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/m², 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 asymptomatic. 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 with 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/m². 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.

**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/m². The diagnosis of benign AN was confirmed, and surgical excision of the thigh lesions was performed. We also recommended nutritional counselling.

**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
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.

**Table 1: Malignant tumours associated with AN**

| Tumour                        | Reference                                      |
|-------------------------------|------------------------------------------------|
| Breast cancer                 | Levine et al., 2010 [27]                       |
| Cholangiocarcinoma            | Scully et al., 2001 [26]                       |
| Clear-cell renal carcinoma    | Ferral de Campos et al., 2016 [25]             |
| Endometrial adenocarcinoma    | Owen et al., 2017 [24]                         |
| Fallopian tube carcinoma      | West et al., 2018 [25]                         |
| Gallbladder adenocarcinoma    | Zaidi et al., 2009 [26]                        |
| Gastric adenocarcinoma        | Yu et al., 2017 [27]                           |
| Gastric diffuse B-cell lymphoma|                                                |
| Gastrintestinal stromal tumor | Park et al., 2013 [29]                         |
| Hepatoblastular carcinoma     | Antoni et al., 2018 [30]                       |
| Rectal adenocarcinoma         | Guntur et al., 2013 [31]                       |
| Insulinoma                    | Patron et al., 2016 [32]                       |
| Lung cancer                   | Owen 2016 [33]                                 |
| Meningioma                    | Driach et al., 2008 [34]                       |
| Mycosis fungoides, Sézary syndrome | Cheng et al., 2015 [35], Fahmy et al., 2016 [36] |
| Oral cancer                   | Singh & Raj 2013 [37]                          |
| Pancreatic adenocarcinoma      | McMeans & Greer 2006 [38]                      |
| Pediatric cancer              | Tammaro et al., 2015 [39]                      |
| Rectal adenocarcinoma         | Marchiner & Redhead 2011 [40]                  |
| Sarcoma                       | Brantlach & Muelaite 2015 [41]                 |

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