

## Case report

# Oral malignant acanthosis nigricans associated with serous endometrial carcinoma: a case report and review of the literature

## 漿液性子宮內膜癌伴口腔惡性黑棘皮病的一宗病例報告暨文獻綜述

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Malignant acanthosis nigricans is a paraneoplastic cutaneous syndrome. Clinical findings such as tripe palms and mucocutaneous papillomatosis in atypical sites such as the oral mucosa are strong indicators of a visceral malignancy. We report on a rare case of oral acanthosis nigricans who presented with a 2.5-month history of diffuse hyperkeratotic verrucous papillomatous lesions in the entire oral mucosa which were symptomatic only when eating. Based on the clinical and histopathological findings, acanthosis nigricans with serous type endometrial carcinoma was diagnosed. However; the patient defaulted follow-up after the diagnosis and she died two months later.

惡性黑棘皮病是一種腫瘤伴生皮膚綜合症。臨床發現如牛胃掌和非典型部位（如口腔黏膜）的黏膜皮膚乳頭狀瘤症，是內臟惡性腫瘤的有力指標。我們報告了一個罕見的口腔黑棘皮病病例，患者整個口腔粘膜炎中有瀰漫性過度角化性疣狀乳頭狀病變，為時兩個半月，僅在進食時才有不適。根據臨床和組織病理學發現，最終被診斷為黑棘皮病伴隨漿液性子宮內膜癌。然而，該患者診斷後未有依時覆診，並在兩個月後身故。

**Keywords:** Endometrial carcinoma, malignant acanthosis nigricans, tripe palms

關鍵詞：子宮內膜癌、惡性黑棘皮病、牛胃掌

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## Introduction

Acanthosis nigricans (AN) consists of reactive changes and be divided into two forms: Benign AN, which is frequently induced by endocrine disorders or medications, and malignant AN (MAN), which is rare and associated with malignancies. It is characterised by dark pigmented, velvety thickening of the skin observed symmetrically in the flexural areas of the skin such as axilla, inguinal and cervical

areas.<sup>1</sup> MAN is a paraneoplastic cutaneous syndrome, which is most often associated with gastric adenocarcinomas. Paraneoplastic findings such as tripe palms and excessive mucocutaneous papillomatosis that occur in atypical locations such as oral mucosa are strong indicators of a visceral malignancy.<sup>1</sup>

We report a case of MAN in association with serous endometrial carcinoma. This has not been reported in the literature previously.

## Case report

A 65-year-old female presented with an acute onset of intraoral swelling that emerged 2.5 months ago to dermatology outpatient clinic. She was diagnosed with diabetes mellitus three years previously and was treated with insulin lispro (humalog 100 IU/ml sc). There was no other significant past medical, drug or family history of malignancy. Patient stated she attended our clinic for the first time and had not received any treatment in the previous 2.5 months. She stated that there was discomfort while she was eating and as a result, she avoided consuming solid food. There was no history of weight loss, fever, night sweating, or weakness.

On examination, there were non-pigmented hyperkeratotic verrucous papillomatous lesions in the entire oral mucosa from vermilion border of upper and lower lips, extending along the buccal mucosa, gingiva and dorsum of tongue. There were findings consistent with tripe palms including exaggerated dermatoglyphic areas in both palms and multiple wart-like verrucous papillomatous lesions on dorsum of the hand (Figure 1). Nail examination and all other systems examinations were normal. Velvety hyperpigmented and hyperkeratotic plaques were observed in bilateral axillary areas and inguinal folds (Figure 2). Routine biochemistry tests, fasting blood glucose, thyroid function tests and viral serology tests were within normal limits. Fasting blood sugar: 143 mg/dl,

HbA1c: 44.72 mmol/mol (normal range: 20-44), Alanine Aminotransferase (ALT): 17 U/L, Alkaline Phosphatase (ALP): 32 U/L; HIV, syphilis and hepatitis serology values were negative. The carcinoembryonic antigen (CEA), alpha fetoprotein (AFP) and carbohydrate antigen (CA) 19-9 were within normal limits while Ca 15-3: 378.6 U/ml (normal range: 0-32.4) and Ca 125: 1789.1 U/ml (normal range: 0-30) levels were elevated. Computed tomography of the abdomen showed increased uterus size, multiple calcifications and soft tissue areas consistent with lymphadenopathy in paraaortocaval area and parailiac spaces. PET/CT studies revealed a severely thickened uterine wall with markedly increased hypermetabolic activity from uterine cavity to the cervix and multiple lymph node involvements were detected. It was therefore reported that a primarily gynaecological malignancy should be considered.

