A nodule in the palatal mucosa

Hélder Antônio Rebelo Pontes, DDS, PhD,[a,d] Lucas Lacerda de Souza, DDS,[a]
Carla Isabelly Rodrigues-Fernandes, DDS,[d] Lais Albuquerque Fernandes, DDS,[a]
Vitória Lacerda Santos, DDS,[a] Ana Beatriz Carvalho de Souza, DDS,[a]
Vinícius Lacerda de Carvalho, DDS,[a,b] Waqas Khan, BDS,[c] Oslei Paes de Almeida, DDS, PhD,[d]
Felipe Paiva Fonseca, DDS, PhD,[e] and Flávia Sirotheau Correa Pontes, DDS, PhD[a]

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CLINICAL PRESENTATION

A 67-year-old male patient was referred to our service with a complaint of an asymptomatic nodule in the hard palate; the nodule had evolved over 12 months and displayed slow growth. The patient did not report any alcoholism or smoking, and his past medical history was noncontributory. Upon general examination, the patient appeared well oriented, and there were no signs of any systemic illnesses or lymphadenopathy. The intraoral examination revealed a dome-shaped nodule with a smooth surface, exhibiting normal-colored overlying mucosa. The nodule was located on the right side of the palate, close to the junction of the hard and soft palate, was firm and nontender on palpation, and measured 12 mm at its largest diameter (Figure 1).

DIFFERENTIAL DIAGNOSIS

Salivary gland neoplasms are the most common differential diagnosis for a hard-palatal mucosal mass; the definitive diagnoses rely heavily on histopathologic presentations. In this section, we describe a pleomorphic adenoma (PA) and a mucoepidermoid carcinoma (MEC) because of their common prevalence. The other salivary gland neoplasms were excluded because of their rarity. Following the initial examination, and given the clinical presentation of the lesion, the differential diagnoses of lipoma, fibroma, neurofibroma (NF), circumscribed neuroma, and myofibroma were also considered.

Because lesions located in the palatal mucosa tend to originate from the minor salivary glands, our first clinical diagnosis was PA.[1-3] PAs are the most common salivary gland tumors, and in 10% of the cases, the minor salivary glands are affected.[1,4] Most PAs of the oral cavity occur in the palate, followed by the lip, buccal mucosa and the floor of the mouth.[1,2,4] Palatal PAs are most commonly seen in female patients between the ages of 40 and 60 years.[1,3] The clinical manifestation of a palatal PA is a slow-growing, painless, firm, rubbery submucosal mass without inflammation or ulceration,[1] usually measuring 1 to 2 cm at the largest diameter[2] and therefore consistent with the present case.

However, tumors located in the palate may also represent malignant salivary gland neoplasms; an MEC is considered the most common salivary gland malignancy by most authors.[4] MECs affect the minor salivary glands in 15% of cases and generally occur in the hard palate[5,6] and are generally observed in middle-aged females.[5,7] Clinically, an MEC can present with nonaggressive characteristics, as a slow-growing, nonulcerated tumor, ranging from normal-colored to bluish swellings.[3,5] Therefore, differentiating a MEC from a PA on a clinical basis may be very difficult, and for this reason, both entities remained on our differential diagnosis list.

Oral lipoma (OL) was also considered for the diagnosis because it is predominantly found in the buccal mucosa, followed by the tongue, lips, and palate.[8-11] A lipoma is a benign tumor composed of mature adipose tissue; it is known to mostly affect patients between 40 and 60 years of age and has a male-to-female ratio of 1:1.92.[8,10,11] OL frequently presents as a normal-colored to yellowish, pedunculated, painless, and well-circumscribed nodule, usually exhibiting a soft consistency and a slow growth pattern.[8,10,11] The diameter of the lesion can vary from 1 cm to 5 cm.[8,9] In the current case, the tumor was more fibrotic than usually observed in OL, and its sessile appearance made this diagnosis less likely.

