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Clinical and histopathological features of a first case of glycogenic acanthosis presenting as an isolated gingival nodule: A case report and a review of the literature

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Abstract

Background: Glycogenic acanthosis is a common benign lesion of the oesophagus. However, extraoesophageal mucosal localisations, which are much rarer, are possible in the larynx and oral mucosa in the form of white, papular or plaque-like lesions. We report a nodular gingival form which, to our knowledge, has not been observed or published in the scientific literature.

Case presentation: This clinical case concerns a 63-year-old female patient in good general health who was diagnosed with glycogenic acanthosis with the original appearance of an isolated, asymptomatic gingival nodule mimicking a pseudotumor or tumour. The diagnosis was confirmed by histological and immunohistochemical examination. No complications or recurrences were noted after removal of the nodule.

Conclusion: Although oral glycogenic acanthosis is included in the differential diagnosis of leukoplakia, this case report suggests that this diagnostic hypothesis should also be considered in the presence of an isolated gingival nodule. This iconographic aid, supplemented by a review of the literature, is designed to assist the odontologist in the diagnostic process, from clinical examination to anatomopathological examination.

Keywords: Glycogenic acanthosis; Gingival nodule; Gingival tumor; Oral leukoplakia.

Abbreviations: GA: Glycogenic Acanthosis; HPV: Human Papillomavirus; HE: Hematoxylin-Eosin; PAS: Periodic Acid Schiff; EMA: Epithelial Membrane Antigen.

Introduction

Glycogenic acanthosis is a benign, asymptomatic lesion of the oesophagus. First described by Rywlin and Ortega in 1970 [1], it is usually discovered by chance during oesophageal endoscopy, with a frequency ranging from 3.5% to 28.3% [2]. Its aetiology remains to be elucidated, although some authors report an association with gastro-oesophageal reflux disease and metabolic disorders (insulin resistance, diabetes, metabolic syndrome) [2,3]. Clinically, this type of lesion manifests itself in the form of whitish, discretely elevated plaques, 2 to 10 mm long, sometimes confluent and frequently reaching the lower third of the oesophagus [4]. Alongside this main location, extra-oesophageal lesions can also be diagnosed, but rarely concomitantly [4]. These are exceptional. To date, 11 cases have been described in the literature, involving only the laryngeal and oral mucosa. In 10 of these cases, the lesions are similar in appearance to conventional oesophageal lesions [2,5]. In the oral cavity, the lesions are mainly located on the cheeks, floor of the mouth and tongue. A single case involved multiple white gingival papules in the context of Cowden's syndrome [6]. Histologically, this type of pathology is characterised by an increase in epithelial thickness (acanthosis) with keratinocytes with clarified cytoplasm, loaded with glycogen. No dysplastic or carcinomatous transformation has been reported, even after long-term follow-up of 5 years [7]. These clinical and histological findings explain why most clinicians specialising in lesions of the oral mucosa classify glycogenic acanthosis as a leukoplakia. However, we report an original case, outside the syndromic context, in the form of an isolated gingival nodule. To our knowledge, there is no other clinical description in the literature or in specialist textbooks. Consequently, within the limits of the exhaustiveness of our research, we are the first to present this new clinical expression, which also requires glycogenic acanthosis to be considered as a differential diagnosis of gingival nodular lesions, which include benign tumours.

Case presentation

A 63-year-old patient was referred by her dental surgeon after the chance discovery of a gingival lesion, "pimple-shaped" in her words. She was rather worried despite the absence of any local or general functional signs and wanted rapid treatment. The medical interview revealed no medical or surgical history and ruled out alcohol or tobacco intoxication. In addition, she was not taking any medication and had no recollection of a traumatic episode.

