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 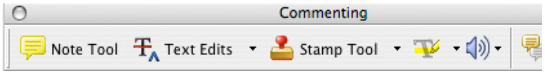

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 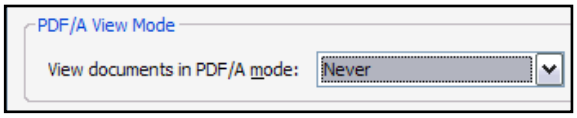

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 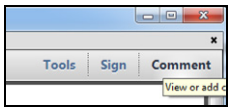

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 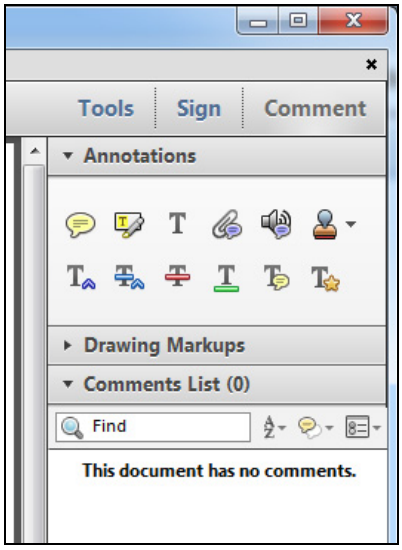
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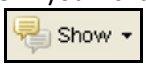
Review	To review your changes, click on the 'Show' button  on the Commenting tool bar. Choose 'Show Comments List'. Navigate by clicking on a correction in the list. Alternatively, double click on any mark-up to open the commenting box.	Your changes will appear automatically in a list below the Comment tool bar. Navigate by clicking on a correction in the list. Alternatively, double click on any mark-up to open the commenting box.
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Pseudoxanthoma elasticum of the palate: a case report and a brief review of the literature

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Pseudoxanthoma elasticum (PXE), which is a genetic, multi-target disorder characterized by progressive calcification and fragmentation of elastic fibers, affects several organs, including the eyes, skin, and cardiovascular system. Diagnosis of PXE is currently based on cutaneous and ocular signs, histopathologic findings, and a patient's family history. PXE-related oral mucosal lesions are rarely reported, possibly due to the potential for misdiagnosis as Fordyce spots; however, when such lesions are reported, they are primarily localized to the vestibular mucosa of the lower lip. Here, we report the case of a female with an intraoral presentation of PXE at the labial and palatal sites. PXE was previously suspected in this patient because of the presence of cardiovascular, ocular, and cutaneous signs; however, a cutaneous biopsy showed findings not consistent with PXE. Incisional biopsy of the palatal lesion confirmed the PXE diagnosis, leading to proper management of the disorder to prevent ophthalmologic and cardiovascular complications. (Oral Surg Oral Med Oral Pathol Oral Radiol 2015;■:e1-e4)

In 1896, J. F. Darier coined the term "pseudoxanthoma elasticum" (PXE) to describe a skin alteration observed 15 years earlier by his colleague D. Rigal. PXE is a rare autosomal recessive disorder resulting from mutations in the *ABCC6* gene. This disorder is characterized by progressive mineralization of both elastic and collagen fibers. Classic signs and symptoms include hypertension, reduced visual acuity, yellow cutaneous papules, and plaques due to cutaneous laxity, which are mainly localized to the neck, groin, armpits and flexural areas of arms and legs.[1,2] Diagnosis of PXE is difficult and time consuming for both the patient and the clinician.

In this report, we describe the case of a female who was diagnosed with PXE by biopsy of a palatal lesion, an uncommon site for this disease to be observed. A review of PXE-related oral mucosa lesions is also reported.

CASE REPORT

In February 2015, a 59-year-old female came to our Oral Medicine Service because of the presence of a white, asymptomatic palatal lesion. During the anamnesis, the patient reported a history of coronary artery disease and arterial hypertension, for which she was being treated with β-blockers and acetylsalicylic acid. In 2004, angioid streaks and choroidal neovascularization had been observed by using fluorescein and indocyanine green angiographies. At that time, the patient had also reported the appearance of multiple, small, yellow lesions on the skin of the antecubital fossa, the axillary and inguinal regions, and the neck. However, in April 2005, a biopsy of the cutaneous lesions located on the neck did not confirm the diagnosis of PXE. In 2010, the patient noted a progressive decrease in visual acuity, and optical coherence tomography detected alterations of the Bruch membrane–retinal pigment epithelium and changes in the thickness of the neuroepithelium in the macular region.