Considering the group of neural lesions, a NF was also considered because it may frequently affect the palate as well as the tongue, lips, and buccal mucosa.[12,13] A NF is a benign neural tumor, which is composed of Schwann cells, endoneurial fibroblasts, and perineural cells.[12,14] It can present as either a solitary lesion or multiple lesions when associated with type-1 neurofibromatosis.[13,14] A NF of the oral cavity mainly affects patients in their 30s; however, it can also be observed in a broad age range, including even

[a]Service of Oral Pathology, João de Barros Barreto University Hospital, Federal University of Pará, Belém, Pará, Brazil.
[b]Dental Private Clinic, Belém, Pará, Brazil.
[c]The School of Clinical Dentistry, Sheffield, UK.
[d]Oral Diagnosis Department, Semiology and Oral Pathology Areas, Piracicaba Dental School, University of Campinas (UNICAMP), Piracicaba, São Paulo, Brazil.
[e]Department of Oral Surgery and Pathology, School of Dentistry, Federal University of Minas Gerais (UFMG), 31270-901, Belo Horizonte, Minas Gerais, Brazil.

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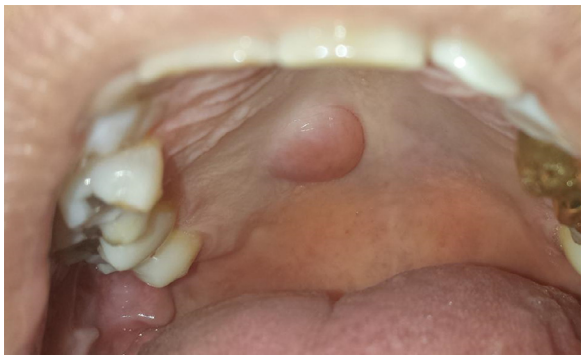

Fig. 1. On the patient's first visit, the clinical presentation of a nodule of 12 months' duration, which was a nonulcerated, dome-shaped, and normal-colored lesion on the hard palate, close to the hard and soft palate junction.

newborns.[12-14] In addition, there is no significant difference in incidence between males and females.[14] Clinically, a NF presents as a slow-growing and asymptomatic nodule, exhibiting a normal color and smooth surface, and can either be either sessile or pedunculated.[13,14] Sizes can vary from a few millimeters to several centimeters.[13] In addition, a solitary, circumscribed neuroma must also be considered because of its clinical presentation as a small nodule with a size never exceeding 1 cm at its largest diameter and commonly affecting the hard palate.[15].

A traumatic fibroma was also initially considered as a possible diagnosis because it usually presents as an asymptomatic and firm nodule. It is more common in females between 40 and 60 years of age,[16-18] most frequently affecting the lips, although virtually all intraoral locations can be affected. However, our patient did not use a dental prosthesis, and during the clinical evaluation and anamnesis, we were unable to identify any traumatic sources that could be associated with the development of a fibroma.

A myofibroma was also included in our differential diagnosis list. It is an uncommon benign spindle cell tumor, which is formed by myofibroblasts and corresponds to only 2.6% of all spindle cell lesions.[19,20] Oral myofibromas frequently affect male patients in the first 2 decades of life.[20,21] In the oral cavity, the mandible is the most affected site, followed by the gingiva, tongue, and palate.[19,20] Myofibromas usually present as well-defined, painless, solitary nodules; however, multiple lesions may be diagnosed in the context of myofibromatosis. Although a myofibroma could be consistent with the current case, the age of our patient was not typical for this diagnosis, and we placed myofibroma as a secondary possibility.

DIAGNOSIS

An incisional biopsy was performed, and microscopically, the lesion revealed a diffuse extracellular deposit of amorphous and eosinophilic material in the submucosal connective tissue, which appeared to be amyloid (Figures 2A to 2C). A mild lymphoplasmacytic infiltrate was also observed (Figure 2D). To confirm the presence of amyloid, Congo red staining was performed. The immunohistochemical staining for serum amyloid A protein was positive and indicated the presence of amyloid A protein deposits (Figure 3A), a kappa light chain (Figure 3B), and a lambda light chain (Figure 3C). Congo red staining showed peach-red coloration on light microscopy (Figure 3D) and apple-green birefringence on polarized light microscopy (Figure 3E). These results pointed to a diagnosis of localized oral amyloidosis until further tests could be done.

