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Acanthosis Nigricans – A Two-Sided Coin: Consider Metabolic Syndrome and Malignancies!

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Abstract

BACKGROUND: Acanthosis nigricans (AN) is acquired hyperpigmentation of the intertriginous body regions. Histologically, AN is characterised by a thickened stratum corneum and a variable amount of acanthosis. Although benign and rarely symptomatic, AN may be a red flag for underlying pathologies.

CASE PRESENTATION: We analysed our patients with AN and could differentiate three different patterns, that are illustrated by one case report each. The is the benign AN associated with metabolic syndrome including obesity. The second type is the paraneoplastic AN malignancy which is associated with a wider range of malignancies. This type may occur before, after or with the clinical appearance of the malignancy. The third type is relapsing AN after complete remission. We present a patient who had a malignant AN and was treated successfully for his cancer. Years later, however, AN relapsed. In that case in association with the appearance of skin tags. Cancer restaging excluded a tumour relapse. His BMI was 31.2 kg/m^2, and the diagnosis of benign AN was confirmed.

CONCLUSIONS: The diagnosis of AN remains incomplete without screening for metabolic syndrome and/ or cancer. The combination of AN and skin tags is more often associated with metabolic syndrome. AN may be considered as a red flag for malignancies and the metabolic syndrome.

Introduction

Acanthosis nigricans (AN) is acquired hyperpigmentation of the intertriginous body regions and sometimes the periareolar skin. Besides the colour change, the disease most often remains asymptomatically. AN can occur as focal or diffuse papillomatous, hyperkeratotic, thickened lesions, which are symmetrically distributed. It rarely affects mucosa such as oral cavities.

Histologically, AN is characterised by a thickened stratum corneum and a variable amount of acanthosis. Horn pseudocysts can occasionally be present. The darker colour of AN is likely due to hyperkeratosis. A subtly mixed cellular infiltrates may be seen [1].

AN can develop in children, adolescents and adults. In children, the commonly affected body region is the neck followed by the axillae [2].

The prevalence of AN differs between ethnic groups. In the US, among native Americans, the prevalence was up to 34.2% followed by African Americans, Hispanics and Caucasians [3].

The pathogenesis of AN is complex. Elevated insulin concentrations result in direct and indirect activation of insulin-like growth factor (IGF)-1

receptors on suprabasal keratinocytes and fibroblasts. Other tyrosine kinase receptors such as epidermal growth factor receptor (EGFR) and fibroblast growth factor receptor (FGFR) may also contribute to hyperproliferation of keratinocytes and fibroblasts [4]. However, in obesity, the insulin concentrations are lower than warranted for such effects [5]. Extensive AN has been associated to hypochondroplasia with FGFR3 mutations [6]. Another possible, but the very rare association is a mutation of the *ELOV1* gene that encoded ELOVL fatty acid elongase 1, which catalyses elongation of saturated and monounsaturated C22-C26-very long-chain fatty acids [7]. Malignancy-associated AN might be explained by elevated levels of growth factors such as transforming growth factor (TGF-α), which can stimulate EGFR [8]. What causes the intertriginous areas to be most responsive has yet not been discovered.

Differential diagnoses

AN may resemble other disorders such as terra firma forme dermatosis [9], confluent and reticulated papillomatosis [10], berloque dermatitis, Riehl's melanosis, poikiloderma of Civatte [11].

Case reports

Case 1: A 48-year-old adipose male presented with hyperpigmented lesions on the thighs and scrotum. His body mass index (BMI) was 36 kg/m^2. He suffered from arterial hypertension and hyperlipidemia. On examination, we observed diffuse brownish hyperpigmentation of thighs and scrotal skin with papillomatosis (Figure 1). No treatment was warranted. We recommended nutritional counselling. The diagnosis of benign AN was confirmed.