Endo-buccal examination revealed an isolated nodular lesion on the vestibular side of the attached gingiva between the teeth of 16 and 17 (Figure 1). The nodule was approximately 5 mm in diameter, firm to the touch, had a sessile base and a smooth surface similar in colour to the surrounding gingival tissue. In addition, a composite restoration was present cervical to 16 but distant from the lesion. Exobuccal examination, palpation of the cervicofacial lymph nodes and overall examination of the oral mucosa revealed no other lesions. On the basis of these clinical elements and in order of priority, the differential diagnosis included benign tumours (fibroma, neurofibroma, shwannoma, etc.) and non-neoplastic lesions characterised by collagenous fibrosis within the chorion (Figure 2). In the first instance, we excluded epithelial tumours secondary to infection by the Human Papilloma Virus (HPV) (papilloma, condyloma acuminata and verruca vulgaris), due to the smooth surface of the nodule's epithelial coating. Indeed, even in mild clinical forms, a slightly rough appearance is visible in HPV-induced oral vegetations. In order to confirm the diagnosis, the nodule was removed during the session under local anaesthetic, without surgical margin, right up to the bone contact, using a scalpel blade. Once removed, the tissue was immediately immersed in a vial containing 10% formalin fixative for inclusion in a paraffin-embedded block and anatomopathological study following serial sections stained with Haematoxylin-Eosin (HE). Histological examination showed epithelial hyperplasia with glycogenic acanthosis, without cytonuclear atypia (anisocytosis, anisokaryosis: disturbances in cyto-nuclear morphology), architectural disorganisation and stigmata of HPV-type viral infestation (koilocytic cell, binucleation, dyskeratosis, azurophilic granulations, etc.). The squamous mucosa was hyperplastic, acanthosic with clarified keratinocytes, which had enlarged and glycogen-laden cytoplasm, only visible after staining with Periodic Acid Schiff (PAS) (Figure 3). PAS staining did not reveal any evidence of candidal superinfection. Given the presence of clarified keratinocytes, we also carried out immunohistochemical staining with Epithelial Membrane Antigen (EMA), which proved negative, revealing only background at the level of the cytoplasmic membrane of certain superficial keratinocytes. In addition, the proliferation index assessed by ki-67 was low and strictly confined to the basal area, which enabled us to confirm our morphological observation using standard staining (HE), which ruled out any dysplastic process (Figure 4). The gingival chorion showed collagenous fibrosis and a moderate polymorphic inflammatory infiltrate, predominantly lymphocytic and plasma cell, of subepithelial topography. Finally, thanks to the histological data, the patient was reassured that her gum lesion was benign. When we contacted her three months after the operation, she was able to confirm that the gum had healed perfectly and that there had been no recurrence. We were also able to check that she did not suffer from gastro-oesophageal reflux.

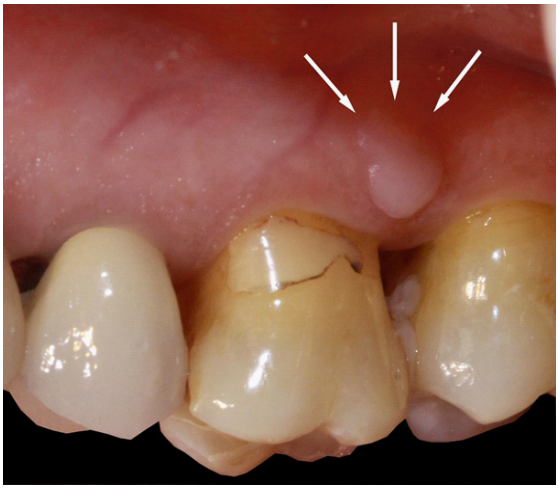

Figure 1: Clinical view shows a well-limited, sessile nodule approximately 7 mm in diameter located on the vestibular side of the attached gingiva between the molars.