MANAGEMENT

The patient was referred to a general practitioner to evaluate for the presence of underlying or associated systemic diseases and to investigate other possible sites of amyloid involvement. Results of complete blood cell count, erythrocyte sedimentation rate, urea, creatinine, uric acid, calcium, albumin, and alkaline phosphatase rates, in addition to electrophoretic examination of plasmatic protein, were unremarkable. Both serum and urine were negative for Bence-Jones protein (BJP). As investigations on the peripheral blood did not reveal any monoclonal immunoglobulins or light chains, a bone marrow biopsy was carried out to detect the clonal dominance of plasma cells through immunohistochemical staining. No evidence of plasma cell dyscrasias was noted. A panoramic radiograph was also taken to evaluate any bone involvement; however, no alterations were observed. Therefore, a diagnosis of a localized amyloidosis was established. It was decided that further treatment would not be required and that the patient would be reevaluated in 6 months. After this period, the patient did not present any signs of recurrence and was systemically healthy.

DISCUSSION

Amyloidosis is a relatively rare disease represented by the extracellular buildup of amyloid, an insoluble proteinaceous fibrillar material. It is found in organs and tissues as a response to inflammatory abnormalities or various cell dyscrasias.[22,23] Schleiden, who noticed these substances in plants, first identified amylaceous materials (amyloid) in 1838. In 1842, Rokitanski introduced the term *amyloidosis* upon discovery of liver and spleen enlargements caused by chronic disease. Nevertheless, 12 years later, Virchow noticed the presence of amylaceous proteins in the human brain and liver. His studies were the gateway for researchers worldwide reporting 31 new extracellular and fibrillar proteins in human amyloidosis.[22,24] Depending on the type of deposited fibrinogen, amyloids can be divided into 30 subtypes, mainly consisting of immunoglobulin light

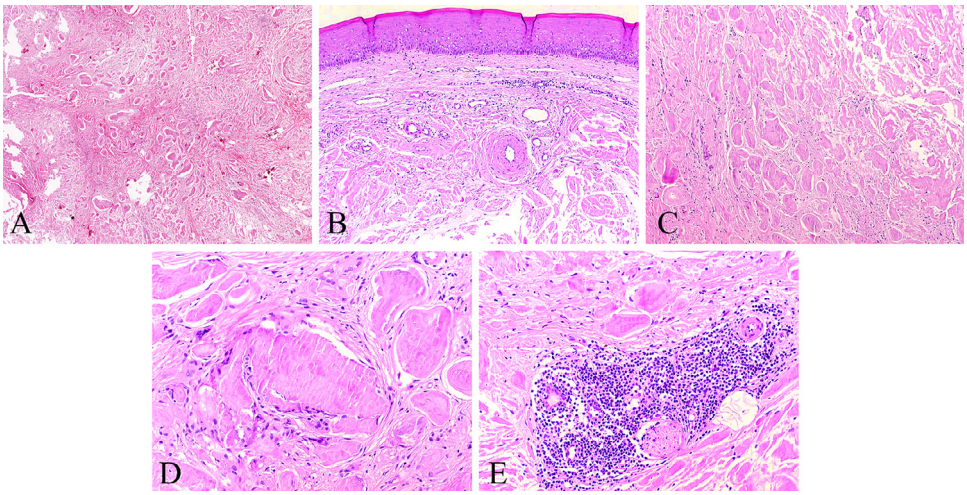

Fig. 2. The histopathologic aspect of the palatal lesion. **(A, B)** Extracellular deposition of amorphous, eosinophilic hyaline-like material in the submucosal connective tissue (hematoxylin and eosin [H&E]; original magnification × 40 and × 100). **(C)** The connective tissue composed of collagen fibrils and hyaline, acellular and amorphous material, consistent with amyloid deposition (H&E; original magnification × 100). **(D)** A higher magnification showing the amyloid deposits (H&E; original magnification × 200). **(E)** Amyloid deposition with peripheral plasmacytic infiltrate (H&E; original magnification × 200). *A high-resolution version of this slide is available as eSlide: VM05659.*

chain amyloidosis (AL), β_2 microglobulin amyloidosis, amyloid A amyloidosis (AA), and transthyretin amyloidosis.[25] Amyloid formation occurs when a protein or peptide loses or fails to acquire its physiologic and functional fold. The misfolded protein then assembles with similar proteins or peptides in a highly ordered fashion to form fibrils that accumulate in the interstitial space. The deposition of amyloids ultimately results in tissue damage and organ dysfunction.[26]

