To the Editor:
A 40-year-old Somalian man presented to the dermatology clinic with lesions on the eyelids, tongue, lips, and hands of 8 years’ duration. He was a former refugee who had faced considerable stigma from his community due to his appearance. A review of systems was remarkable for decreased appetite but no weight loss. He reported no abdominal distention, early satiety, or urinary symptoms, and he had no personal history of diabetes mellitus or obesity. Physical examination demonstrated hyperpigmented velvety plaques in all skin folds and on the genitalia. Massive papillomatosis of the eyelid margins, tongue, and lips also was noted (Figure 1A). Flesh-colored papules also were scattered across the face. Punctate, flesh-colored papules were present on the volar and palmar hands (Figure 2A). Histopathology demonstrated pronounced papillomatous epidermal hyperplasia with negative human papillomavirus (HPV) type 16 and HPV-18 DNA studies. Given the appearance of malignant acanthosis nigricans with oral and conjunctival features, cutaneous papillomatosis, and tripe palms, concern for underlying malignancy was high. Malignancy workup, including upper and lower endoscopy as well as serial computed tomography scans of the chest, abdomen, and pelvis, was unrevealing.

Laboratory investigation revealed a positive Schistosoma IgG antibody (0.38 geometric mean egg count) and peripheral eosinophilia (1.09 ×10³/μL), which normalized after praziquantel therapy. With no malignancy identified over the preceding 6-month period, treatment with acitretin 50 mg daily was initiated based on limited literature support.1-3 Treatment led to reduction in the size and number of papillomas (Figure 1B) and tripe palms (Figure 2B) with increased mobility of hands, lips, and tongue. The patient underwent oculoplastic surgery to reduce the papilloma burden along the eyelid margins. Subsequent cystoscopy 9 months after the initial presentation revealed low-grade transitional cell carcinoma of the bladder. Intraoperative mitomycin C led to tumor shrinkage and, with continued treatment with daily acitretin, dramatic improvement of all cutaneous and mucosal symptoms (Figure 1C and Figure 2C). To date, his cutaneous symptoms have resolved.

This case demonstrated a unique presentation of multiple paraneoplastic signs in bladder transitional cell carcinoma. The presence of malignant acanthosis nigricans (including oral and conjunctival involvement), cutaneous papillomatosis, and tripe palms have been

**PRACTICE POINTS**

- Paraneoplastic conditions may present secondary to urologic malignancy. Providers should perform thorough malignancy screening, including urologic cystoscopy, in patients presenting with paraneoplastic signs and no identified malignancy.
- Oral retinoids, such as acitretin, may be used as an adjuvant treatment to treat paraneoplastic cutaneous symptoms. The definitive treatment is malignancy management.
individually documented in various types of gastric malignancies. Acanthosis nigricans often is secondary to diabetes and obesity, presenting with diffuse, thickened, velvety plaques in the flexural areas. Malignant acanthosis nigricans is a rare, rapidly progressive condition that often presents over a period of weeks to months; it almost always is associated with internal malignancies. It often has more extensive involvement, extending beyond the flexural areas, than typical acanthosis nigricans. Oral involvement can be either hypertrophic or papillomatous; papillomatosis of the oral mucosa was reported in over 40% of malignant acanthosis nigricans cases (N=200). Cases with conjunctival involvement are less common. Although malignant acanthosis nigricans often is codiagnosed with a malignancy, it can precede the cancer diagnosis in some cases. A majority of cases are associated with adenocarcinomas of the gastrointestinal tract. Progressive mucocutaneous papillomatosis also is a rare paraneoplastic condition that most commonly is associated with gastric adenocarcinomas. Progressive mucocutaneous papillomatosis often presents rapidly as verrucous growths on cutaneous surfaces (including the hands and face) but also can affect mucosal surfaces such as the mouth and conjunctiva. Tripe palms are characterized by exaggerated dermoglyphics with diffuse palmar ridging and hyperkeratosis. Tripe palms most

FIGURE 1. A–C, Progressive mucocutaneous papillomatosis and oral/conjunctival malignant acanthosis nigricans at initial presentation, after 4 months of treatment with acitretin 50 mg daily, and 6 weeks following intraoperative mitomycin C after 9 months of continued treatment with daily acitretin.

FIGURE 2. A–C, Tripe palms on initial presentation, after 4 months of treatment with acitretin 50 mg daily, and 6 weeks following intraoperative mitomycin C after 9 months of continued treatment with daily acitretin.
often are associated with pulmonary malignancies. When
tripe palms are present with malignant acanthosis nigri-
cans, they reflect up to a one-third incidence of gastroin-
testinal malignancy.12,13

