

Unerupted Teeth, A New Symptom Of Amyloidosis?

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1. Abstract

Amyloidosis are rare diseases related to the pathological aggregation and accumulation of misfolded proteins in the extracellular space generating insoluble deposits. This may occur in almost any tissue and organ, leading to severe structural damages and functional impairments. Oral manifestations are frequent in systemic amyloidosis and represent 9% of the localized forms. The most common are: macroglossia, cutaneous or oral mucosa lesions (petechiae, xerostomia) and periodontal involvement. Teeth involvement (pain, mobility or loss) is only described as secondary to periodontal alterations. Abnormalities of teeth eruption have not yet been reported in amyloidosis.

In this case report we highlighted uncommon oral manifestations - multiple mandibular impacted teeth and cystic peri-coronary bone lesions - in a 58-year-old patient, with an established diagnosis of severe hereditary ATTR amyloidosis, and illustrated the difficulties of etiologic diagnosis and therapeutic management of such oral and dental lesions in this context.

2. Introduction

Amyloidosis, also known as amylosis, is a large group of diseases that result from the pathological aggregation and accumulation of misfolded proteins in the extracellular space of different organs and tissues, generating insoluble deposits called amyloid. Amyloidosis is a rare

disease, the number of people affected is difficult to evaluate and little epidemiological data are available. Incidence was estimated at 5 to 13 per million of population per year, according to data from British, American and Swedish studies. The prevalence estimated by the UK study would be about 20 per million of population [1,2].

Many different types of amyloidosis have been described and their nomenclature is based on the nature of the protein that forms the amyloid fibrils. These polypeptide aggregates are most often precursor forms of the mature soluble protein. Currently 36 proteins known to be able to form amyloid fibrils have been identified in human and their number is increasing as new discoveries are reported in this field [3,4]. The amyloid deposits are mainly composed of specific fibrillary proteins, but other components are also present, especially serum amyloid P component (SAP) and proteoglycans (heparan sulfate proteoglycan, HSPG) which are ubiquitous molecules. Amyloid fibrils measure approximately 10 nm diameter and can be histologically identified by Congo Red staining, with a specific green and yellow birefringence when combined with polarized light microscopy, regardless of the type of fibrillary protein. [1,5]

The major forms, among a wide variety, are AL amyloidosis (deposition of monoclonal immunoglobulin light chain; systemic or localized form); AA amyloidosis (reactive, inflammatory form, with deposition of Apo Serum amyloid A; systemic form); hereditary forms including A β 2M amyloidosis (deposition of β 2 microglobulin; systemic form) and hereditary ATTR (deposition of transthyretin, with numerous genetic variants; systemic form). Hereditary forms are genetic pathologies with autosomal dominant inheritance. [6]

The deposition of the amyloid can affect almost all tissues and organs. The progression is insidious and may lead to severe structural damage and functional impairments. The clinical manifestations are very diverse and rather nonspecific to a type of amyloidosis. These conditions contribute to the difficulty of diagnosis and delay the therapeutic interventions. The main organs affected are the heart, kidney, digestive tract, liver, skin, peripheral nerve and eye, as well as the central nervous system, with disastrous consequences.

Depending on the site and extent of the amyloid deposit, systemic or localized amyloidosis have been described. Systemic amyloidosis may be primary or secondary to other diseases (rheumatic disease, malignant tumors, infectious diseases, inherited diseases or idiopathic conditions). About 45% of systemic forms are secondary or reactive AA amyloidosis.⁵ Localized forms of amyloidosis are limited to specific organs or sites and have an excellent prognosis while systemic amyloidosis may be life threatening.[7]

Oral cavity can be affected by amyloidosis as a manifestation of a

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systemic or localized form. The most common of the oral manifestations are: cutaneous or oral mucosa lesions (petechiae, papulae, xerostomia); palate lesions; gingival lesions; macroglossia (not described in hereditary forms); periodontal involvement.[7,8,9] Teeth involvement - pain, mobility or loss - is only described as secondary to periodontal tissues alterations.⁹ Abnormalities of teeth eruption associated with amyloidosis have not yet been reported.

