J Oral Res
oral and craniofacial sciences

Case

Intraoral Acanthosis nigricans and its clinical relevance as a manifestation of a paraneoplastic syndrome: A case report.

Acantosis nigricans intraoral y su relevancia clínica como manifestación de un síndrome paraneoplásico: Reporte de un caso.

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Receipt: 03/01/2018 **Revised:** 04/03/2018
Acceptance: 04/11/2019 **Online:** 08/05/2019

Abstract: Malignant-or-paraneoplastic acanthosis nigricans is a verrucous and hyperpigmented tumor affecting the mucosa and skin. In most cases malignant acanthosis nigricans is a distant manifestation of an intra-abdominal primary cancer. While the diagnosis of malignant acanthosis nigricans is challenging, some specific clinical and histopathological findings could lead to an accurate diagnosis. A rare clinical case of a 59-year-old female, who was referred to the maxillofacial surgery service due to a painful oral lesion in the palatine region, is presented. Upon examination, papillomatous lesions were observed on the hard palate, that were later diagnosed as intraoral malignant acanthosis nigricans secondary to gastric cancer. Both local and systemic evaluations are discussed, highlighting the relevance of a multidisciplinary approach consistent with the fact that these manifestations, although infrequent, should generate suspicion among clinicians and therefore motivation to perform a diligent and complete study since it can reveal the presence of a malignant pathology.

Keywords: Acanthosis nigricans; palate, hard; stomach neoplasms; surgery, oral; mucous membrane.

Resumen: La acantosis nigricans maligna o paraneoplásica es un tumor verrugoso e hiperpigmentado que afecta la mucosa y la piel. En la mayoría de los casos, la acantosis nigricans maligna es una manifestación distante de un cáncer primario intraabdominal. Si bien el diagnóstico de acantosis nigricans maligna es desafiante, algunos hallazgos clínicos e histopatológicos específicos podrían conducir a un diagnóstico preciso. Se presenta un caso clínico raro de una mujer de 59 años, que fue derivada al servicio de cirugía maxilofacial debido a una lesión oral dolorosa en la región palatina. En el examen, se observaron lesiones papilomatosas en el paladar duro, que posteriormente se diagnosticaron como acantosis nigricans maligna intraoral secundaria a cáncer gástrico. Se discuten tanto las evaluaciones locales como las sistémicas, destacando la relevancia de un enfoque multidisciplinario consistente con el hecho de que estas manifestaciones, aunque poco frecuentes, deberían generar sospecha entre los clínicos y, por lo tanto, motivación para un estudio diligente y completo, ya que puede revelar la presencia de un patología maligna.

Palabras Clave: *Acantosis nigricans; paladar duro; neoplasias gástricas; cirugía bucal; membrana mucosa.*

Cite as:
Francisca Donoso-Hofer F & de la Maza-Acevedo J. Intraoral Acanthosis nigricans and it´s clinical relevance as a manifestation of a paraneoplasic syndrome: A case report.
J Oral Res 2019; 8(3):249-253.
DOI: 10.17126/joralres.2019.037.

ISSN Online 0719-2479 - www.joralres.com © 2019

INTRODUCTION

Acanthosis nigricans (AN) is a dermatological condition characterized by symmetrical verrucous and hyperpigmented lesions found in large cutaneous folds and oral and vaginal mucosa.[1] Although it is mostly considered a benign skin disease, its clinical importance relies on the expression of

endocrine disorders such as insulin-resistant and underlying neoplastic processes.[2-4] It can be classified as benign, malignant or paraneoplastic, auto-immune, syndromic associated, drug induced or hereditary,[3-5] in which the clinical differences are not significant, and are histologically similar.