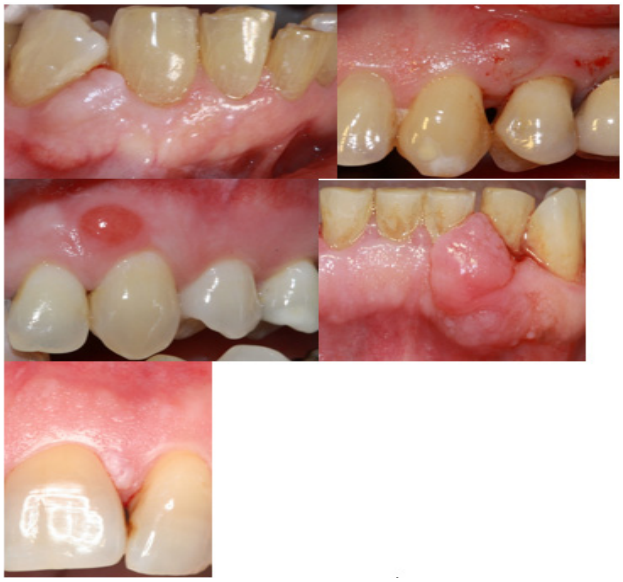

Figure 2: Clinical differential diagnoses of a well-defined, solitary, sessile, firm and asymptomatic gingival swelling. Connective tissue neoplasms; Examples: fibroma **(A)**, peripheral ossifying fibroma **(B)**, peripheral odontogenic fibroma **(C)**. Reactive lesion: fibrous epulis **(D)**, Epithelial tumors: condyloma **(E)**.

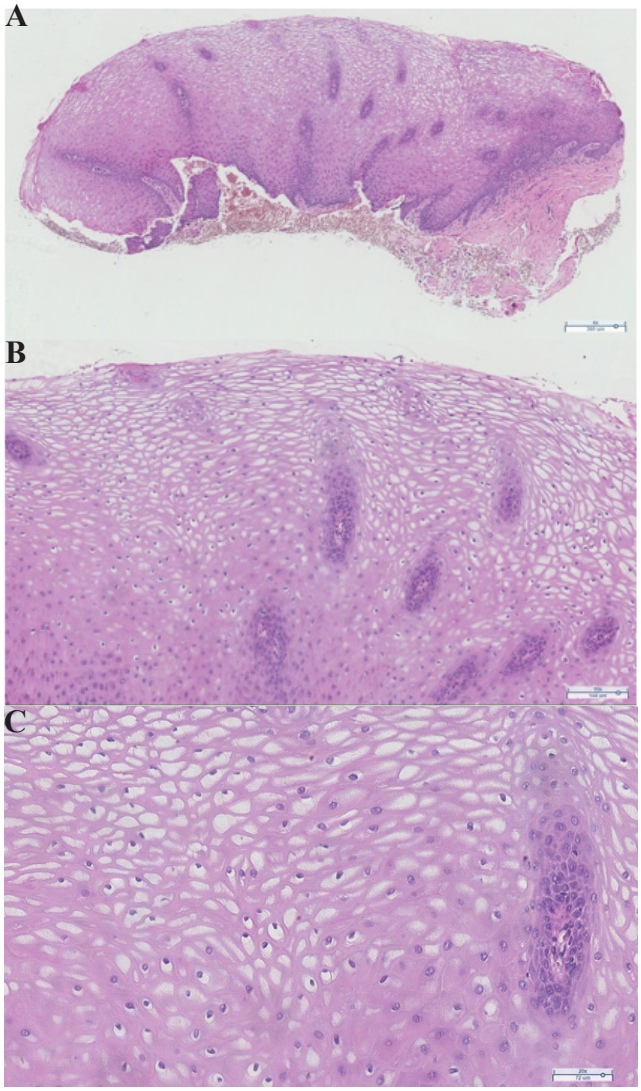

Figure 3: (HE) staining. Photomicrograph of the lesion shows. **(A)** Epithelial hyperplasia at low power (HE, x40); **(B)** clarified keratinocytes within the superficial and the spinous layer at medium-power (HE x 100); **(C)** and no evidence of HPV-infection (koilocytes, binucleations, dyskeratosis) at high power (HE x200).