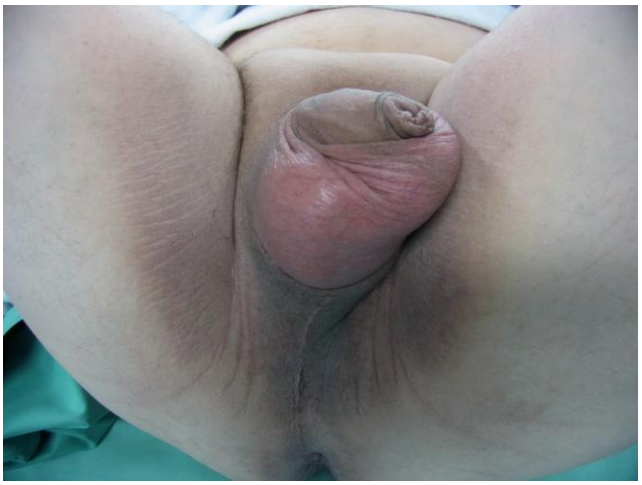

Figure 1: Figure 1: Benign AN in an obese man

Case 2: A 39-year-old male presented with a relapse of intertriginous AN. His medical history was remarkable for kidney cancer in 2012 that was found after the first episode of AN and completely removed by surgery. The diagnosis of AN malignancy was confirmed. Five years later he demonstrated with a relapse of AN brownish-blackish hyperpigmentation in association with skin tags after complete remission in 2013 (Figure 2). We performed a computerised tomography of the abdomen and laboratory investigation that gave no hint of cancer relapse. His BMI was 31.2 kg/m^2. The diagnosis of benign AN was confirmed, and surgical excision of the thigh lesions was performed. We also recommended nutritional counselling.

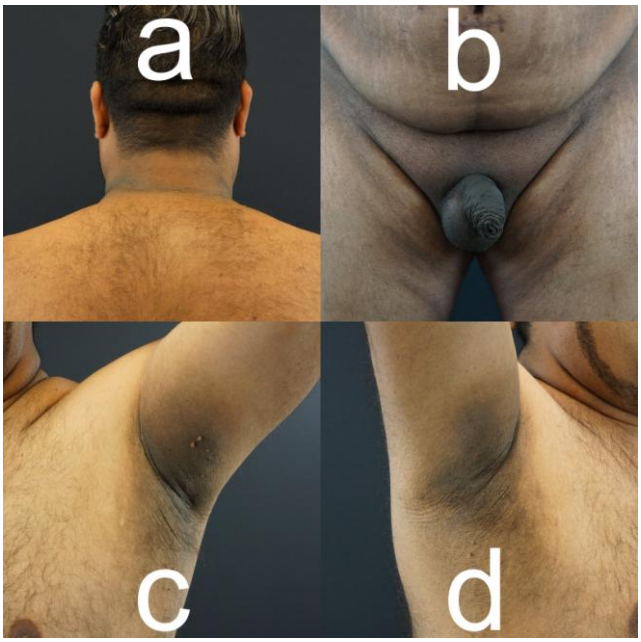

Figure 2: Relapse of AN after successful kidney cancer treatment on the neck (a), groins, scrotum and thighs (b), and axillae (c, d). In the axillae, skin tags are seen

Case 3: A 62-year female presented with brownish hyperpigmentation of the neck, the back and the anal fold was presented by the department of oncology (Figure 3). She suffered from cholangiocarcinoma with peritoneal metastases and was treated by chemotherapy with gemcitabine and cisplatin — An developed shortly after tumour diagnosis. Malignant AN was confirmed, and anti-pruritic topical therapy with 5% polidocanol ointment was recommended.

Acanthosis nigricans and the metabolic syndrome

The major features of the metabolic syndrome are insulin resistance, visceral adiposity, atherogenic dyslipidemia and endothelial dysfunction [12]. AN has a strong association with overweight in adults, adolescents and children. Obesity in adults is defined as 30 kg/m², whereas in children and adolescents, overweight is defined as ≥ the 95th percentile of the

sex-specific BMI-for-age growth chart [13]. In a Turkish study on obese adults, 47.3% suffered from AN [14].