The prevalence of AN varies from 7% to 74% according to age, race, degree of obesity and concomitant endocrinopathy.[6] In fact, in a study of 12,000 cancer patients, only 2 patients had malignant acanthosis nigricans (MAN). In 20-50% of MAN cases, there is some manifestation in the oral cavity.[7]

The great majority (90%) of MAN are associated with abdominal malignancies, of which 70% to 90% are gastrointestinal.[6]

The mechanisms underlying MAN are unclear, but some growth factors secreted from distant neoplastic cells stimulate the proliferation of keratinocytes and dermal fibroblasts at cell receptor level.[8,9]

Since MAN is detectable by clinical methods, a better characterization would be valuable for the early detection of intra-abdominal cancers.

The case of a female patient with intraoral MAN secondary to gastric cancer is presented. Its main intraoral and systemic clinical characteristics are discussed, emphasizing the diagnostic study performed and the importance of the multidisciplinary evaluation and treatment.

CASE

A 59-year-old female patient is referred with a chief complaint of two-month progression of a painful extensive palatal tumor. Pain is caused by the mechanical stimuli preventing correct chewing and swallowing resulting in a weight loss of 4 kilograms. No other symptoms are mentioned.

The patient does not report any relevant personal or family history, nor any smoking or alcohol consumption habits. She does not identify with any ethnic group and currently does not have a job occupation. Physical examination revealed a large exophytic and digitiform lesion compromising the whole hard palate, even reaching the palatine faces of the anterior superior teeth. The consistency of the lesion is spongy and friable. (Figure 1)

Both armpits were hyper pigmented. No similar injuries were observed in other flexural areas.

Under the initial clinical suspicion of human papillomavirus (HPV) lesion, an incisional biopsy was programmed, and cytological brush sample was taken to detect and genotype HPV by conventional polymerase chain reaction (PCR) and DNA macroarray (HPV LCD-Array Kit 3.5, Chipron), respectively. Due to the clinical context of the patient, the following laboratory tests were requested: Hemogram, erythrocyte sedimentation rate (ESR), human immunodeficiency virus (HIV) screening, blood glucose, basal insulin and 2-hour post glucose insulin, and a thyroid panel.

Figure 1. Large exophytic and digitiform lesion which compromise to the entire hard palate and the palatine faces of the anterior superior teeth.

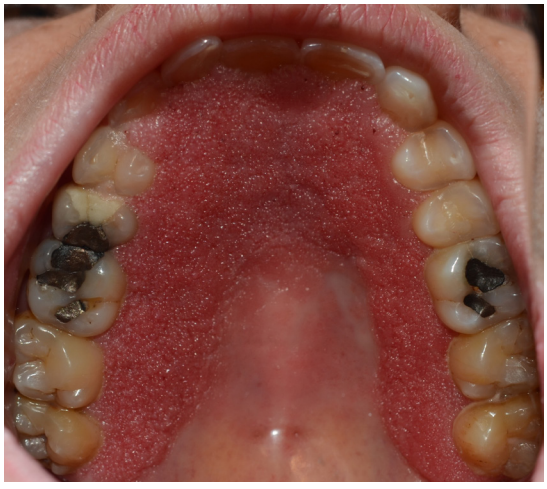

Figure 2. Exophytic and digitiform epithelial proliferation was observed in relation to connective tissue. The histopathological diagnosis corresponds to papillomatosis.

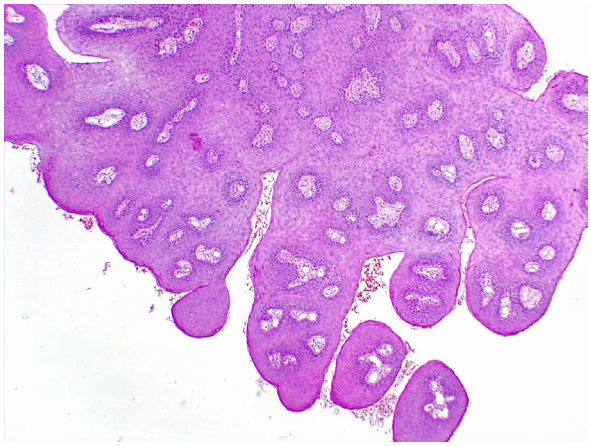

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Figure 3. Topical treatment with 90% trichloroacetic acid once a week produced a superficial necrosis. (white area on the photograph).

