

Oral Acanthosis Nigricans: Case Report and Comparison with Literature Reports

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SUMMARY Acanthosis nigricans (AN) is a rare condition which may affect oral cavity. There are two forms of AN: benign and malignant. Benign AN may be hereditary, or may be related to systemic diseases or drugs. Malignant AN is most often associated with gastric adenocarcinoma but cancers of other sites and types may also occur. This case report is based on a case of a 78-year-old woman suffering from invasive bladder papillary transitional cell carcinoma accompanied by extensive papillomatous areas of normal mucosal color and soft consistency involving the lips, buccal mucosa and hard palate. Verrucous changes with tiny pigmented macules were also found on the skin of the right ear auricle. Oral lesions occurred after the tumor had been diagnosed, i.e. after third operation for tumor recurrence. The fifth operation for tumor recurrence resulted in slight improvement of oral changes. It is concluded that the severity of oral changes is in correlation with tumor progression. The occurrence of oral lesions may be an indicator of tumor progression.

KEY WORDS: acanthosis nigricans, cancer, oral cavity

INTRODUCTION

Acanthosis nigricans (AN) is a mucocutaneous disorder which is characterized by the presence of hyperpigmented papillary lesions on the skin and papillomatous lesions in the oral cavity (1). There are two forms of AN, benign and malignant. Benign AN may be hereditary, or may be related to systemic diseases such as diabetes, obesity, Cushing's syndrome or Addison's disease. Certain drugs such as nicotinic acid, systemic corticosteroids, estrogens, insulin and fusidic acid may play a role as well (1). Insulin-resistant diabetes and

hyperinsulinemia are the most common conditions associated with the benign form of AN. Malignant AN is a rare condition that is always associated with neoplasms. Searching through the Medline we found 8 cases of oral AN described from 1999 to 2007 (2-9).

Adenocarcinomas are the most common malignancies found in patients with malignant AN (10). Malignant AN is most often associated with gastric adenocarcinoma but cancers of other sites and types may also occur (1).

The pathogenesis of malignant AN remains unclear. A current hypothetical mechanism is the secretion of large amounts of transforming growth factor α (TGF- α) by the tumor into the circulation, which is thought to stimulate keratinocyte growth *via* an endocrine route (11). AN is characterized by hyperpigmented plaques commonly affecting the axillae, nape and sides of the neck. Pruritus and hyperkeratosis of the palms and soles have also been reported (2). Oral AN is characterized by extensive papillomatosis of the lips, palate, gingiva and tongue (3). Histologic analysis shows hyperkeratosis and irregular acanthosis, but no hyperpigmentation (2). Papillary hyperplasia of the epithelial lamina is also present (2-4,7,8). This report is based on a case of a patient suffering from oral AN and diagnosed with advanced invasive bladder papillary transitional cell carcinoma.

CASE REPORT

In September 2006, a 78-year-old woman was referred to the Department of Oral Medicine, School of Dental Medicine, University of Zagreb, Croatia, for evaluation of papillomatous lesions of the vestibular and buccal oral mucosa, lips and skin. Her medical history included diabetes mellitus and hipercholesterinemia as well as taking oral antidiabetics and antilipemic drugs. Two and a half years before oral lesions developed, the diagnosis of invasive papillary transitional cell carcinoma of the right bladder had been established. Due to the tumor recurrence, the patient was surgically treated four times within 2 years. The patient refused to undergo the indicated radiotherapy, and chemotherapy was not performed. Between the third and the fourth operation, she started to notice discomfort in the oral cavity. Shortly afterwards, due to developed changes on the oral mucosa, the patient was referred to a maxillofacial surgeon who took biopsies from the lower lip and hard palate.



Figure 1.a Papillomatous changes of the lips.

Histologic analyses showed fibrovascular papillomatous connective tissue covered by hyperkeratotic epithelium. These findings were consistent with the diagnoses of papilloma and fibroepithelial polyp.

