Case Reports in Dermatology

Case Rep Dermatol 2017;9:30–37

DOI: 10.1159/000456652
Published online: February 10, 2017

Case and Review

Severe, Malignant Acanthosis Nigricans Associated with Adenocarcinoma of the Endometrium in a Young Obese Female

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Keywords
Malignant acanthosis nigricans · Benign acanthosis nigricans · Endometrial adenocarcinoma

Abstract
Acanthosis nigricans (AN) is a dermatopathy associated with insulin-resistance, drugs, endocrine disorders, chromosomal abnormalities (benign AN), and neoplasia (malignant AN). Malignant AN (MAN) is a rare paraneoplastic skin syndrome most commonly associated with gastric adenocarcinoma and other intra-abdominal malignancies. We report the case of a 28-year-old female with AN associated with obesity, insulin resistance, and endometrial adenocarcinoma. Although rare, MAN is often an initial sign of malignancy and must trigger extensive investigation, particularly in patients with sudden development of possibly paraneoplastic dermatoses or in patients diagnosed with benign AN with any atypical features.

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Introduction

Acanthosis nigricans (AN) is a cutaneous eruption characterised by symmetric velvety hyperpigmented, verrucous plaques of the intertriginous surfaces of the axilla, neck, inframammary, and mucocutaneous regions and can be classified as benign or malignant [1]. Benign cases are typically associated with obesity and insulin resistance, while malignant AN (MAN) has been associated with intra-abdominal malignancies including gastric, oeseophageal, pancreatic, and hepatic duct adenocarcinomas and also rarely gynaecological malignancies [1]. We present the case of a 28-year-old female with AN associated with a combination of benign and malignant aetiologies. She initially presented with benign features of obesity and insulin resistance; however, the progressive nature of her AN later manifested as a paraneoplastic dermatosis of endometrial adenocarcinoma.

Case Report

A 28-year-old morbidly obese female was referred to the dermatology clinic with a pruritic, hyperpigmented facial eruption. Similar hyperpigmentation was present on her neck, axillae, and forearms. The patient reported this profound increase in pigmentation occurred after she gained approximately 30–40 kg over the last 8 years since the birth of her first child. She also reported that this had dramatically worsened in the last 12 months. She had been using intermittent topical corticosteroids for the last 5 years with minimal effect.

The patient reported a history of irregular menstrual cycles with associated menorrhagia. She had been feeling otherwise well with no constitutional symptoms and denied any alteration in her bowel habit, melaena, or per rectal blood loss. There were no genitourinary symptoms.

Her background medical issues included morbid obesity, sleep apnoea, and a recent diagnosis of bilateral cataracts, requiring surgery. She reported a positive family history of diabetes and breast cancer but denied any personal history of diabetes or malignancy.

The patient did not take any regular medications and had no known allergies. She was a smoker and consumed alcohol occasionally. She was currently unemployed and lived with her 7-year-old daughter.

On examination, the patient was obese with a BMI of 49. There was widespread hyperpigmentation with marked skin thickening of her axillae, arms, abdominal folds, face, and ears (Fig. 1, Fig. 2). There was sparing of the nose and vermillion border of her upper lip. She had macrocephaly with a prominent nose, round face and a “buffalo hump”. There were no skin tags or oral and tongue changes. Examination of the scalp revealed cerebriform folding of the skin consistent with cutis verticis gyrata.

Her cardiorespiratory and abdominal examinations were unremarkable. There was no adenopathy. Multiple punch biopsies were performed which showed psoriasiform hyperplasia, moderate dermal fibrosis, and superficial to mid-perivascular and perifollicular inflammation consistent with AN.

Given the extensive presentation of AN, the patient subsequently underwent extensive investigations for potential endocrinopathies and to exclude underlying malignancy. She had an oral glucose tolerance test, which revealed severe insulin resistance. Serological investi-

gation showed a mild polycythaemia with a haemoglobin level of 163 g/L, with an otherwise normal full blood count and iron studies. She had an elevated ALT of 49 U/L, but other liver function tests were normal. Total cholesterol was elevated at 5.5 mmol/L with an LDL of 4.05 mmol/L, and triglycerides were 2.1 mmol/L.