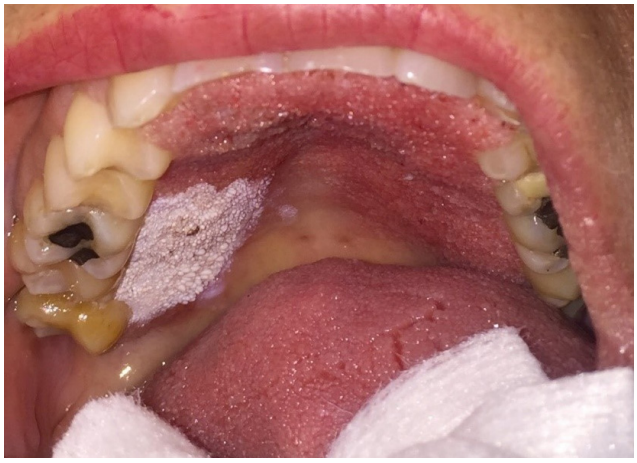
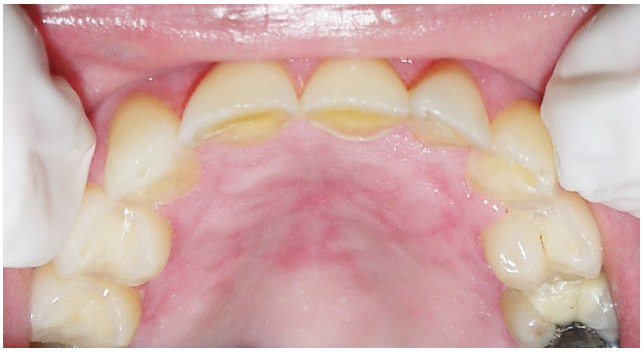


Figure 4. After three months of topical treatment almost complete lesion resolution is observed.



Exophytic and digitiform epithelial proliferation was observed in the histopathological study in relation to connective tissue with plenty of inflammatory infiltrate, predominantly lymphocytic with foci of polymorphonuclear neutrophils and plasma cells. The histopathological diagnosis corresponds to papillomatosis. (Figure 2)

The patient was examined in a teaching hospital and her complementary studies were performed in the hospital and in the associated university. Hemogram results showed no alterations, the HIV test was negative and thyroid hormones were within normal ranges.

The ESR was increased to 80mm/hour (normal range of 1 to 20mm/hour). Glucose was slightly high and out of the normal range with a value of 101mg/dl (normal range of 70 to 99mg/dl) and so was insulin at 120 minutes with a value of 94.6µlU/ml (normal range of 1.9 to 60µlU/ml). Both detection and genotyping tests for HPV were negative. A topical treatment of 90% trichloroacetic acid once a week (Figure 3), was performed to reduce the tumor volume. The patient was referred to the internal medicine department to assess metabolic alteration and axillary AN. After three months of treatment, the palatal tumor was reduced almost in its entirely, while food intake was improved. (Figure 4)

However, the patient did not regain her normal weight and started to report sporadic discomfort in the abdominal region. An upper gastrointestinal endoscopy was requested denoting a gastric tumor. The histopathological study concluded a moderately differentiated adenocarcinoma in the antral and gastric mucosa.

DISCUSSION.

Acanthosis nigricans shows no predilection for gender or age; nevertheless, patients with endocrine disorders are more likely to experience the disease as a benign manifestation.[10]

Skin and mucosal membranes involvement in AN is proportional to insulin resistance level[7] but in some non-endocrine cases, it might be due to underlying primary neoplastic processes such as gastric, colonic, uterine and ovarian adenocarcinoma[2,3,11] and less frequently, is associated with renal urothelial carcinoma or Hodgkin's and non-Hodgkin's lymphomas.[9,12,13]

In general, oral AN manifests as areas of generalized papillomatosis. In the oral mucosa and palate, less severe lesions are usually observed, which may be irregular, diffuse or velvety. Regardless of location, the lesions seldom present pigmentation and may cause pain and dysphagia.[11,7]

In the reported case, the papillomatous lesion appeared on the hard palate, compromising even the palatine faces of the anterior superior teeth due to its considerable thickness. Contrary to what is described in the literature,

the palatal lesion was quite aggressive, preventing correct feeding. Due to the high clinical suspicion of an HPV palate lesion, a 90% trichloroacetic acid treatment was started achieving a satisfactory outcome.

