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Oral Florid Papillomatosis Associated with Malignant Acanthosis Nigricans – a Case Report with a Review of the Literature

*Valentina Broshtilova[1], Tzetomila Vuteva[1], Vesel Kantardjiev[1], Mary Gantcheva[2,3]**

[1]Department of Dermatology and Venereology, Military Medical Academy, Sofia, Bulgaria
[2]Institute of Experimental Morphology, Pathology and Antropology with Museum, Bulgarian Academy of Science, Sofia
[3]Acibadem City Clinic Mladost, Sofia

*Corresponding author e-mail: mary_gant@yahoo.com

Oral florid papillomatosis is best defined as a type of verrucous carcinoma with local invasion and minimal dysplasia as well as a low incidence of metastases. Human papilloma virus infection is considered to trigger and perpetuate the disease, hence, its role in the the pathogenesis of the oncogenic process is still obscured. Herein, a very anecdotal case of HPV-driven oral florid papillomatosis in association with some clinical features of malignant acanthosisnigricans is presented. A comprehensive review of literature with a deductive clinical comparison of the two paraneoplastic syndromes is highlighted.

Key words: oral florid papillomatosis, HPV, paraneoplastic syndrome, acanthosis nigricans maligna, oral cavity

Introduction

Oral florid papillomatosis (OFP) is considered a locally aggressive form of verrucous carcinoma with a low metastatic potential. OFP affects predominantly the mouth; however, the larynx, nose, and genitalia can also be involved [5]. It manifests with cracking and enlargement of the lips, tongue and buccal mucosa. Interestingly, the oral form of acanthosis nigricans corresponds to the same clinical picture. Thus, the verification of the two prodromal neoplastic conditions is extremely difficult and relies only on histological grounds.

Herein, we report a case of OFP in association with darkening and thickening of the skin on the neck, clinically corresponding to acanthosis nigricans. A speculation on the probability of co-existence and common pathogenetic pathways of two paraneoplastic syndromes is presented.

Case Report

A 66-year-old man complained of verrucous lesion that appeared a month ago on the lips, oral commissures, buccal mucosa, and the tongue. He claimed on cracking of the lips, whitening of the tongue, and dry mouth. The lesions were sensitive when eating spicy food, which causes functional impairment. The patient noticed hoarsening of the voice with one-month duration and suffered dry cough for 4-5 months. He had a Covid-19 infection 7 months ago, after which he lost 5 kg from his body weight. He was a heavy smoker for more than 40 years.

On physical examination, confluent hyperplastic papules were detected on the buccal mucosa, oral commissures, lips and tongue. Hyperpigmented, velvet-like plaques extended on the flexular aspect of the neck. The distal phalanges of the fingers were thickened and larger (**Fig. 1**); there were accentuated dermatoglyphic ridges of the palms (**Fig. 2**). A 4-mm punch biopsy specimen of the buccal mucosa demonstrated pseudoepitheliomatous hyperplasia (**Fig.3**). The κeratinocytes were large, with centrally located nuclei and cytoplasm, filled with eosinophilic particles that stained positive with p16 (**Fig. 4**). Histological picture corresponds to HPV-associated epithelial lesion in the context of oral florid papillomatosis. A bronchoscopy verified a mild interstitial fibrosis with suspected tumor infiltration that required additional VATS (video-assisted thoracic surgery) examination. The patient was referred to thoracic surgery department for staging and appropriate treatment.

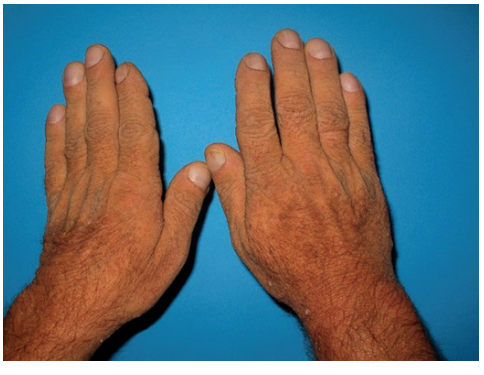


Fig. 1.