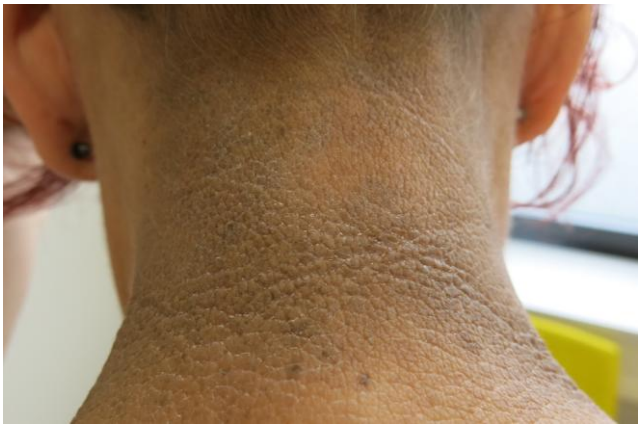

Figure 3: Malignant AN in a woman with cholangiocarcinoma

Overweight and obese children with AN demonstrate significantly higher levels for uric acid, fasting glycemia, insulin, glutamic oxalacetic transaminase, and homeostasis model assessment index than those without AN [15]. This suggests that AN is a marker of increased risk for metabolic syndrome in children, but the same has been demonstrated for other age groups as well [16]. Here, AN often is coexistent with multiple skin tags in contrast to malignant AN. Patients with AN showed be investigated for other symptoms of the metabolic syndrome such as blood pressure (BP), fasting lipoprotein profile, fasting glucose, haemoglobin A1C, fasting insulin, alanine aminotransferase (ALT), hyperlipidemia or hyperuricemia [17]. Women with polycystic ovary syndrome (POCS) show an increased prevalence of metabolic syndrome, type 2 diabetes (DM2) and cardiovascular disease. AN can be a cutaneous marker for POCS [18].

Acanthosis nigricans and cancer

AN is a possible paraneoplasia. Paraneoplasia is a disorder related to malignancy. It can frequently the first sign of a subjacent malignant tumour. Although relatively rare, they need to be recognised to make an early diagnosis and improve the prognosis of the malignancy [19]. The malignant conditions that have been associated with AN are tumours of the gastrointestinal tract, gynecologic and urogenital tumours among others, although gastric cancer is the most common (Table 1). In most cases, AN occurs concomitantly (61.3%), however, in 17.6% of cases, the lesions occur before the tumour detection and in 21% of cases, after the tumour has become obvious [20]. In contrast to non-malignant AN, mucous membranes, in particular, the oral cavity, can be affected.

Table 1: Malignant tumours associated with AN

Tumour	Reference
Breast cancer	Levine et al., 2010 [21]
Cholangiocarcinoma	Scully et al., 2001 [22]
Clear-cell renal carcinoma	Ferraz de Campos et al. 2016 [23]
Endometrial adenocarcinoma	Deen et al., 2017 [24]
Fallopian tube carcinoma	West et al., 2018 [25]
Gallbladder adenocarcinoma	Ziadi et al., 2009 [26]
Gastric adenocarcinoma	Yu et al., 2017 [27]
Gastric diffuse B-cell lymphoma	Mignogna et al., 2009 [28]
Gastrointestinal stromal tumor	Park et al., 2013 29]
Hepatocellular carcinoma	Antonio et al., 2018 [30]
Ileocecal adenocarcinoma	Gunduz et al., 2013 [31]
Insulinoma	Patra et al., 2016 [32]
Lung cancer	Owen 2016 [33]
Meningioma	Dainichi et al., 2008 [34]
Mycosis fungoides, Sèzary syndrome	Cheng et al., 2015 [35]; Fahmy et al., 2016 [36]
Ovarian cancer	Singh & Rai 2013 [37]
Pancreatic adenocarcinoma	McGinnes & Greer 2006 [38]
Prostate cancer	Tammaro et al., 2016 [39]
Rectal adenocarcinoma	Marschner & Reinhardt 2011 [40]
Sarcoma	Brantsch & Moehrle 2010 [41]

In conclusion, although AN by itself is most often an asymptomatic disease without significant impairment, the diagnosis is of great importance to identify underlying pathologies. The most important is the metabolic syndrome in overweight and obese patients of any age. The second is the role of malignant AN as an obligate paraneoplasia.

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