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**Photo Vignette**

**Three paraneoplastic signs in the same patient with gastric adenocarcinoma**

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**Abstract**

This is the report of a 76-year-old male with typical lesions of acanthosis nigricans maligna (ANM), florid cutaneous papillomatosis (FCP), and tripe palms (TP) for 2 years. He did not have any gastrointestinal complaints. Pathologic findings of skin supported the diagnosis of ANM. Because gastric adenocarcinoma is the most common neoplasm associated with these paraneoplastic dermatoses, further tests were carried out. Endoscopic examination was performed and an adenocarcinoma of the esophagogastric junction was confirmed. Meanwhile, multiple small polyps in the middle and the lower thirds of the esophagus were observed. The patient was referred for further evaluation and subsequent surgical resection of the tumor.

Acanthosis nigricans (AN) is a hyperkeratotic mucocutaneous eruption of heterogenous etiology, which is characterized by hyperpigmentation, velvety cutaneous thickening, intensified skin markings, and development of verrucous excrescences typically involving the intertriginous areas. AN is classified into benign and malignant forms on the basis of clinical associations. Malignant acanthosis nigricans (MAN) tends to be extensive and involves mucosal surfaces, mostly in elderly people. Florid cutaneous papillomatosis (FCP), also known as the Schwartz-Burgess syndrome, is characterized by the rapid appearance of multiple verrucous lesions that are clinically indistinguishable from common warts [1]. Tripe palms (TP) is characterized by diffuse, yellowish palmar hyperkeratosis, with enhancement of the epidermal ridges on the hands (dermatoglyphics), resembling intestinal villousities [1]. The association of these three paraneoplastic dermatoses (FCP, ANM and TP) in the same patient has been reported. Herein, we report an elderly male with three paraneoplastic dermatoses for two years. On the initial presentation, he did not report any systemic complaints; diagnostic tests confirmed the presence of a gastric adenocarcinoma.

**Case synopsis**

A 76-year-old man presented with a 30-year history of depigmentation of the skin on his head, trunk, and upper limbs. The lesions began on the trunk, particularly on the nape, and subsequently occurred on his head and upper limbs. Two years prior to presentation, the skin on his face and intertriginous areas began to become thickened, coarse, and hyperpigmented. He ignored these changes and did not accept any treatments. Six-month prior to presentation, papillomatous to verrucous plaques of the lips and buccal oral mucosa and hyperkeratosis of the palms and soles appeared. Meanwhile, the pain from his tongue troubled him, so he visited the oral medicine department in a local hospital and was diagnosed with papillary hyperplasia of

squamous epithelium. Subsequently, the patient accepted intramuscular injection of interferon, which was prescribed by a dermatologist whose diagnosis was multiple verrucae, based on clinical appearance. He noted a little improvement of pain from his tongue. His past history revealed no previous illnesses and no drug allergy. He was in good clinical condition without fever, weight loss or dysphagia. He did not have any familial history of endocrine disorders.

On physical examination, the patient presented with a dirty-looking appearance with diffuse brownish hyperpigmentation and velvety thickening, typically located in skin folds. There were many irregular depigmented patches on his head and trunk. Hyperpigmented velvety plaques were present on the face, neck, axillae, umbilicus, groin, sacroiliac area, and the dorsal aspects of his hands and feet (**Figure.1a-e**). Many soft papillomas and warty nodules studded the affected surface. The lesions were 3-5 mm sized, skin-colored to dark brown, verrucous papules and a few of these were flat with a "stuck on" appearance, morphologically resembling seborrhoeic keratoses. Some lesions were acuminate and morphologically resembled verrucae vulgaris. A diffuse velvety thickening and prominent ridges of the palms and soles were noted. Thickening and papillation without hyperpigmentation was evident on the lips, gingiva, and hard plate. The tongue was thickened and furrowed.

Histopathologic examination of the plaque (**Figure 2a**) and papillomas (**Figure 2b**) on the face revealed an increased number of melanocytes with papillary hypertrophy and hyperkeratosis, which were compatible with the histopathology findings of AN and FCP, respectively.

Based on clinical and histopathology features, the patient was diagnosed as having malignant AN, TP, and FCP. Classical clinical features of these paraneoplastic syndromes prompted us to investigate the patient, although he was completely asymptomatic. The patient was admitted to our department for further examination. The laboratory findings including liver function test, urinary function test, thyroid function tests, and electrolytes were all within the normal range. Serological tests for syphilis, HIV, HBsAg, and HCV were negative. Tumor markers including alpha-fetoprotein showed a normal range. Chest X-ray and ECG were normal.

In view of the strong suspicion of gastrointestinal malignancy, upper gastrointestinal tract (GIT) endoscopy was performed and revealed multiple protruding lesions showing epithelial hyperplasia of the esophagus. On the posterior side of the cardiac area, a mass measuring approximately 2.5 cm in diameter, with central ulceration, suggestive of a gastric tumor was observed. A biopsy was performed and revealed a gastric adenocarcinoma. No metastases were detected elsewhere. The patient was transferred to department of surgery for gastrectomy.

## Discussion

ANM is a well-known paraneoplastic dermatosis that accounts for 20% of all AN cases. There is extensive mucocutaneous involvement and rapid progression in association with a visceral malignant tumor, usually a gastric adenocarcinoma [1-3]. Because the tumors associated with MAN are highly malignant, it is of the utmost importance to recognize the condition in adults. If the diagnosis of malignant acanthosis nigricans is suspected, a vigorous effort must be made to identify the responsible tumor. Most importantly, it often precedes the diagnosis of a new or recurrent tumor. In our case, the skin changes preceded the detection of malignancy by 2 years, during which the skin lesions progressed, although the patient was still in good health.