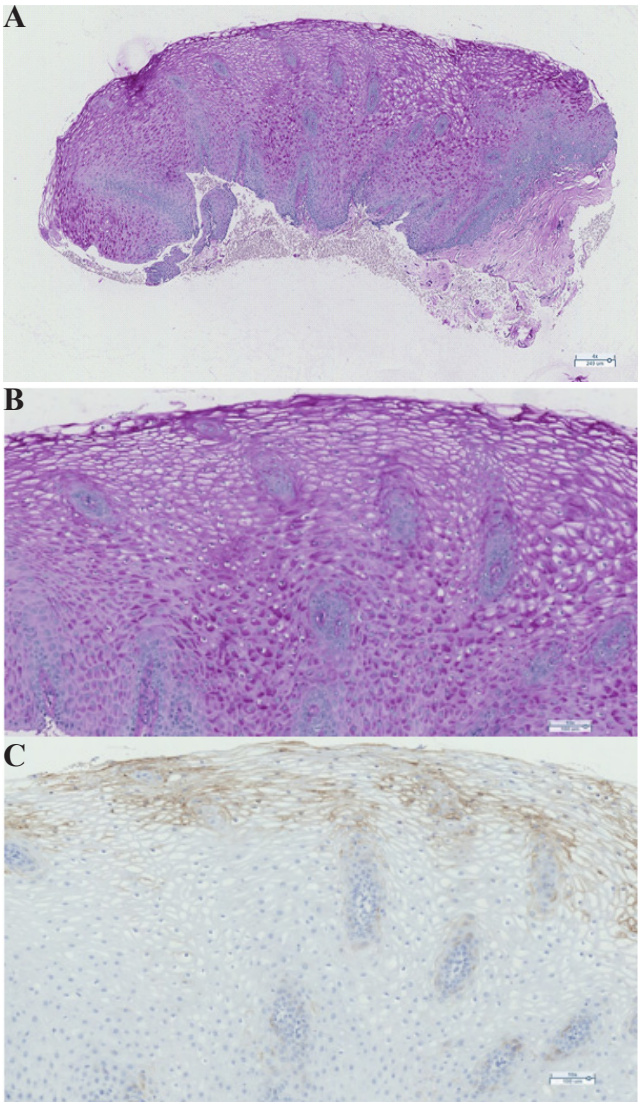

Figure 4: PAS staining and immunohistochemical findings. **(A & B)** PAS staining of the specimen shows abundant intra-cellular glycogen deposits within the keratinocytes (dark purple). Original magnification x 40 (a) and x 100 (b). **C)** Immunohistochemical study shows a negative staining for EMA (note the membranous background noise within the superficial keratinocytes) (Original magnification x 100).

Discussion

Only 11 cases of extraoesophageal glycogenic acanthosis have been described in the literature (Table 1). This condition affects more women than men, with a ratio of 7:5, and the age range is between 22 and 79 years, with an average of around 60 years. In order of prevalence, the oral location is the most common, with 9 cases, followed by laryngeal involvement, which is less frequent [2,5]. In the oral cavity and in the majority of clinical situations, the pathology is comparable to leukoplakia, isolated on the tongue and floor of the mouth [7,10] or bilaterally on the inside of the cheeks [4,8,11,12] mimicking white sponge naevus or lichen planus. Only one author has reported a gingival location as part of Cowden's syndrome, presenting as multiple papillomatous papules [6]. In our patient's case, the association with this syndrome could be ruled out because of the absence of specific general and mucocutaneous manifestations, and also because of the isolated nature of the gingival nodule and its non-papillomatous appearance. Regarding the risk of evolution, whatever the oral or oesophageal location of the lesions, there are no cases reported in the literature of extensive evolution or malignant transformation. In fact, given the lack of

Table 1: Reported cases of extra-esophageal GA.