In terms of investigation for endocrinopathy, she had an undetectable growth hormone, a low IGF-1 at 7 nmol/L, a low 24-h urinary free cortisol and normal thyroid function tests. FSH and LH were significantly depressed, and she had elevated testosterone and free androgen index.

The patient was referred to gynaecology where she underwent a further panel of investigations. A hysteroscopy with dilation and curettage and Mirena insertion was performed. A CT of the chest, abdomen, and pelvis revealed no abnormalities, and tumour markers were also unremarkable, with a nonsignificant CA 125 level of 16 kU/L. Histology of the curettings confirmed grade 1 adenocarcinoma of the endometrium, and the patient was scheduled for a formal hysteroscopy/dilation and curettage in 3 months time. Additionally, the patient was referred to dietetics for education regarding diet and weight reduction and was referred for a formal sleep study to investigate her sleep apnoea.

Discussion

AN is a cutaneous eruption characterised by symmetric velvety hyperpigmented, verrucous plaques of the intertriginous surfaces of the axilla, neck, inframammary, and mucocutaneous regions [1]. AN is a cutaneous marker of systemic diseases, which can be classified into benign and malignant forms. Benign AN can be familial, drug induced, or correlated with a variety of endocrinopathies, notably insulin resistance and obesity. The benign form is usually insidious in onset and less widespread in distribution. In contrast, MAN is most commonly related with intra-abdominal malignancies and very rarely gynecological carcinomas [1]. MAN is usually rapid in onset, widespread in distribution, and sometimes has facial involvement. It can also be associated with skin tags, multiple seborrheic keratosis (the sign of Leser-Trelat), or ridged velvety lesions on the palms (tripe palms) [1].

The pathophysiology of AN is unknown but thought to involve one or more stimulating factors, which ultimately cause the epidermal proliferation that is seen on histopathological section. In MAN, the proposed etiology is thought to involve tumour secretion of a peptide with growth factor properties – potentially transforming growth factor-alpha, insulin growth factor-1, or melanocyte-stimulating hormone alpha [1]. Histopathology of biopsies typically reveals papillomatosis, hyperkeratosis, and acanthosis and an increased number of basal melanocytes. Interestingly, MAN tends to follow the course of an underlying malignancy – often spreading with tumour progression, then regressing with successful therapy. Recurrences of AN occurring with cancer recurrence or metastases have also been reported.

Gynaecological malignancies have rarely been reported with MAN including 6 cases of ovarian cancer, 5 cases of endometrial carcinoma, and 2 cases of cervical carcinoma (Table 1). These patients presented with MAN between the ages of 47–83 years, with an average age of 59.5 years. Tripe palms and MAN occurring in the axillae are the most common sites occurring in 77 and 85% of the cases, respectively.

Compared to previous cases, our case is of particular interest because our patient's AN could be due to a combination of both benign and malignant aetiologies – which has not previously been reported. The patient initially had features consistent with a benign form including an insidious onset at a young age associated with insulin resistance and obesity. This was then followed recently with a rapid year-long deterioration of the condition associated with widespread hyperpigmentation and hyperkeratosis involving the axillae, arms, abdominal folds, ears, and the face – suggestive of MAN. Compared to previous cases of gynaecological malignancy associated with MAN, our case also presented at a much younger age and also at an unusually young age for the diagnosis of endometrial carcinoma.

Our patient also had cutis verticis gyrata, a rare clinical finding with cerebriform thickening of the scalp, manifesting as deep furrows and convoluted ridges. This condition is commonly due to systemic disease, inflammatory dermatoses, underlying nevoid abnormalities, or trauma [2]. The condition has rarely been described in association with malignancy, and although the cause of our patient's cutis verticis gyrata is not clear, the fact that it appeared in association with this patient's endometrial carcinoma is of note.