Two punch biopsy samples were taken from axillary and buccal lesions of the patient. Histological examination showed prominent acanthosis, hyperkeratosis, papillomatous with minimal subepithelial inflammation (Figure 3).

As the clinical and histopathological findings were consistent with MAN, a gastroenterology consultation was requested. Endoscopy and colonoscopy findings were normal. Patient was also referred to the gynaecology department for evaluation of gynaecological malignancy. However, the patient refused any intervention or treatment. Patient presented to our outpatient clinic with abdominal swelling approximately three months later. Ascites in the abdomen was detected during physical examination and nodular masses. After review by the gynaecology department, USG and abdominal tomography detected calcification in some of the nodular masses in the endometrial cavity. Biopsy findings of these lesions was consistent with stage 4 serous endometrial carcinoma. The patient defaulted follow-up appointments for treatment after the diagnosis and she died two months later.

## Discussion

Malignant acanthosis nigricans associated with abdominal malignancy was first reported by Pollitzer in 1890.<sup>1</sup> MAN is very rare compared to the benign form. Although most frequently associated with gastric adenocarcinoma, MAN can be associated with several intra-abdominal malignancies such as pancreas, ovarian, bladder, cervix, endometrial, and esophageal malignancies.<sup>2</sup>

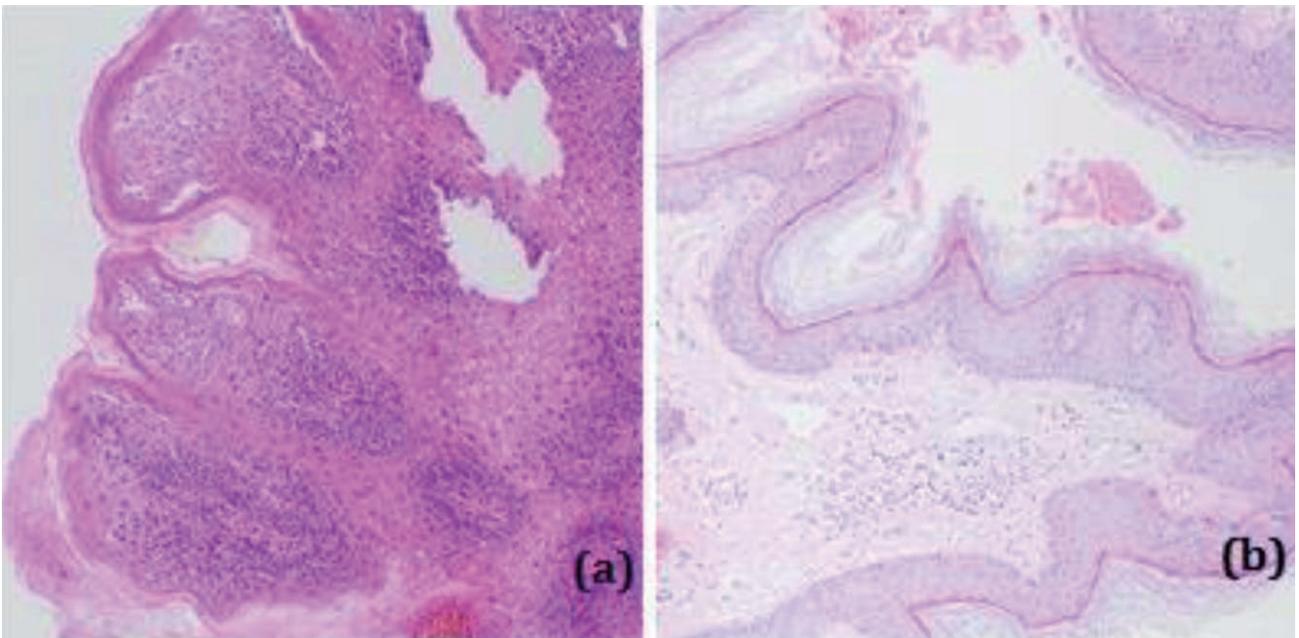
The pathogenesis of excessive verrucous papillomatous formations in mucocutaneous areas in MAN which is considered to be due to epidermal hyperproliferation emerging from stimulation by Insulin-like-growth-factor 1 (IGF-1), Transforming Growth Factor (TGF- $\alpha$ ) and Epidermal Growth Factor (EGF).<sup>1,2</sup> Tripe palms is characterised by prominent dermatoglyphics and with rugose hyperkeratotic areas likened to stomach lining of beef in the palmar area and is regarded as a