Amyloidosis is classified into systemic and localized forms; systemic amyloidosis has been further divided into 3 categories: primary, secondary, and familial.[24,25,27] Primary amyloidosis, also known as "AL amyloidosis," is the most prevalent form and is associated with plasma cell or lymphoid neoplasms, including Waldenström macroglobulinemia, mucosa-associated lymphoid tissue lymphoma and multiple myeloma. The most frequently affected organs are the kidneys, liver, heart, and nerves; involvement of the gastrointestinal tract is also common.[25]

Secondary or reactive systemic amyloidosis (AA form) generally affects patients suffering from inflammatory diseases or chronic infections. Associated conditions include rheumatoid arthritis; tuberculosis; Crohn disease;

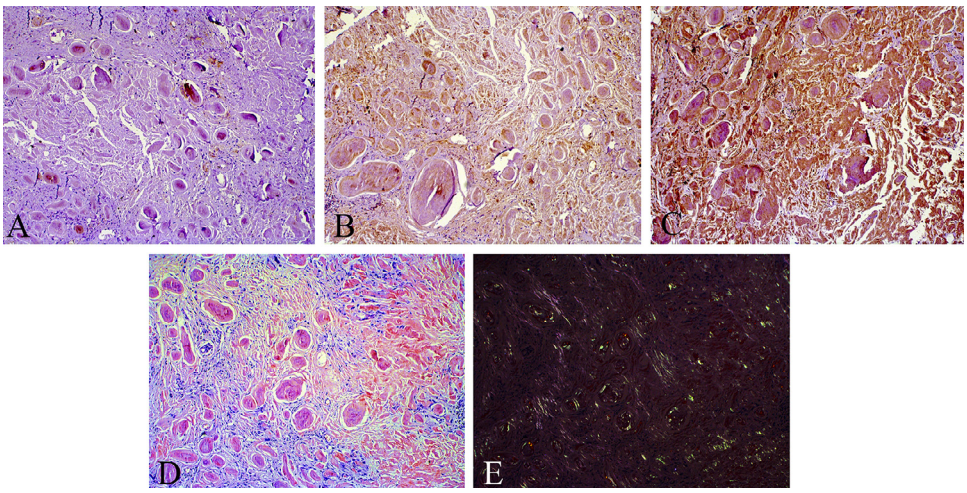

Fig. 3. Immunohistochemistry analysis. **(A)** Positive immunohistochemical staining against amyloid A protein (× 100). **(B)** Staining against immunoglobulin kappa light chains (× 100). **(C)** Immunohistochemical staining against immunoglobulin lambda light chain (× 100). **(D)** Light microscopically red homogeneous material is seen in Congo red staining (× 100). **(E)** The same area shows anisotropy with green color in polarized light (× 100).

chronic sepsis; malignant tumors (e.g., Hodgkin lymphoma); and hereditary diseases, such as familial Mediterranean fever. This heredity disease is the most common complication of secondary amyloidosis.[22,27,28] Furthermore, secondary amyloidosis may also be present in patients undergoing daily dialysis because of the amyloid material regularly being deposited in the joints.[24] All of the internal organs can be affected; however, the kidneys, liver, and spleen are the most commonly affected organs. Familial amyloidosis, also referred to as "hereditary amyloidosis," is an autosomal dominant genetic disease characterized by mutations in the genes encoding lysozyme, transthyretin, α-chain or apolipoprotein A-I, and fibrinogen A.[27,29]