Although rare, MAN is often an initial sign of malignancy and should trigger extensive investigation. This should include a review of systems including gastrointestinal symptoms, constitutional symptoms and a detailed gynaecological history. Initial investigations should include routine blood tests, chest X-ray, and also possible referral for endoscopy, breast examination, Pap smear, pelvic examination/ultrasound, and other abdominal imaging if relevant. In patients diagnosed with benign AN, any atypical features or poor response to treatment should also raise the possibility of underlying malignancy. This was depicted by the dual aetiologies in our patient and shows that physicians should have a low threshold for thorough investigation if malignancy is a possibility.

Statement of Ethics

The authors state that the patients gave their informed consent. The research complies with all ethical guidelines for human studies.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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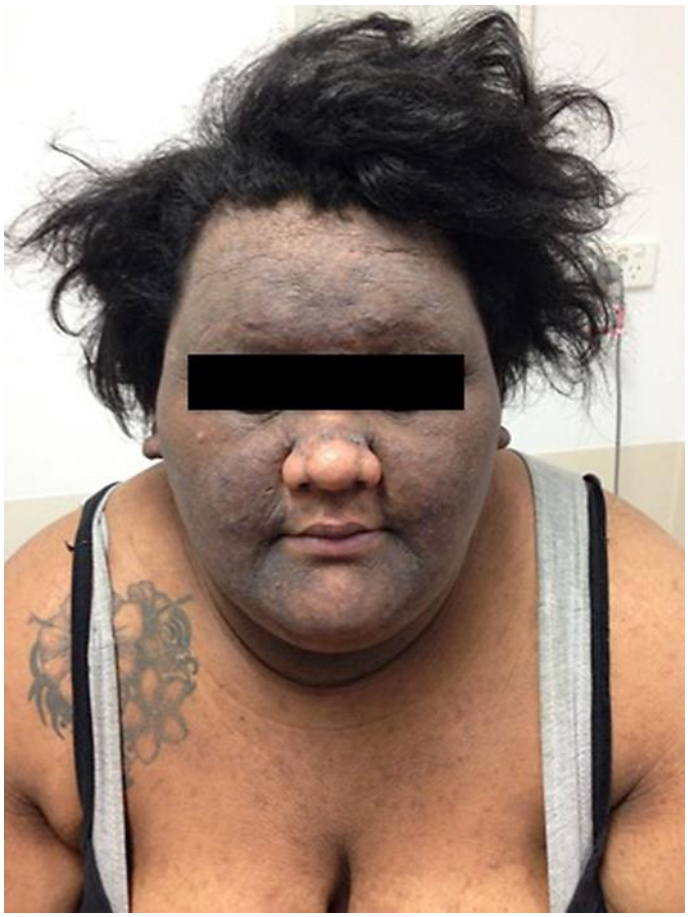

Fig. 1. Facial distribution of the patient's MAN.