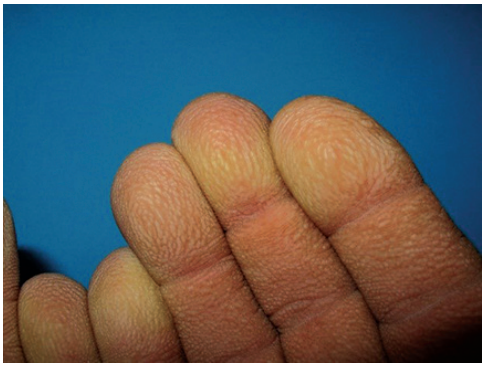
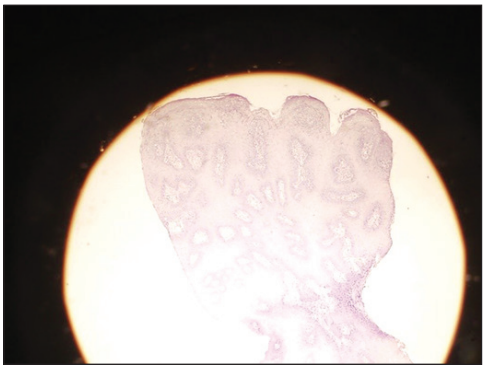


Fig. 2

Fig. 1. Raised formations, velvety white, rough thickening of the skin of the hands; enlargement of the distal parts of the tips of the nails and fingers.

Fig. 2. Velvety white, rough thickening of the skin of the palms with an emphasis on normal dermatoglyphic ridges.



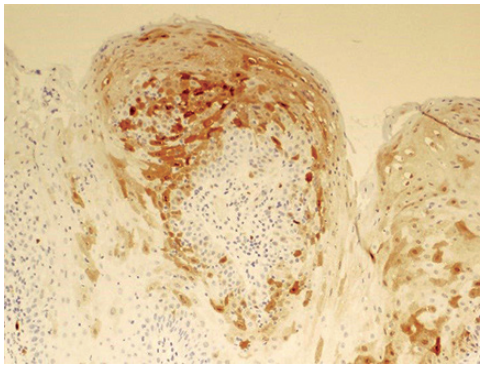


Fig. 3. **Fig. 4.**

Fig. 3. Pseudoepitheliomatous hyperplasia (H&E, x 200).

Fig. 4. Immunohistochemical staining for P16 is positive in 50% of the keratinocytes.

Discussion

OFP is a rare neoplasm that occurs in adults in their 4-5 decade with a very low incidence of 1-3 / 1 million persons each year [3, 7]. It was first reported by Lauren V. Ackerman under the term: oral verrucous carcinoma [11]. The condition represents an uncommon low-grade squamous cell carcinoma that is clinically evident as a slowly but relentlessly enlarging warty tumor, histologically characterized by local invasion with minimal, if any dysplasia, and biologically characterized by a low incidence of metastases. Even large, long-durated and infiltrative tumors do not evolve distant metastases [1].

The suspected pathogenetic factors encompass infection with human papillomavirus (HPV) and tobacco use. Perhaps, chemical and HPV viral co-carcinogens work together [12]. A number of HPV types are associated with squamous cell carcinoma, including HPV types 16 and 18 [6]. Hypothetically, the oncogenic potential of HPV exerts via two oncoproteins, E6 and E7 that promote the degeneration of p53 by means of a ubiquitin-dependent pathway. The E7 oncoprotein can similarly complexed with retinoblastoma (Rb) and inactivate it. OFP is a disease of cells that escape the control mechanisms of orderly cell growth and acquire the ability to proliferate and invade normal tissues [2].

Other risk factors are chronic inflammation or irritation, caused by poorly fitted dentures, alcoholism, immunosupression [3].