During the oral examination, two yellow-white macules on the soft palate (Figure 1A) and small confluent papules of the same color at the lower lip mucosa (Figure 1B) and on the floor of the mouth were observed. A skin examination revealed the presence of multiple, bilateral, yellow papules on the skin of the antecubital fossa (Figure 2A) and the loss of dermal elasticity on the neck and in the axillary and inguinal regions (Figure 2B).

With the patient's informed written consent, a tissue sample from the palatal lesion was collected by incisional biopsy and processed with hematoxylin and eosin stain (Figures 3A and 3B). Microscopy using orcein and von Kossa staining showed fragmented elastic fibers and intralesional calcium deposits, respectively (Figures 3C and 3D). On the basis of histopathologic, ophthalmologic, cardiovascular, and dermatologic data, the diagnosis of PXE was confirmed.

Our patient appeared in good general health, and since a definitive therapy for this genetic disorder is still not available, she was clinically managed with just a preventive approach, by means of specialist's follow-up visits, for early detection of ocular and cardiovascular diseases. Moreover, the patient did not perceive her skin lesions as unaesthetic, and refused any plastic dermatologic treatment.

DISCUSSION

Due to the multi-target nature of PXE, both the diagnosis and management of this disease require multiple clinical specialists, including dermatologists, ophthalmologists, pathologists, cardiologists, and oral medicine specialists. Asymptomatic skin manifestations,

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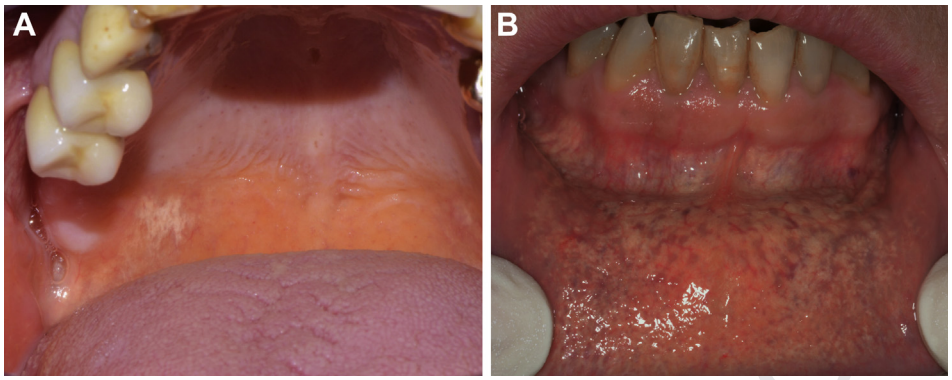

Fig. 1. **A**, Whitish-yellow macula of the soft palate. **B**, Multiple yellowish papules of the lower lip mucosa.

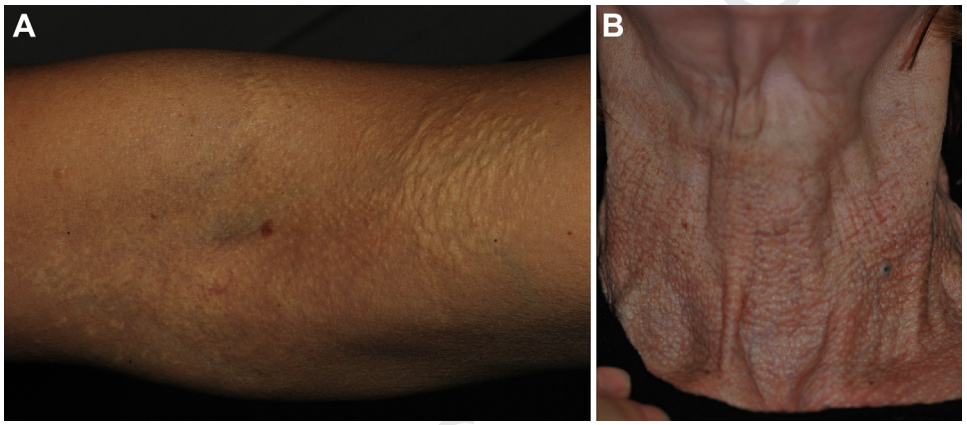

Fig. 2. **A**, Yellow confluent papules in close proximity to the left antecubital fossa. **B**, Lesion on the neck with loss of skin elasticity.