Clinical examination at our Department revealed extensive papillomatous areas of normal mucosal color and soft consistency involving the lips (Fig. 1a), buccal mucosa (Fig. 1b) and hard palate. Verrucous changes with tiny pigmented macules were also present on the skin of the right ear auricle. The diagnosis of AN was established according to clinical and histologic findings and the patient's medical documentation.

The patient refused another biopsy due to general weakness. A swab for *Candida albicans* culture and cytobrush smear for human papilloma virus (HPV) detection were obtained from papillomatous lesions. *Candida albicans* was highly positive by semiquantitative evaluation according to the previously published Budz-Jørgensen's criteria (12). We prescribed two-week therapy with miconazole 2% oral gel. HPV DNA was not detected by using the polymerase chain reaction (PCR) technique on the cytobrush smear from papillomatous lesions. Isotretinoin (0.5%) in Orabase was prescribed for local therapy for its antiproliferative effect. The patient noticed slight improvement of oral lesions.



Figure 1.b Papillomatous changes of the buccal mucosa.



Figure 2. Decreased lesions of the lips after the fifth operation

By the end of 2006, the patient underwent her fifth operation for tumor recurrence. Following the surgery, oral lesions decreased (Fig. 2); however, in May 2007 the patient died from tumor recurrence and general weakness.

DISCUSSION

In this case report, a malignant form of AN appearing on the oral mucosa, perioral skin and skin of the right ear associated with advanced invasive bladder papillary transitional cell carcinoma is described. In previous reports, malignant AN has been most commonly associated with gastric adenocarcinoma (6-7,9,13-18). Carcinomas of the pancreas and biliary tract were also found (2,4,5). Other carcinomas such as those of the esophagus, bladder, testes, breast, uterus and lungs have been reported with less frequency. In the report by Cairo *et al.* (3), AN was associated with lung and bladder carcinoma in the same patient. As the latter was at an early stage, confined to the superficial bladder epithelium, it seems reasonable to hypothesize that the occurrence of malignant AN was more likely linked to lung carcinoma. Additional evidence may be the fact that AN progressed despite surgical eradication of the bladder tumor (3). Bottoni *et al.* (8) also report on malignant AN associated with lung carcinoma.

AN may involve any part of oral mucosa and extend to pharyngeal and esophageal mucous membranes (3). In previous reports, there has been only one case report describing malignant AN limited to buccal mucosa (19). Unlike skin lesions, oral AN seems to be rarely pigmented or not pigmented at all (1,2).

Approximately 40% of malignant AN showed oral lesions (20). During the 1968-1998 period, there were 14 cases of malignant AN involving oral cavity, as reported by Ramirez-Amador

et al. (2). Eight cases of malignant AN involving oral cavity published by Medline from 1999 to 2007 are shown in Table 1. Although the number of described cases in comparison with the number of cases reported by Ramirez-Amador *et al.* (2) has increased, gastric adenocarcinomas is still the most common associated malignancy (Table 2). Our assumption is that the discrepancy in the number of cases described in our report and those included in Ramirez's report is more likely to be due to the fact that we had an easier access to Internet browsing and literature data than to the actual increased prevalence of the disorder. According to our report (Table 1), in seven of eight cases malignancy was diagnosed after AN had developed. These data show the importance of the correct diagnosis of oral and cutaneous manifestations of AN and additional diagnostic procedures in the detection of internal malignancy. It has been recommended that patients with a clinical picture of AN, apart from routine hematological and biochemical analyses, should undergo chest x-ray, mammography, cervical cytology, prostate-specific antigen assay and possibly endoscopy of the complete gastrointestinal tract (4). Kleikamp *et al.* (6) found increased levels of the tumor markers CA 19-9, CA 72-4 and CEA in serum of a patient with malignant AN.