Histopathological diagnosis was papillomatosis. In multiple areas of the sample, keratinocytes displaying koilocyte-type changes were observed.

Although one of the pathognomonic characteristics for a squamous papilloma histopathological diagnosis is the presence of koilocytes, it is difficult to make the differential diagnosis between a squamous papilloma caused by HPV infection and an intraoral MAN that expresses a paraneoplastic process when the clinical features are not conclusive for either. Histopathologically the lesions of intraoral AN present acanthosis and epithelial papillary hyperplasia, with absence of melanin deposits,[7] as it was observed in the present case.

Despite achieving a successful treatment of the palatal tumor, the patient did not regain her normal weight and started to report sporadic discomfort in the abdominal region. An upper gastrointestinal endoscopy showed a moderately differentiated adenocarcinoma, present in the gastric and antral mucous membranes.

Gastric body carcinomas are clinically silent until a very late stage or are associated with vague symptoms such as anorexia or epigastric discomfort.[14] In the present case, the patient had rather non-specific gastrointestinal symptoms, which contributed to the late diagnosis.

The so-called classical manifestations correspond to an advanced stage of the disease and are often non-specific.[14] In the current scenario, the clinical sign confirming the suspicion of an abdominal pathology is the persistent in regaining weight despite normalizing food intake after treatment of a palatal pathology.

The appearance of AN in patients with metabolic disorders can be explained by hyperinsulinemia states. The interaction between excessive levels of circulating insulin and insulin-like growth factor receptors (IGF-1R), epidermal growth factor receptor (EGFR) and fibroblast growth factor receptor (FGFR) exerts an effect on the proliferation of fibroblasts, melanocytes and dermal keratinocytes.[1,15]

In MAN, transforming growth factor alpha (TGF-α) and its receptor participate in the progression of tumors through autocrine and paracrine secretion. When this factor is secreted, and circulates in large quantities in the bloodstream, it could cause proliferation of epidermal cells.[8,16] The gastric carcinoma pathophysiology in paraneoplastic processes is similar. Koyama *et al.,*[17] observed in their immunohistochemistry studies the expression of TGF-α and EGFR in histological sections obtained directly from gastric carcinoma. TGF-α would stimulate the proliferation of keratinocytes via EGFR, and the manifestations of neoplasia would be mediated by an endocrine mechanism.[18]

When AN is expressed as part of a paraneoplastic syndrome, it is clinically indistinguishable from AN associated with other causes. However, there are some characteristics that can alert of its malignant origin such as an abrupt onset in patients over 40 years old, fast dissemination, more severe, extensive, symptomatic and hypertrophic lesions, and mucosal involvement.[6,19]

Another important clinical characteristic of MAN is the lesion regression after a satisfactory treatment and its recurrence when the tumor returns.[4] It is essential to request complementary tests to rule out a viral origin of the papillomatous lesion, the metabolic disorder associated with cutaneous AN and the support of an experienced histopathologist in the proper differential diagnosis of this kind of lesions.

We consider that the present clinical case represented an important challenge for the treating team since it involved an infrequent presentation of a rare pathology. The aggressiveness of the intraoral papillomatous lesion along with the absence of molecular markers for HPV (the main etiological agent) despite satisfactory symptomatic treatment and the absence of a clear etiology of an intraoral manifestation should alert us that we can be facing a malignant acanthosis nigricans that masks a neoplastic process.

Conflict of interests: There is no conflict of interest among the authors.
Ethics approval: None.
Funding: Self-financed.
Authors' contributions: All authors worked on the elaboration of this case.
Acknowledgements: None.

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