which are often the first clinical signs of PXE, usually occur between the first and second decades of the patient's life. The skin lesions are typically small, yellow papules (1-5 mm in diameter), which occasionally coalesce to form plaques. Lax and wrinkled areas of skin are also observed. Typically, lesions are localized to the neck, axillary, and inguinal regions; the periumbilical area; and the antecubital and popliteal fossae.[1,2]

Approximately 85% of patients with PXE exhibit angioid streaks (i.e., bilateral pigmented lines that radiate from the optic disk)[3] caused by dehiscence of the Bruch membrane, which appears thickened, calcified, and abnormally fragile because of the degeneration and the calcification of retinal elastic fibers. Angioid streaks are characteristic, but not pathognomonic, since they are also associated with a number of other hereditary disorders, including Paget disease, hemoglobinopathies, and other syndromes (Ehlers-Danlos, Marfan, Sturge-Weber syndromes). Other ocular signs of PXE include chorioretinal atrophies (salmon spots), optic disk drusen, choroidal neovascularization, and disciform scars.[2]

The presence of cardiovascular manifestations, including decreased peripheral pulse, arterial hypertension, angina pectoris, and claudication intermittens, all of which are related to the progressive calcification of elastic arterial walls, also contributes to the diagnosis of PXE.[2] Retinal and gastrointestinal hemorrhages have also been observed in patients with PXE due to the fragility of the calcified submucosal vessels.[4]

The currently accepted diagnostic criteria for PXE, as established at the 1992 consensus meeting,[3,5,6] require that patients fulfill a combination of major and/or minor criteria, as summarized in Table I. Major criteria include characteristic skin lesions (yellow cobblestone lesions in flexural area), typical histopathologic findings of lesional skin (elastic tissue and calcium or von Kossa stains), and distinctive ocular lesions (angioid streaks, peau d'orange, or maculopathy) in adults older than 20 years. Minor criteria are characteristic histopathologic features of nonlesional skin (elastic tissue and calcium or von Kossa stains) and family history of PXE in first-degree relatives. The presence of three major criteria are classified as "certain PXE" (category I); patients without typical skin