Authors	Year	Country	Gender	Age	Medical record	Clinical findings	Size	Multifocality	Localization
Fyfe et al.	1998	USA	M	79	Hypertension, arteriosclerosis	White plaque (leukoplakia)	-	Solitary	Larynx (subglottic area)
Nishizawa et al.	2009	Japan	F	53	Cowen Syndrome	Papillomatosis	-	Multiple	Gingiva and labial mucosa
Montebugnoli et al.	2010	Italy	M	72	None	White plaque (leukoplakia)	4 cm	Solitary	Tongue border
Jinbu et al.	2012	Japan	M	46	Cutaneous pruritus, obsession, depressive state, stiff shoulders, esophageal GA	White plaques (leukoplakia)	-	Bilateral	Jugal mucosa
Akahori et al.	2017	Japan	F	41	None	White plaques (leukoplakia)	-	Bilateral	Jugal mucosa
			F	72	None	White plaque (leukoplakia)	-	Solitary	Floor of the mouth
Schulz et al.	2018	Brazil	M	56	None	White plaque (leukoplakia)	3 cm	Solitary	Posterior tongue border
Mahmood et al.	2019	UK	M	78	None	White plaque (leukoplakia)	3cm	Solitary	Ventral surface of tongue and floor of the mouth
Asakura et al.	2021	Japon	F	52	Thigh melanoma	White plaques (leukoplakia)	-	Bilateral	Jugal mucosa
Sakuyama et al.	2022	Japan	F	22	None	White plaques (leukoplakia)	-	Bilateral	Jugal mucosa
Plawecki et al.	2022	USA	F	49	Mild obesity, GERD	White plaque (leukoplakia)	-	Solitary	Larynx (vocal folds)
Strokov, Dridi (present case)	2024	France	F	63	None	Firm nodule	5 mm	Solitary	Attached gingiva

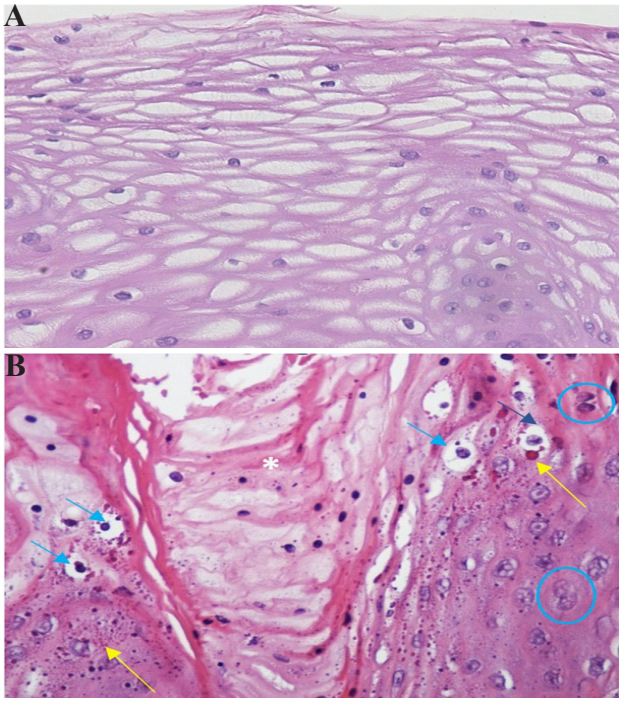

Figure 5: Histopathological differential diagnosis between acuminate condyloma and gingival glycogenic acanthosis. **A.** Photomicrograph of gingival glycogenic acanthosis, original magnification (x200): pale clear cells, without viral infection signs. **B:** Photomicrograph of oral acuminate condyloma, original magnification (x200): koilocytosis (blue arrow), binucleation (blue circle), azurophile granulations (yellow arrow), confluent parakeratosis (asterix).