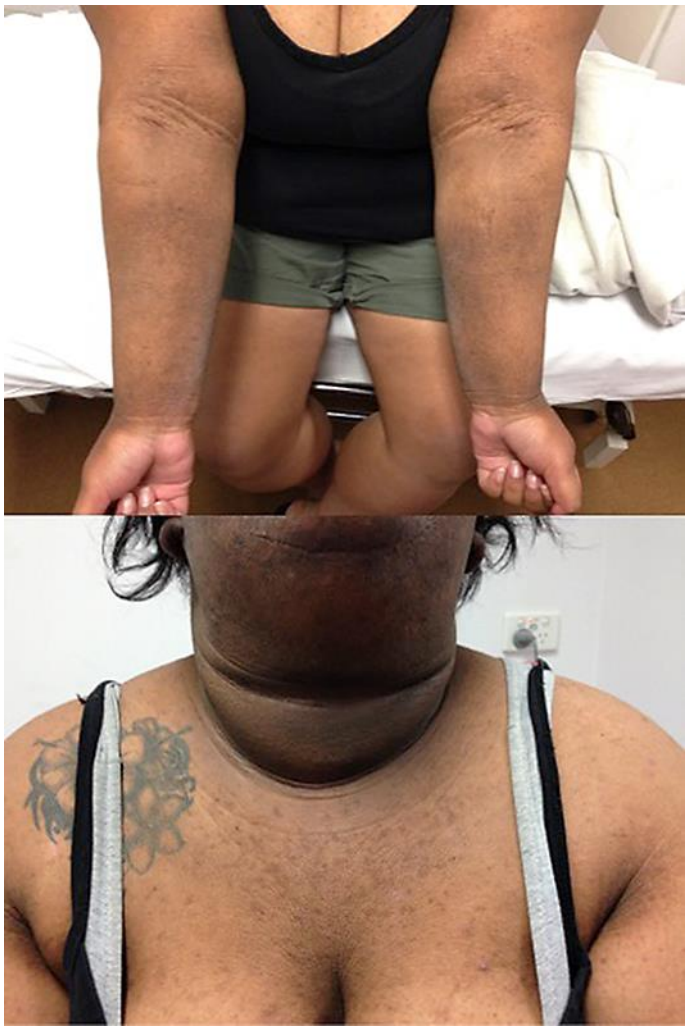

Fig. 2. Distribution of the patient's MAN.

Table 1. Previously reported cases of malignant acanthosis nigricans (MAN) associated with gynaecological malignancies

First author [ref.], year	Patient age, years/ gender	Presentation	MAN distribution	Malignancy
Dingley [14], 1957	56/F	Warts presenting on arms, legs, and trunk; dry/sore tongue and cheeks; no B symptoms	Arms, legs, trunk, face, oral, palms, soles, anus, groin, axillae	Ovarian adenocarcinoma
Curth [3], 1962	55/F	Vaginal discharge, postmenopausal bleeding	Dorsa of hands, forearms, back, trunk, legs, umbilicus, axillae, perianal and vulvar	Endometrial carcinoma
Mikhail [4], 1979	58/F	Condylomata of the perineum	Face, oral involvement, palms and soles, perineal region, inframammary region, vulva, anus, gluteal cleft, upper thigh, axillae	Cervical squamous cell carcinoma
Requena [5], 1995	83/F	8 months of increasing hyperkeratosis of palms, 5 months of anorexia and weight loss, and 3 months of night sweats	Palms, dorsum of hands, axillae and groin	Ovarian carcinoma
Gorisek [6], 1997	54/F	Postmenopausal menorrhagia	Tripe palms, dorsal neck, axilla, inframammary region, abdominal folds, inguinal and forearms; oral involvement also	Endometrial adenocarcinoma
Mekhail [1], 2002	69/F	Hypothyroidism, obesity	Tripe palms, face, neck, axillae, groin and inframammary region	Endometrial adenocarcinoma
Tsai [7], 2004	55/F	Cervical cancer	Palms, dorsum of hand, soles, thighs, neck, axillar, waist	Cervical cancer
Longshore [8], 2003	69/F	Anorexia, weight loss	Face, axillae, groin, hands, soles, inframammary folds	Endometrial adenocarcinoma
Kebria [9], 2006	52/F	Weight loss	Neck, axillae, inframammary, palms and soles, groin and oral involvement, tripe palms	Ovarian adenocarcinoma
Oh [10], 2010	57/F	No B symptoms	Neck, axillae, groin, oral, forearms, palms and soles	Ovarian adenocarcinoma
Singh [11], 2013	47/F	Fatigue, weight loss, and night sweats for 8 months	Face and body	Ovarian adenocarcinoma
Chu [12], 2014	59/F	Previous endometrial carcinoma (9 years before)	Face, elbows, pudendum, groin, axillae, nipples	Endometrial carcinoma
Garzitto [13], 2015	60/F	Vitiligo and AN; otherwise well, no B symptoms	Axillary, inframammary region, inguinal, genital, perioral, tripe palms	Ovarian adenocarcinoma