Correlated improvement of mucosal malignant acanthosis nigricans and metastatic urothelial carcinoma with oncologic therapy

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Key words: acanthosis nigricans; malignant acanthosis nigricans; mucosal; mucosal papillomas; oral; paraneoplastic; squamous papillomas.

INTRODUCTION

Malignant acanthosis nigricans (AN) is a rare paraneoplastic phenomenon, most often associated with underlying gastrointestinal malignancy.[1,2] There are several reports of this entity and its diagnostic challenges in the literature,[3-10] but the course of cutaneous manifestations is not well-defined, making it difficult to counsel patients regarding potential clinical outcomes. In this article, we report a case of malignant AN, presenting as mucosal papillomatosis, with near-complete resolution correlated with treatment of the underlying malignancy.

Abbreviation used:

AN: acanthosis nigricans

CASE REPORT

An 87-year-old woman presented to the dermatology clinic with a 4-month history of rapid-onset, verrucous papules coalescing into plaques involving the lower portion of the left eyelid margin, vermilion upper lip, oral commissures, tongue, buccal mucosa, hard palate, and posterior aspect of oropharynx (Fig 1, *A* to *C*). There were no significant findings in the palms or intertriginous sites. She reported that in the previous year, she had similar papules on the bilateral ocular conjunctiva that recurred despite cryotherapy and serial excisions. Pathology of the eyelid specimens showed benign squamous papillomas.

Her medical history was significant for a high-grade papillary urothelial carcinoma of the urinary tract and kidney 15 years prior to the presentation to dermatology. She underwent cisplatin-based chemotherapy and nephrectomy with remission for 14 years. At the time of our initial evaluation, her review of systems was unremarkable. Skin biopsy at the oral commissure was performed, which revealed a benign squamous papilloma. In situ hybridization studies for human papillomavirus, both high- and low-risk types, were negative.

Given the clinical concerns for mucosal malignant AN, an extensive evaluation was performed to screen for underlying malignancy. Complete blood count, metabolic panel, lactate dehydrogenase, and serum protein electrophoresis were unremarkable. Computed tomography scan of the chest, abdomen, and pelvis revealed enlarged para-aortic and left supraclavicular lymph nodes. There was no palpable cervical lymphadenopathy during her initial oncology evaluation, 1 month after presentation to dermatology. Positron emission tomography scan showed increased uptake in the hard palate and upper lip, cervical, left supraclavicular and periaortic lymph nodes (Fig 1, *D*), and diffusely in the esophagus and sigmoid colon. Biopsies obtained from the proximal and distal esophagus during esophagogastroduodenoscopy revealed squamous papillomas. Biopsy of the left supraclavicular and periaortic lymph nodes demonstrated metastatic urothelial carcinoma.

The patient underwent 1 cycle of carboplatin-gemcitabine, but multiple systemic toxicities developed in her, and this was discontinued. She

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Fig 1. A to C, Involving the lower portion of the left eyelid margin, upper vermilion lip, oral commissures, hard palate, and posterior aspect of oropharynx, there are numerous verrucous papules coalescing into plaques. **D,** The positron emission tomography scan report shows that there is dramatic hypermetabolic activity of the left supraclavicular lymph nodes.

transitioned to pembrolizumab and completed 2 cycles. We prescribed topical tretinoin 0.025% cream, which she applied nightly to the vermilion upper lip. Six months from initial dermatology evaluation, the findings on the hard palate, buccal mucosa, tongue, posterior aspect of the oropharynx and upper lip had significantly improved (Fig 2, *A* to *C*). The inferior eyelid conjunctival papillomas improved but persisted. After a third dose of pembrolizumab, repeat positron emission tomography scan demonstrated no abnormal metabolic uptake (Fig 2, *D*), consistent with no evidence of disease.

DISCUSSION

Classically, AN presents as hyperpigmented, velvety, or verrucous plaques in intertriginous sites and is a cutaneous manifestation of endocrinopathies including insulin resistance and diabetes mellitus.[2] Rarely, AN represents a paraneoplastic phenomenon; this can be characterized by various clinical manifestations including the classic velvety hyperpigmented plaques and mucosal papillomatosis, and can be accompanied by other paraneoplastic signs, including tripe palms or the sign of Leser-Trélat.[1-3,6,9,10] The pathophysiology of malignant AN is not entirely clear, but may be related to growth factors, including insulin-like growth factor and transforming growth factor-β, secreted from tumors.[1,2] Mechanistically, the cutaneous findings should resolve with regression of the underlying malignancy.

This case helps to establish a correlation between successful oncologic treatment and resolution of mucosal papillomas, which can be functionally and cosmetically problematic. Of the reported cases of malignant AN, several describe clinical improvement with treatment of the underlying malignancy.[4,6,8,10] Others document attempted treatment of the cutaneous findings with oral retinoids,[3,6,7,9] UV light therapy,[9] and/or methotrexate[7] with variable outcomes. There are also several reports that do not comment on the course of cutaneous findings, in some cases due to rapid clinical deterioration and ultimately patient death.[5,7] In our case, the patient's malignant AN resolved with treatment of the underlying malignancy. Because we were able to evaluate her clinical findings before her next scheduled surveillance imaging, we speculated that her cutaneous improvement would predict oncologic improvement as well. This was proven to be accurate on her

Fig 2. A to C, After 1 cycle of gemcitabine-cisplatin and 2 cycles of pembrolizumab, the oral lesions resolved. Eyelid lesions improved but were still present. **D,** The positron emission tomography scan report shows that there is resolution of hypermetabolic activity in the left supraclavicular lymph nodes.

surveillance positron emission tomography scan, which showed no evidence of disease.

Improvement of malignant AN may indicate cancer response to therapy prior to imaging surveillance confirmation. The sudden onset of cutaneous or mucosal papillomas should raise suspicion for underlying malignancy and neoplastic evaluation should be performed without delay.

Conflicts of interest

None disclosed.

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