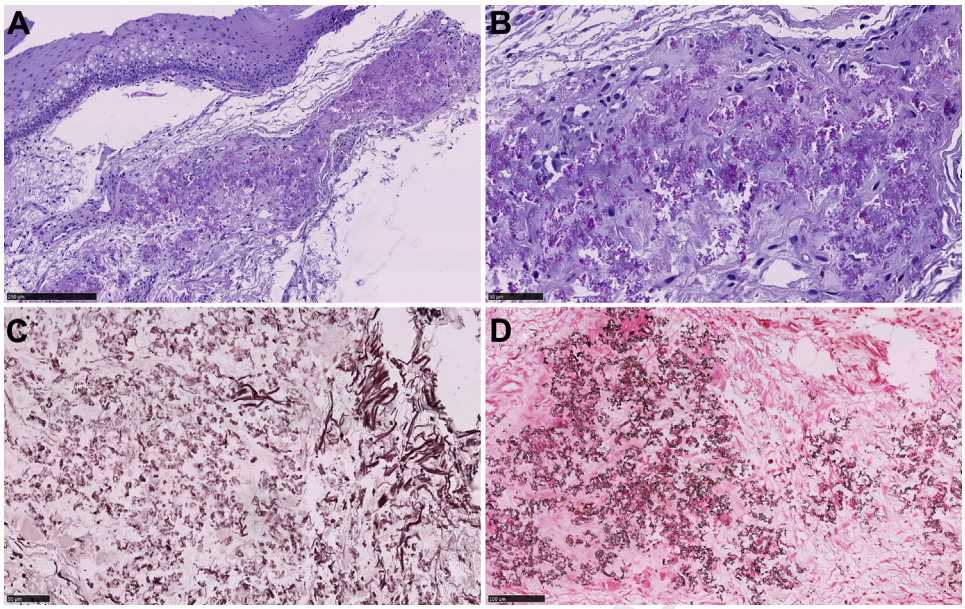

Fig. 3. **A**, Typical granular appearance of elastic degenerative fibers in the stroma below normal oral epithelium (H&E). **B**, The stroma beneath the oral epithelium shows degenerative changes that affect the elastic fibers (*see inset*); the latter appear fragmented, thickened and dispersed as granular material amidst normal appearing collagen fibers. **C**, Degenerated and fragmented elastic fibers detected with Orcein staining: The random arrangement is evident here, since Orcein staining can specifically highlight the elastic fibers. **D**, The von Kossa technique shows calcium deposition on the elastic degenerated fibers.

Table I. Pseudoxanthoma elasticum (PXE) classification according to major and minor criteria identification (Consensus meeting, 1992)

Category	*Diagnostic criteria*
I	Three major criteria
IIa	Angioid streaks and two minor criteria
IIb	Angioid streaks and characteristic histopathologic features of nonlesional skin
IIc	Angioid streaks and family history
IId	Two minor criteria without angioid streaks

signs, but presenting angioid streaks, in addition to one or two minor criteria, belong to categories IIa-IId, namely, "uncertain PXE." Although there is growing acceptance for molecular analysis in the diagnosis of this genetic disorder, its utility is still debated.[7] Histopathologic examinations using von Kossa and Orcein staining is still the preferred diagnostic procedure, since it allows for the observation of PXE-related alterations, including granular, fragmented, and calcified elastic fibers in both skin and oral mucosal lesions. Specifically, von Kossa staining is used to visualize calcium deposits, and Orcein detects altered morphology in elastic fibers.[1,8]

Lesions in the oral cavity of PXE patients appear as white-yellow papules or macules, with a cobblestone-like or reticular pattern, localized to the vestibular mucosa of lower lip and, less commonly, to the soft palate, buccal mucosa, and tonsillar areas.[1,3,8] Frequently, however, these lesions are misdiagnosed as Fordyce spots by those who are not oral medical specialists.[8]

With the exception of two case reports,[1,9] epidemiologic data on the frequency of oral mucosal lesions in PXE are limited. Nozzi et al.[10] reported the occurrence of oral mucosal lesions in 83% of patients with PXE. In half of those cases, lesions were observed on the lower lip mucosa, and in 33% of patients, oral lesions were also observed on the hard or soft palates and/or the vestibular mucosa of the upper lip.[10] This frequency of oral lesions, however, is not fully consistent with other data. A large clinical trial published in 2006 by Christen-Zäch et al.[6] analyzed 142 patients with PXE and found oral lesions in 7.7%. These data are consistent with another study by Goette et al., where 5% of patients were found to have oral lesions.[8] Two other investigations observed slightly higher incidences of oral lesions among patients with PXE at 21%[11] and 19%.[12] In other studies, dental anomalies, including oligodontia and amelogenesis imperfecta, were also associated with PXE.[4,13,14] In 2013, Nadeau et al. also described the first case involving the coexistence of temporomandibular disorders and PXE.[15]

Oral mucosal lesions are usually asymptomatic and do not require a specific treatment; however, dental management is recommended for individuals with one of the specific disorders mentioned above. In general, because a specific and effective therapy for PXE is still lacking, the management of these patients consists of

prophylactic measures and lifestyle adjustments, including healthy eating, avoidance of tobacco use, and weight and cholesterol control to minimize the occurrence of cardiovascular complications.[2,3,5] Plastic surgery is also an appropriate option when skin lesions are deemed cosmetic problems.[3]

CONCLUSIONS

This case emphasizes the importance of accurate intraoral examinations of patients with PXE and supports the utility of an incisional biopsy of oral lesions to confirm diagnosis, particularly when a skin biopsy fails to diagnose PXE.

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