Despite the individual presentation of these para-
e neo pelagic signs in a variety of malignancies, synchronous
presentation is rare. A brief literature review only identified
6 cases of concurrent acanthosis nigricans, tripe palms,
and progressive mucocutaneous papillomatosis with an
underlying gastrointestinal malignancy.1,11,14-17 Two addi-
tional reports described tripe palms with oral acanthosis
nigricans and progressive mucocutaneous papillomatosis
in metastatic gastric adenocarcinoma and renal urothelial
carcinoma.7,18 An additional case of all 3 paraneoplastic
conditions was reported in the setting of metastatic
cervical cancer (HPV positive).39 Per a recent case report
and literature review,20 there have only been 8 cases of
acanthosis nigricans reported in bladder transitional cell
carcinoma,20-27 half of which have included oral malignant
acanthosis nigricans.20-23 Only one report of concurrent
cutaneous and oral malignant acanthosis nigricans and
tri pe palms in the setting of bladder cancer has been
reported.20 Given the extensive conjunctival involvement
and cutaneous papillomatosis in our patient, ours is a
rarely reported case of concurrent malignant mucocuta-
n eous acanthosis nigricans, tripe palms, and progressive
papillomatosis in transitional cell bladder carcinoma. We
believe it is imperative to consider the role of this malig-
nancy as a cause of these paraneoplastic conditions.

Although these paraneoplastic conditions rarely co-
 occur, our case further offers a common molecular
pathway for these conditions.28 In these paraneoplastic
conditions, the stimulating factor is thought to be tumor
growth factor α, which is structurally related to epidermal
growth factor (EGF). Epidermal growth factor receptors
(EGFRs) are found in the basal layer of the epidermis,
where activation stimulates keratinocyte growth and
leads to the cutaneous manifestation of symptoms.28
Fibroblast growth factor receptor 3 mutations are found in
most noninvasive transitional cell tumors of the bladder.29
The fibroblast growth factor pathway is distinctly differ-
ent from the tumor growth factor α and EGF pathways.30
However, this association with transitional cell carcinoma
suggests that fibroblast growth factor receptor 3 also may
be implicated in these paraneoplastic conditions.

Our patient responded well to treatment with
acitretin 50 mg daily. The mechanism of action of retinoids
involves inducing mitotic activity and desmosomal shed-
ing.31 Retinoids downregulate EGFR expression and
activation in EGF-stimulated cells.32 We hypothesize that
these oral retinoids decreased the growth stimulus and
thereby improved cutaneous signs in the setting of our
patient’s transitional cell cancer. Although definitive ther-
apy is malignancy management, our case highlights the
utility of adjunctive measures such as oral retinoids and
surgical debulking. While previous cases have reported
use of retinoids at a lower dosage than used in this case,
oral lesions often have only been mildly improved with
little impact on other cutaneous symptoms.1,2 In one case
of malignant acanthosis nigricans and oral papilloma-
tosis, isotretinoin 25 mg once every 2 to 3 days led to a
moderate decrease in hyperkeratosis and papillomas, but
the patient was lost to follow-up.3 Our case highlights
the use of higher daily doses of oral retinoids for over 9
months, resulting in marked improvement in both the
mucosal and cutaneous symptoms of acanthosis nigri-
cans, progressive mucocutaneous papillomatosis, and
tri pe palms. Therefore, oral acitretin should be considered
as adjuvant therapy for these paraneoplastic conditions.

By reporting this case, we hope to demonstrate the
importance of considering other forms of malignancies
in the presence of paraneoplastic conditions. Although
gastric malignancies more commonly are associated with
these conditions, bladder carcinomas also can present
with cutaneous manifestations. The presence of these
paraneoplastic conditions alone or together rarely is
reported in urologic cancers and generally is considered
to be an indicator of poor prognosis. Paraneoplastic con-
ditions often develop rapidly and occur in very advanced
malignancies. The disfiguring presentation in our case
also had unusual diagnostic challenges. The presence of
these conditions for 8 years and nonmetastatic advanced
malignancy suggest a more indolent process and that
these signs are not always an indicator of poor prognosis.
Future patients with these paraneoplastic conditions may
benefit from both a thorough malignancy screen, includ-
ing cystoscopy, and high daily doses of oral retinoids.

REFERENCES

Malignant acanthosis nigricans, florid cutaneous papillomatosis and
tri pe palms syndrome associated with gastric adenocarcinoma. Postepy

2. Lee HC, Ker KJ, Chong W-S. Oral malignant acanthosis nigricans and
tri pe palms associated with renal urothelial carcinoma. JAMA Dermatol.
2015;151:1381-1383.

3. Swineford SL, Drucker CR. Palliative treatment of paraneoplastic acan-
thosis nigricans and oral florid papillomatosis with retinoids. J Drugs

4. Wick MR, Patterson JW. Cutaneous paraneoplastic syndromes
[published online January 31, 2019]. Semin Diagn Pathol. 2019;
36:211-228.


7. Curth HO. Dermatoses and malignant internal tumours. Arch Dermatol

8. Krawczyk M, Mykala-Ciśle J, Kołodziej-Jaskula A. Acanthosis nigri-
cans as a paraneoplastic syndrome: case reports and review of literature.

tosis with adenocarcinoma of stomach in a 35 year old male. Indian J

papillomatosis: mucocutaneous markers of an underlying gastric

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