Surgical treatments for OFP are probably best and radiation therapy is generally considered a last resort. In oral verrucous carcinomas, irradiation is reported to produce highly malignant behavior with metastases, but some still use this treatment with confidence [3]. Safe therapeutic outcome with no evidence of anaplastic transformation after radiation is reported [13]. Many believe that radiation is an excellent choice for small and large oral and other types of verrucous carcinomas, with results comparable to surgery**.** Combined radiochemotherapy with vinblastine, methotrexate, and bleomycin is effective in the treatment of verrucous carcinoma of the head and neck [4]. It could be

successfully used with inoperable verrucous carcinoma or as an alternative to surgery. Photodynamic therapy using a topical application of 20% 5-aminolevulinic acid followed by multiple 3-min fractionated irradiations with a light-emitting diode (LED) red light may be an effective and successful treatment modality for oral verrucous carcinoma**.** Photodynamic therapy with systemic administration of the photosensitizer photocarcinorin proves to be equally beneficial. Bleomyciniontophoretic therapy, intra-arterial bleomycin, oral and intra-arterial methotrexate have been used with some success in small groups of OFP patients [9].

We report a clinical amalgam of OFP and acanthosis nigricans, evolving in the context of unspecified pulmonary malignancy. Acanthosis nigricans maligna (ANM) is a paraneoplastic syndrome, defined as a condition that arises in association with a malignancy elsewhere in the body but without malignant nature per se. It is a rare dermatopathy that occurs in men and women over age 40, without racial predilection or known familial association.

Clinically, ANM showed symmetric, hyperpigmented plaques with variable amounts of epidermal hypertrophy, ranging in color from yellow to brown or black, often with overlaid papillomas. The most common body sides affected are flexural zones and the posterior neck, but also mucosal surface involvement is frequent and may be the only clinical symptom present. Any mucosal surface can be involved, and as regards the oral cavity, disease affects the lips, tongue, palate, buccal and gingival mucosa.

ANM is primarily associated with adenocarcinomas. Accordingly, the progression of the tumor leads to ANM worsening, while tumor regress resorbs the skin changes [10]. The ANM suspected pathogenetic mechanism is related to a substance secreted either by the tumor or in response to the tumor, which closely correlates to transforming growth factor (TGF)-alpha that is structurally similar to epidermal growth factor. TGF-alpha and epidermal growth factor have been identified in lesional skin cells. Reports of urine and serum TGF-alpha levels normalizing after surgical tumor removal exist, with subsequent regression of skin lesions [8]. Remarkably, the oral form of ANM and OFP are clinically undistinguishable. Both conditions feature papillomatous proliferation, which is due to oversecretion of growth factors synthesis. The verification rests on identification of HPV inclusion bodies that are proven to present in our case by the p16 stain positivity.

The comparative analysis of the epidemiological, clinical and therapeutic characteristics of both entities is summarized on **Table 1**.

Table 1. Comparative analysis of the epidemiological, clinical and therapeutic characteristics

	Oral florid papillomatosis	**Acanthosis nigricans maligna**
Etiology	HPV 6,11,16,18,33	Paraneoplasia
Age	in adults	mostly in adults, but also in young
Manifestation	independent disease	paraneoplastic process

Table 1

	Oral florid papillomatosis	Acanthosis nigricans maligna
Localization	oral cavity, genitals, extremities	predilection sites (side parts of the neck, body folds, axillae, groin), oral cavity
Treatment	surgical excision, laser therapy, cryotherapy	underlying disease, local treatment, systemic treatment, surgical excision
Prognosis	poor	very bad/lethal

Conclusions

The reported association of OFP and ANM is a rare combination of peculiar paraneoplastic syndromes that requires thorough systemic work-up to verify underlying malignancy. The clinical similarities can be related to the overexpression of growth factors caused either by the neoplastic process or by the viral-induced keratinocytic hyperproliferation. Dermatological prodromes should be well-identified and rapidly diagnosed, since they facilitate an early identification of the related malignancy. Accummulation of clinical cases may further elucidate the intimate pathogenetic mechanisms and give some helpful clues for more specific verification of the underlying process.

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