1) and SS (xerostomia e xerofthalmia) for about 6 months. Therefore was performed, in other center, a dual biopsy of minor salivary glands in suspicion of Sjögren's Syndrome (SjS). Nevertheless the result of histologic examination (performed in standard hematoxylin-eosin) and rheumatologic valuation has excluded this hypothesis. In March 2018 has come to the attention of our Clinic for a worsening macroglossia (Figure 2) responsible for dysphagia of partial obstruction of the upper respiratory tract, therefore were performed head and neck TC (Figure 3) and ultrasound of salivary glands; complete blood exams with rheumatologic markers (RF, ESR; ENAs and ANAs tests; HCV test). These new results ruled out again Sjögren's syndrome but they showed the onset of nephrotic syndrome. A new biopsy of the minor salivary glands was then performed with specific request for "Congo Red" staining in the suspicion of amyloidosis. The histological report confirmed this by identifying AL amyloidosis. The patient was then sent to a clinical department for therapeutic management.

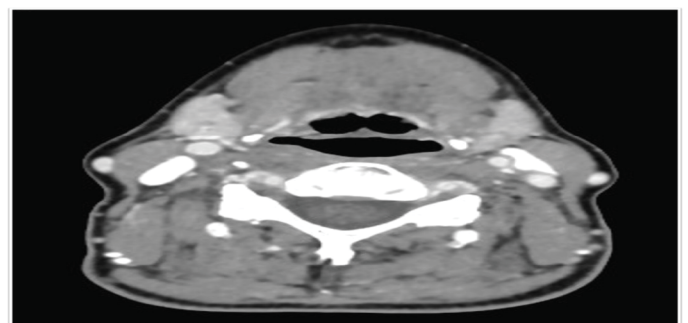


Figure 1. Submandibular swelling.

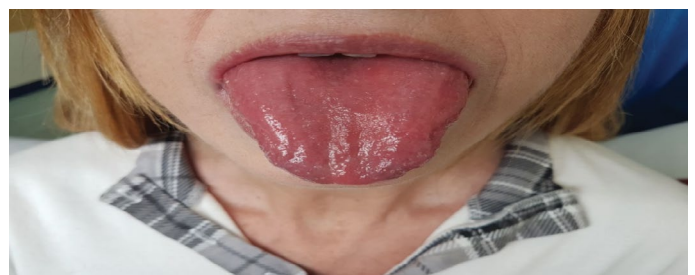


Figure 2. Macroglossia.

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Received 26 May 2020; Accepted 13 June 2020; Published 20 June 2020



Figure 3. Salivary gland CT.

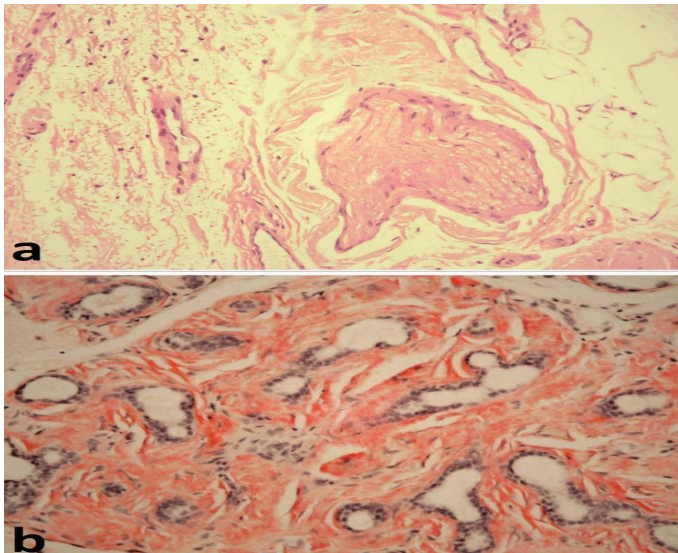


Figure 4. Histological specimens of minor salivary gland (a) Hematoxylin and Eosin staining; (b) Congo red staining.

Discussion

As previously mentioned AL amyloidosis is pathology of accumulation of amyloid substance, composed of light chains of immunoglobulins and represents the most frequent form of amyloidosis. The process of amyloid formation results in cellular injury, tissue damage, and organ dysfunction through mechanisms that are still incompletely understood. Organ dysfunction can result from the mass action exerted by amyloid deposits with disruption of tissue structure and from proteotoxicity. The clinical onset of AL amyloidosis is often subtle and multifaceted, therefore, very similar to that of other systemic diseases. The most frequent initial manifestations are renal, followed by those affecting the cardiovascular system. As regards the head-neck district, macroglossia is a rather specific sign of AL amyloidosis, although it is present only in 15% of cases. Dysphagia and/or infiltrative obstruction of the upper airways are other possible clinical pictures associated with AL amyloidosis [3]. The amyloidotic infiltration of the salivary and lacrimal glands, however, can lead to a rare and deceptive presentation of AL amyloidosis, the Sicca Syndrome (SS). The latter, in fact, mimicking the clinical onset of a Sjogren syndrome directs the clinical suspicion towards this type of autoimmune

disease [4]. SjS is an autoimmune systemic disease that targets exocrine glands (in particular, lacrimal and salivary glands), which through the triggering of an inflammatory process subsequently results in a loss of function.

The molecular targets of the inflammatory response operated by T lymphocytes and amplified by the production of pro inflammatory cytokines such as IL-17 and IL-7, are two ribonucleoproteins: Ro/SSA and La/SSB expressed by the glandular epithelium [5]. The etiopathogenetic motive of SjS is not known, although a sharing of genetic factors and environmental factors has been observed. SjS has a marked clinical variability, in fact it can present with a procession of non-specific symptoms, even if the typical presentation of this pathology is precisely with SS, for the infarction by the inflammatory process of the exocrine glands, in particular the salivary glands, which in some cases can be responsible for the swelling of the same, just like in amyloidosis. The clinical profile of the patient in our case report could suggest SjS, although some symptoms, such as macroglossia and the occasional finding of nephrotic syndrome, were not typical of this pathology. It was these nonspecific symptoms, in addition to negative histological examination for SjS that prompted us to repeat the biopsy of the minor salivary glands, this time with the specific diagnostic question of amyloidosis. In fact, as for amyloidosis, the diagnosis of histological certainty of SjS. What differentiates them is the coloration of the sample; while for SjS, hematoxylin and eosin staining method (H and E) is performed, which demonstrates lymphocytic infiltration of the minor salivary glands; in the case of amyloidosis, it is necessary to use the Congo Red staining, able to highlight the amyloidotic precipitates, which with the standard staining would not be displayable (Figure 4).

Conclusion

The illustrated clinical case provides a starting point for reflection on the clinical utility of the request for Congo Red staining in addition to the standard (H and E) one in the biopsy analysis of the minor salivary glands, in the case of the finding of a SS associated with swelling of the glands submandibular, even in the absence of macroglossia, that is more specific sign of amyloidosis. The ENT specialist should therefore also consider the less common causes of these disorders, such as AL Amyloidosis, especially in the presence of previous negative biopsy tests for SjS.

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How to cite this article: Tropiano Paolo, Agostini Giovanni, Di Maio Pasquale, Ricci Giampietro. "Chronic Swelling of the Submandibular Glands and Sicca Syndrome: An Unusual ENT Presentation of AL Amyloidosis." *Clin Case Rep* 10 (2020): 1361. DOI: 10.37421/jccr.2020.10.1361