An unerupted tooth is a mature tooth that has not erupted after the physiological date (24 months beyond the expected age) and whose peri-coronary sac has no communication with the oral cavity.[10] It is completely covered by the oral mucosa with or without bone tissue. The prevalence of unerupted tooth according to the studies ranges from 16.5 % in a study conducted in 3874 patients to 28.5 % in a study on 7486 patients. [11,12]

Among the main etiologies of unerupted teeth we can list several local factors, including gingival fibromas, gingival hyperplasia, alveolar dental ankylosis.[13] Systemic causes may also explain dental impaction: deficiency of vitamin A, of vitamin D, systemic infections as tuberculosis or syphilis, hormonal disorders as hypoparathyroidism, metabolic diseases or idiopathic etiology when any causal factor is found.[14-19] Impacted teeth may also occur due to genetic factors (hereditary or not) or being part of genetic syndromes phenotype (see Table I)[20-32]. The presence of dental inclusions is therefore a signal that must lead the clinicians to perform further investigation, including genetic test, for early diagnosis, prevention and treatment.

For the first time we described the clinical case of a patient with genetically diagnosed amyloidosis, who shows many impacted teeth without any known etiology.

Table I: Prevalence of impacted teeth in genetic syndromes – examples in specialized studies.

SYNDROME	PREVALENCE	DENTAL IMPACTION (%)	REFERENCES
Trisomy 21	1/800 pregnancies USA : 9.2/10 000 birth	5.9 %	Shapira J ²⁰ , Kamer AR ²¹
Gardner Syndrome Adenomatosis coli	1/8300 to 1/14000	4 - 38 % 10 times more than the general population.	Järvinen HJ ²² , Kubo K ²³ , Davies DR ²⁴ , Wolf J ²⁵
Cleidocranial Dysplasia or Scheuthauer Syndrome	1/1 000 000	In a longitudinal study of 12 patients, all of them showed dental impactions.	Ha SW ²⁶
Robinow Syndrome	200 known cases	56 to 67% of delayed eruptions. Unerupted teeth are described	Grothe R ²⁷ , Kantaputra PN ²⁸
Lowe Syndrome	1/500 000	Frequent delayed eruptions Unerupted teeth are described	Brooks JK ²⁹ , Ruellas AC ³⁰ , Harrison M ³¹
Gorlin Goltz Syndrome	1 à 9/100 000	Unerupted teeth are described	da Silva Pierro VS ³²

3. Case Report

Mr. X, a 58-year-old patient from Guadeloupe, was referred to our specialized consultation in the Oral and Dental Rare Disease Competence Center, in the setting of an University Hospital (Paris area, France). The consulting purpose was an oral cavity check-up post-liver and cardiac graft, carried out in France in November 2018. This double transplantation results from a severe cardio-hepatic failure, due to his hereditary genetic ATTR amyloidosis (Val 122 fake antisense homozygous mutation of the TTR gene), confirmed on a fat-tissue biopsy performed in 2017.

The panoramic X-Ray of the maxillae carried out as part of this assessment (Figure 1) revealed multiple mandibular impacted teeth associated with clinically asymptomatic cystic peri-coronary bone lesions. The results of the panoramic examination have been comforted by a Cone Beam Computed Tomography (CBCT).



Figure 1: Panoramic radiograph of the maxilla and mandibula showing multiple dental impactions in a 58-year-old man with severe hereditary ATTR amyloidosis.