clinical knowledge, the precautionary principle prevails. In the first instance, a diagnostic biopsy is essential to establish the differential diagnosis with tumour lesions. Once a definite diagnosis has been made, the patient should be reassured and clinical monitoring instituted, with no indication of total removal of the lesion if it is large (over 3 cm) [12]. The histological characteristics of glycogenic acanthosis are similar for all mucosal sites and correspond to acanthosis due to glycogen overload of the keratinocytes. The accumulation of intracellular glycogen in the attached gingival epithelium is thought to be in response to an underlying inflammatory process [13]. Since the keratinocytes are more voluminous, this leads to an increase in the thickness of the epithelium. In response to this type of aggression, it is possible to envisage a modification of the gingival tissue, either in the form of keratosis, which is clinically expressed by a whitish appearance of the lesions, or in the form of fibrosis, which pushes back the epithelial lining and leads to the formation of a nodular mass, as in our patient's situation.

In all cases, the presence of clarified keratinocytes requires a differential histological diagnosis with other pathologies that can cause this type of cellular alteration, such as clear cell acanthoma and HPV-induced vegetations (Table 2). Clear cell acanthoma is a benign skin tumour that can exceptionally be seen in the oral cavity as a firm, reddish nodule [14]. However, in such circumstances, the epithelium is the site of psoriatic hyperplasia characterised by keratinocytes with pale, clarified cytoplasm (well stained by PAS), with altered neutrophil exocytosis in its superficial layers, forming micro-abscesses. An immunohistochemical study using Epithelial Membrane Antigen (EMA) confirms the diagnosis, revealing diffuse and intense positivity in the cytoplasm of clarified keratinocytes [14]. EMA, whose immunoreactivity is well preserved in paraffin sections,

is considered to be a very effective marker for establishing the epithelial nature of neoplastic cells. It is a glycoprotein belonging to the mucin group, bound to the plasma membrane, and normally expressed in secretory epithelial cells. Its cytoplasmic and membrane expression is intense and diffuse within squamous clarified cells in the presence of clear cell acanthoma [15]. HPV-induced vegetations can be isolated in immunocompetent patients without other concomitant mucocutaneous lesions. Viral papillomas and oral condylomata acuminata are essentially generated by HPV 6 and 11. Their characteristics allow them to be differentiated fairly easily. These lesions generally take the form of papules, pinkish to whitish in colour, with a discrete or marked papillomatous surface. Histological examination reveals a hyperplastic, acanthosic squamous lining with exophytic growth and papillomatous architecture with epithelial projections supported by fibro-vascular axes. A viral origin may be suggested by certain stigmata of infestation that are inconsistently present within the superficial epithelial layers, such as azurophilic granulations, dyskeratoses, binucleations and, in particular, koilocytes, which indicate an induced HPV infection. These are epithelial cells altered by viral infection, with a non-uniform perinuclear halo and a small, dense, eccentric pycnotic nucleus [16]. Finally, histological examination ruled out the diagnosis of fibrous epulis, which corresponds to an advanced stage of inflammatory epulis. In this case, the elementary lesion takes the form of a nodule that is firm to the touch, may be pedunculated, and is covered by more or less normal mucosa. Histopathologically, there is a massive proliferation of fibroblasts associated with the presence of tangled bundles of mature collagen fibres [17].

Conclusion

Although oral extra-oesophageal localisations of glycogenic acanthosis are rare, this type of pathology must be evoked at the time of diagnosis, in the presence not only of papular or plaque-like leukoplakia mimicking white sponge naevus or lichen planus, but also in the presence of an isolated gingival nodule mimicking a pseudotumour or tumour. The diagnosis is histological and the prognosis is excellent. Management is straightforward and accessible to all practitioners. Nevertheless, clinical studies are needed to elucidate the pathological process and risk factors.

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Patient gave consent for her personal and clinical details along with any identifying images to be published in this study.

Availability of data and materials: All data generated or analyzed during this study are included in this published article.

Competing interests: The authors declare that they have no competing interests.

Funding: Not applicable.

Author's contributions: SMD performed the oral examination and the biopsy while SS performed the histological examination of the specimen. Drafting of the manuscript: SMD, SS. Revision of the manuscript: ALE. All authors read and approved the final manuscript.

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