**Figure 1.** (a,b) Papillomatous and velvety oral lesions. (c) Multiple wart-like verrucous papillomatous lesions on the dorsum of the hand. (d) Tripe palms consisting of exaggerated dermatoglyphic areas in the palmar region.



**Figure 2.** (a) Velvety hyperpigmented and hyperkeratotic plaques in bilateral axillary areas and (b) inguinal folds.



**Figure 3.** (a) Oral specimen shows, acanthosis, papillomatous and minimal subepithelial inflammation (H&E x 100). (b) Axillary biopsy: Epidermal hyperkeratosis and dermal finger-like papillomatous hyperplasia (H&E x 100).

variant of AN. It accompanies paraneoplastic malignancies at a rate of 90%, most notably and frequently gastric cancers.<sup>2</sup> The clinical diagnosis can be confirmed with skin biopsy. It does not have any specific histopathological findings but it can be frequently accompanied by hyperkeratosis, papillomatosis and hyperpigmentation at basal layer.<sup>2</sup> Endometrial cancer (EC) is the most frequently associated gynaecological malignancy and can be divided into two groups: Type 1 EC has good prognosis while type 2 EC (serous and clear cell carcinoma) is very aggressive although it is very rare and seen frequently in women with older age.<sup>3</sup>

As far as we know, our case is the first MAN case accompanied by serous type EC. Oral MAN cases accompanied by gynaecological malignancies in the literature are summarised in Table 1. It is resistant to conventional treatments such as systemic

corticosteroids, etretinate, topical corticosteroids, calcipotriol and salicylic acid. The most efficacious treatment method is treatment of the underlying primary cancer with subsequent regression of the cutaneous findings.<sup>2</sup> The clinicians' role is to detect acanthosis nigricans and tripe palms as early indicators and precursors of cancer. A high index of suspicion for malignancy, in particular abdominal malignancy with the appropriate screening is essential.

## References

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**Table 1.** Previously reported cases of oral malignant acanthosis nigricans associated with gynaecological malignancies

Article	Patient	Clinic presentation	MAN locations	Malignancy
Dingley <sup>4</sup> 1957	56/F	Dry, sore tongue	Axillae, face, oral involvement, palms and soles, arms, legs	Ovarian adenocarcinoma
Mikhail <sup>5</sup> 1979	58/F	Wart-like growth on the perineal region	Oral, face, axillae, palmoplantar, vulvar, perineal region	Cervical squamous cell carcinoma
Gorisek <sup>6</sup> 1997	54/F	Postmenopausal menorrhagia	Oral involvement, tripe palms, axilla, inframammary region, abdominal folds, inguinal and forearms	Endometrial adenocarcinoma
Kebria <sup>7</sup> 2006	52/F	Leser Trélat sign and weight loss	Oral involvement, neck, axillae, inframammary region, tripe palms	Ovarian adenocarcinoma
Oh <sup>8</sup> 2010	57/F	Hyperpigmentation of whole body and thickened palms and soles	Buccal mucosa, tongue, axillae, neck, groins, palms and soles	Ovarian adenocarcinoma
Chu <sup>9</sup> 2014	59/F	Oral papillomatosis and sialorrhoea	Oral, face, axillae, nipples, elbows, pudendum	Endometrial adenocarcinoma
Garzitto <sup>10</sup> 2015	60/F	Vitiligo and acanthosis nigricans	Perioral involvement, axillae, inframammary region, inguinal, genital and tripe palms	Ovarian adenocarcinoma

- in a patient with gastric adenocarcinoma. *Int J Dermatol* 2004;43:530-2.
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