Although asymptomatic, as part of the immunosuppressive treatment of this patient, these impacted teeth and associated lesions have been considered as potentially infectious risk foci and surgical management under general anesthesia was therefore recommended and realized. Excision of the cysts, avulsion of the unerupted teeth when their topography permitted and the benefit/risk ratio was favorable (teeth: 44 - lower right first bicuspid, and 34 - lower left first bicuspid), as well as coronectomies with ablation of the peri-coronary cysts (teeth: 35- lower left second bicuspid, 36 - lower left first molar, 45 - lower right second bicuspid and 46 - lower right first molar) have been performed.

In this surprising and atypical clinical picture and regarding the patient's medical history, a more in-depth investigation was conducted in parallel with the surgical care. The assessment of patient's family history by a specific questionnaire revealed that patient's brother and one of his six sisters present some unerupted teeth, suggesting a familial component (hereditary or environmental) in this clinical feature. However, no obvious, already described causes explaining these dental inclusions have been identified. Patient's brother and sister, aged 31 and 34 respectively and who do not live in metropolitan France, did not benefit of investigations, therefore the status of a possible amyloidosis diagnosis remains uncertain. Finally, a more specific genetic screening was performed to search for a known genetic anomaly associated with multiple unerupted teeth using the salivary test Oragene.DNA[®] designed for maxillofacial genetic disorders. Unfortunately, this test did not allow the association of any known genetic anomaly of the oral sphere with this clinical picture of impacted teeth.

4. Discussion

In this case report we highlighted some particular oral manifestations - presence of multiple mandibular impacted teeth, associated with clinically asymptomatic cystic peri-coronary bone lesions - in a 58-year-old patient, with an established diagnosis of hereditary ATTR (hATTR) amyloidosis.

To our knowledge there is no other similar description among specialized studies. With the complex example of this patient we have illustrated the difficulties of diagnosis and therapeutic management of such oral and dental lesions.

4.1. Clinical Aspects

As we mentioned above, various oral manifestations may occur in systemic amyloidosis. The forms located in the oral cavity represent only 9% of all amyloidosis.[33] Clinically 25% of patients with systemic amyloidosis have macroglossia with an enlarged, poorly mobile tongue affecting elocution, feeding (mastication, swallowing) and breath. Oral mucous membranes often show bruises, papules and ulcers and when the salivary glands are affected, xerostomia is almost systematic.[7,34,35] In contrast, the presence of unerupted teeth seems to be uncommon.

Dental eruption is a complex phenomenon involving multiple molecular and cellular mechanisms, whose understanding is still incomplete. To this day, the theory of multifactorial eruption has been accepted by many authors.[36,37] In some cases teeth remain unerupted and submucosal.

The discovery of an unerupted tooth is fortuitous since it is asymptomatic.[38] However, when the risk of infection is present, the decision to perform surgery can be taken. This was the case in our patient with an already diagnosed severe ATTR amyloidosis, undergoing immunosuppressive therapy and presenting numerous unerupted teeth in association with cystic lesions, found out during an oral cavity assessment after heart and liver transplantation.

Patients with suspected amyloidosis are often directed to us (by different departments of our hospital or by other physicians) for labial biopsy of minor salivary glands in order to clarify diagnosis. Furthermore, patients with an established diagnosis of amyloidosis, like Mr X, are referred for

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oral cavity assessment or treatment. Following this first case associating amyloidosis with dental inclusions, we intend to design and start a systematic clinical trial enrolling patient referred to our consultation. This will allow us to better identify and record the oral manifestations of different types of amyloidosis, with a focus on the occurrence of impacted teeth in these patients.

Cardiac involvement frequently occurs in amyloidosis, especially in AL and ATTR (hereditary or wild) types, being the main cause of morbidity and mortality. Deposition of amyloid in cardiac tissues may lead to restrictive cardiomyopathy and cardiac failure.[1] Our patient was subject to this feature and finally requested a heart and liver graft. In this clinical context, therapeutic management has been complicated at all levels, including oral care and surgery. Other clinical manifestations may be discovered in patients with hATTR amyloidosis, including sensory and motor neuropathy, autonomic dysfunctions or less common, renal involvement. In these circumstances, the prognostic becomes poor without treatment.