FCP, characterized by the rapid appearance of multiple verrucous lesions, are clinically indistinguishable from common warts. However, the histology of these lesions shows pronounced hyperkeratosis, irregular acanthosis, and serrated papillomatosis. Vacuolation in the upper epidermis, parakeratosis or eosinophilic inclusions, the features suggestive of verruca vulgaris, are generally absent. Our histopathologic findings indicated no evidence of a papillomavirus etiology of the warty skin lesions.

FCP is an obligatory paraneoplastic syndrome always associated with an internal malignancy. The most common of its associations is gastric adenocarcinoma. Its association with ANM is one of several of its features that support its legitimacy as a true paraneoplastic disorder. The oral cavity and lips can be affected by florid papillary growths. The occurrence of oral lesions may be an indicator of tumor progression [4]. The severity of oral changes correlates with tumor progression.

Moreover, in our case, the esophagus had been involved, which presented with multiple protruding lesions showing epithelial hyperplasia.

Tripe palms is a descriptive term of acanthosis nigricans of the palms, which are clinically characterized by the presence of thickened, velvety plaques with pronounced dermatoglyphics. It is usually associated with ANM, and in most cases with an underlying malignancy [5]. Its recognition should prompt a full diagnostic work-up for tumor.

The association of these three paraneoplastic dermatoses (FCP, ANM, and TP) in the same patient, apparently with a common pathogenic mechanism, is noteworthy [1]. The etiopathogenesis of ANM, as well as FCP and TP, remains to be fully clarified. Several investigators have suggested that a tumor-produced humoral factor could possibly play a role in the development of these conditions. A current hypothetical mechanism is the secretion of large amounts of transforming growth factor alpha (TGF- $\alpha$ ) by the tumor into the circulation that is thought to stimulate keratinocyte growth via an endocrine route [3,5-7]. The common pathogenic pathway of the disease is the activation of tyrosine kinases, which exert mitogenic and antiapoptotic effects on the keratinocytes [8]. Various peptides, such as urogastrone, ACTH, human growth hormone, and thyroid-stimulating hormone, have also been implicated as being potentially causative factors. Vitiligo and adenocarcinoma of the stomach may have occurred in this patient by chance. It is, however, there is a possible relationship between the widespread vitiligo and adenocarcinoma. Sidi et al believed that the late occurrence of vitiligo in an elderly patient maybe an early heralding sign of a malignancy [9,10].

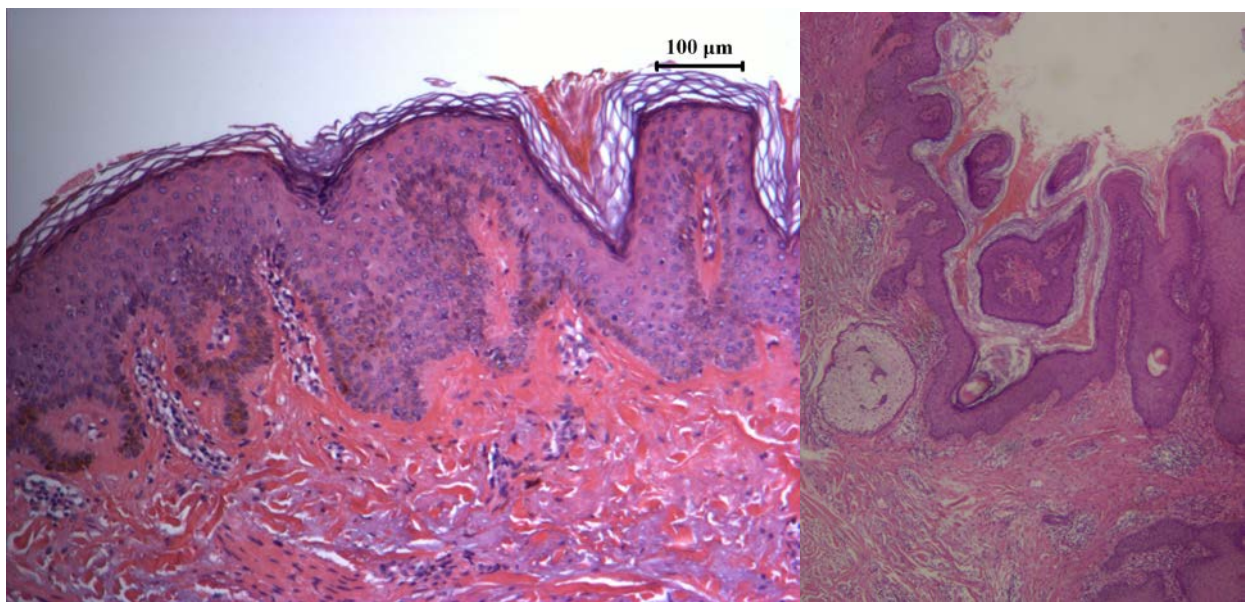
Our case highlights the coexistence of these cutaneous markers of internal malignancy thereby necessitating a thorough search for the underlying primary malignancy. Early recognition of these cutaneous hallmarks offers an opportunity for early diagnosis, treatment of the internal malignancy, and monitoring for tumor recurrence.





**Fig.1** Clinical manifestations of the patient. **a.** Dirty-looking appearance with diffuse hyperpigmentation and velvety thickening on his face. **b.** The thickened and furrowed tongue. **c.** many irregular depigmented patches on his head and trunk. **d.** Diffuse velvety thickening and prominent ridges of the palms. **e.** Many soft papillomas and warty nodules studded on the back of hands.





**Fig.2** Histopathologic examination of the plaque (a) and papilloma (b) on the face revealed an increased number of melanocytes, with papillary hypertrophy and hyperkeratosis.

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