Histological analysis of the previous reports on AN in the oral cavity showed hyperkeratosis, acanthosis and finger-like structures of epithelial lamina (2-4). These histological findings correspond well to the histological data in our case.

In our patient, PCR typing of HPV showed no reactivity for HPV. In the study by Ramirez-Amador *et al.* (2), PCR typing of HPV showed weak reactivity for HPV type 35. Bottoni *et al.* (8) found no HPV using PCR technique. Other authors (13,16) found no HPV antigens using immunohistochemistry either. The result of Ramirez-Amador *et al.* may be considered as an incidental finding (2).

Since the lesions of malignant AN are clinically indistinguishable from the benign forms, this fact addresses the importance and necessity of additional diagnostic procedures in the detection of internal malignancy. In our case, a reduction of oral lesions was observed after operative cancer treatment, which was consistent with previous observations on AN to decrease following chemotherapy administration (5,9). The occurrence of clinical signs and/or aggravation of oral AN may suggest recurrence or metastasis of the primary tumor, as shown in our case.

Table 1. Oral acanthosis nigricans (AN) published by Medline 1999-2007

Author Year of publication (ref. no.)	Diagnosis of AN (before/ after diagnosis of malignancy)	Oral signs and symptoms	Other signs and symptoms	Associated malignancy
Ramirez-Amador <i>et al.</i> 1999 (2)	Before	Papillomatosis of upper vermillion and lip mucosa, buccal mucosa, hard and soft palate, gingiva and dorsum of the tongue	Discrete hyperpigmented cutaneous plaques; papillomatous lesions on the esophagus; palm hyperkeratosis	Gallbladder adenocarcinoma
Anderson <i>et al.</i> 1999 (9)	Before	Papillomatous lesions on perioral area and palate	Pruritus; generalized wartlike growths; papillomatous lesions of the eyelids; discharge and pain of perineum; acanthotic areas on the chest wall and nipples	Gastric adenocarcinoma
Bottoni <i>et al.</i> 2000 (8)	Before	Papillomatous and verrucous lesions on lips and mouth	Diffuse hyperpigmentation; hyperkeratosis of the nipples; papillomatous and verrucous lesions of the conjunctivae	Lung carcinoma
Scully <i>et al.</i> 2001 (4)	Before	Mild gingival swelling, diffuse thickening of lower labial mucosa	Generalized pruritic skin papules, of the axillae and groin; slightly keratotic palms and soles	Gallbladder adenocarcinoma
Cairo <i>et al.</i> 2001 (3)	Before	Papillomatosis of vestibular mucosa, dorsum of the tongue, palate and gingiva; burning sensations	Subtle changes on the neck skin, axillae, internal surface of the thighs, with hyperpigmented and thickened areas	Bladder and lung carcinoma
Pentenero <i>et al.</i> 2004 (7)	After	Papillomatosis of lips, buccal mucosa and palate; sore palate	Verrucous, slightly pigmented papules in the axillae and on the dorsal surface of the hand; small, brown hyperkeratotic exophytic lesions on the back	Gastric adenocarcinoma
McGinness and Greer 2006 (5)	Before	Verrucous papillomatous papules and plaques on the vermillion, buccal mucosa and tongue	Tripe palms	Pancreatic adenocarcinoma
Kleikamp <i>et al.</i> 2006 (6)	Before	Papillomatous to verrucous lesions of the lips and buccal mucosa	Hyperkeratosis of the palms and soles	Gastric adenocarcinoma

Table 2. Comparison of literature data according to the incidence of gastric adenocarcinoma during observation period

Author (ref. no.)	Period (yrs)	No. of acanthosis nigricans cases described	Incidence of associated gastric adenocarcinoma
Ramirez-Amador <i>et al.</i> (2)	30	14	6/14 (42%)
Canjuga <i>et al.</i>	8	8	3/8 (37.5%)

It is concluded that the occurrence of oral lesions may be an indicator of tumor progression.

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