The therapeutic management of oral lesions in patients with systemic severe amyloidosis is challenging and must consider the surgical procedure complexity as well as the risk/benefit balance of the intervention.

4.2. Diagnostic considerations

Effective therapeutic management requires the earliest possible diagnosis. In case of suspicion of amyloidosis, a complete clinical assessment is necessary prior to other explorations. The identification of fibril amyloid protein in salivary gland biopsy or abdominal fat aspirate by Congo Red staining is the gold standard diagnostic test for amyloidosis, but the typing of the responsible protein needs supplementary investigations.[39,40,41] In front of a clinical picture with unerupted teeth and/or other structural abnormalities, it is necessary to consider a genetic component, or the presence of an underlying syndrome with potentially multiple and even serious consequences. Thus, this patient presented a severe form of hereditary ATTR amyloidosis validated by specific genetic tests, while genetic analysis targeting oral syndromes, also performed, have shown negative results. The question in such a context is whether the presence of impacted teeth is eventually related to amyloidosis or other etiology.

Diagnostic tools such as Oragene. DNA® (salivary genetic test), non-invasive and easy to use seems appropriate and could greatly facilitate outpatient diagnosis by the general practitioner. The conditioning of these tests allows the stabilization and the safe transportation of the genetic material up to the Rare Oral and Dental Diseases Reference Center in the Civil Hospital of Strasbourg (France). Here the sample is analyzed and compared to a database of known genetic abnormalities associated with oral and dental manifestations.

However, it still happens, as in the case of Mr. X, that the test fails to detect abnormalities commonly associated with these events, either because of

their absence or because they may not yet have been identified and indexed in databases. The hATTR Val122I genetic variant found in our patient is carried by 3 – 4% of African American population and is associated with late onset amyloid cardiomyopathy.[42] For these reasons, genetic counseling and screening may be helpful to identify patient's family members potentially carrying the mutation and should be performed.

4.3. Perspectives

Patients with suspected amyloidosis are often directed to us (by different departments of our hospital or by other physicians) for labial biopsy of minor salivary glands in order to clarify diagnosis. Furthermore, patients with an established diagnosis of amyloidosis, like Mr X, are referred for oral cavity assessment or treatment. Following this first case associating amyloidosis with dental inclusions, we intend to design and start a systematic clinical trial enrolling patients referred to our consultation. This will allow us to better identify and record the oral manifestations of different types of amyloidosis, with a focus on the occurrence of impacted teeth in these patients.

5. Conclusion

Amyloidosis is a group of rare diseases due to amyloid accumulation that can occur in almost any tissue and organ. Localized forms have usually good prognostic, while the evolution of the more frequent systemic forms may be life threatening. Oral manifestations of amyloidosis are found in systemic as well as in localized forms of the disease.

With this case report we have shown the importance of the early diagnosis in the optimal therapeutically management of both systemic amyloidosis and oral lesions. Oral cavity check-up is suitable to be completed before initiating any heavy treatment of the systemic disease.

Clinical suspicion of amyloidosis must be the subject of adequate investigations, allowing the identification of the amyloid fibrils and the typing of the involved protein. Among these diagnostic approaches, genetic tests are appropriate, easy to use tools and able to accurately confirm or label an amyloidosis diagnosis. In a long-term perspective, a larger utilization of these genetic tools is advisable. Moreover, the results of these tests will feed the genetic databases, allowing to find new correlations between the different clinical, biological and genetic parameters. Genetic counseling and screening are also helpful to identify a possible risk of hereditary transmission of amyloidosis.

Finally, with the only example of our patient we did not have enough elements to find an association of the unerupted teeth with amyloidosis. Therefore, the presence of impacted teeth in this context, although uncommon, should be further explored to better understand whether this manifestation is associated with amyloidosis.

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