Localized amyloidosis is a rare subtype that is mostly idiopathic because there are no associated systemic diseases, and it involves a limited site.[22,24,25] The lesion is formed as a result of amyloid being deposited in a single tissue or organ, although the pathogenesis of this phenomenon remains unknown.[29] Although localized amyloidosis in the head and neck region is rare, it usually represents a benign condition. The most commonly involved sites are the thyroid, larynx, and subglottis. In the oral cavity, amyloidosis frequently affects the tongue and the buccal mucosa.[23,27] Amyloidosis mostly occurs in male patients over older than 40 years of age, and this is consistent with the reported case.[22] Localized amyloidosis only occurs when the site of deposition is consistent with the production site of amyloid. In the current case, the lesion presented as an asymptomatic lesion with normal-colored mucosa, according to the literature.[22,30]

Microscopically, the deposition of amyloid protein inside the connective tissue is indicative of amyloidosis. Combination of Congo red staining and polarized light microscopy is the gold standard method for confirmation of amyloidosis. Once stained with Congo red, under polarized light microscopy, the deposits of protein fibrils will show apple-green birefringence.[22] Immunohistochemistry may be used to identify amyloid subtypes. The majority of cases of oral amyloidosis show kappa light chain positivity.[22,30]

Usually, oral amyloidosis is secondary to the systemic type, whereas localized oral amyloidosis is relatively rare.[25,27] Once amyloid deposits are observed, it is important to determine whether the amyloidosis is systemic or localized. Investigation of the subtype, the involved organs, and the underlying diseases is equally important.[25] The workup must include clinical cardiac evaluation (electrocardiography, echocardiography, troponin, and N-terminal pro-brain natriuretic peptide). Kidney tests (renal function urine routines, 24-hour proteinuria), liver function tests, and tests of the nervous system (physical examination, autonomic nerve function, and nerve conduction) must also be perfomed.[25,30] The presence of free immunoglobulin light chain in urine has diagnostic significance and is known as BJP. AL amyloidosis can be ruled out if the immunoglobulin free light chain (κ:λ) ratio is within the normal range and the immunofixation of serum and urine is negative. Further bone marrow biopsy can be performed to analyze the plasma cells quantitatively. AA amyloidosis can be caused by many types of inflammation, including, but not exclusive to, chronic inflammatory arthritis, tuberculosis, chronic sepsis, familial Mediterranean fever, vasculitis, Crohn disease, chronic osteomyelitis, bronchiectasis, and a few malignancies.[25,27] In the present case, the results of the blood cell count, erythrocyte sedimentation rate, urea, creatinine, uric acid, calcium, albumin, and alkaline phosphatase rates were not significant. Additionally, the results of the electrophoretic examination of the plasmatic protein BJP, as well as the results of the peripheral blood examination and bone marrow biopsy, initially suggested the diagnosis of localized amyloidosis. After performing additional laboratory tests and imaging examinations (bone marrow biopsy, gamma-glutamyl transferase concentration, immunoglobulin M and IgA serum concentrations, monoclonal IgG peak and computed tomography), along with regular follow-ups, our patient was diagnosed with localized amyloidosis.[25]

The prognosis for systemic amyloidosis is poor, and it is not commonly associated with localized amyloidosis. The current literature does not suggest that localized amyloidosis may progress to the systemic form.[22,24,27,29] Localized forms, however, do have a better prognosis, particularly in cases involving the head and neck. There are still no standards for the management of local amyloidosis. Surgical intervention is indicated if functional impairment, resulting from the presence of a voluminous mass, leads to oropharyngeal blockage and obstruction of the upper airways.[22,24,25,27]

CONCLUSIONS

A diagnosis of amyloidosis in the oral cavity is challenging because of its rarity and ability to mimic other conditions. As the oral manifestations might be the only signs of the disease, the dentist should be aware of its appearance to achieve an early diagnosis.

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Reprint requests:

Hélder Antônio Rebelo Pontes
Department of Oral Pathology
João de Barros Barreto University Hospital
Mundurucus Street, No. 4487, Zip Code 66073-000
Guamá, Belém, Pará, Brazil.
Harp@ufpa.br