

Acanthosis nigricans: An extensive review

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Abstract

Acanthosis nigricans (AN) is a velvety, hyperpigmentation of the skin that usually occurs in intertriginous areas. AN is most commonly associated with benign disorders like diabetes, insulin resistance, endocrinopathies and exogenous medications, but can be a valid cutaneous marker of a wide range of internal malignancies, which makes it important for the physicians across specialties to have awareness about it. With an increase in the prevalence of obesity and diabetes in recent decades, the prevalence of AN has also shown a significant increase. This article will review in detail the epidemiology, pathophysiology, clinical features and treatment of acanthosis nigricans in the light of the literature.

Key words

Acanthosis nigricans (AN), insulin resistance, endocrine disorders, obesity, paraneoplastic syndrome, growth factors, hyperpigmentation, differential diagnosis.

Introduction

Acanthosis nigricans (AN) is a dermatosis with aesthetic implications and is characterized by the focal or diffuse development of a velvety, hyperpigmented cutaneous thickening in intertriginous areas. This hyperpigmentation, which has poorly defined borders, usually occurs in skin fold areas symmetrically, such as the back of the neck, axilla and groin, and may rarely involve oral mucosa.¹ The lesions may be related to a wide range of benign conditions and may occur as a paraneoplastic manifestation of various potentially fatal malignancies. There are reports in literature recommending the utilization of AN as a straight-forward, non-invasive and cost-effective clinical marker for screening, prevention, diagnosis and follow up.²⁻⁶ The term acanthosis nigricans was originally proposed by Paul Gerson Unna in

1889, but the first case was described by Pollitzer and Janovsky in 1891.⁷

This review discusses in detail the epidemiology, pathophysiology, clinical features and treatment of acanthosis nigricans in the light of literature.

Methods

The observational studies, review articles and case reports dealing with acanthosis nigricans were searched in PubMed, HINARI, Google Scholar, Web of Science and Cochrane library databases. The search was based on the keywords: acanthosis nigricans, paraneoplastic syndrome and metabolic syndrome. Only the literature published in English up to June 2020 was included and all articles in languages other than English were excluded. Preference was given to articles published in the last two decades, but references from earlier dates that appeared as cross-references in the included articles were also reviewed and used if found highly significant, particularly from the historical point of view.

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Pathogenesis

The definite pathogenesis for AN has not yet been ascertained, although several factors have been suggested that may be involved in the development of acanthosis nigricans in various disorders.⁸

- i) Increased circulating insulin result in direct and indirect activation of keratinocyte insulin-like growth factor (ILGF) receptors, particularly IGF-1. At high concentrations, insulin may displace IGF-1 from IGF binding protein. Increased circulating IGF may lead to suprabasal keratinocyte and dermal fibroblast proliferation. Other tyrosine kinase receptors such as fibroblast growth factor receptor (FGFR), epidermal growth factor receptor (EGFR) may also play a contributory role in the hyperproliferation of keratinocytes and fibroblasts.⁹
- ii) Increased transforming growth factor (TGF) appears to be the mechanism for malignancy-associated acanthosis nigricans. TGF acts on epidermal tissue via the epidermal growth factor receptor.
- iii) Early development of extensive acanthosis nigricans (AN) is a key feature in some patients who have hypochondroplasia (HCH) and are supposed to be related to the Fibroblast growth factor receptor (FGFR) 3 mutations. Muguet Guenot L *et al.*¹⁰ in 2019 reported that the Lys650Thr mutation was the predominantly reported mutation of FGFR 3.
- iv) Malignancy-associated AN might be possibly explained by the elevated levels of growth factors such as alpha transforming growth factor (TGF- α), which can stimulate the epidermal growth factor receptor (EGFR). Normalization of urine and serum TGF-alpha levels with subsequent regression of skin lesions have been reported

to occur after surgical tumor removal.¹¹ However, it has not yet been discovered, as to what causes the intertriginous areas to be most affected though perspiration or friction may be playing a contributory role.¹²⁻¹⁴

- v) Very long-chain fatty acids (VLCFAs) are essential for the functioning of biological membranes. ELOVL fatty acid elongase-1 catalyzes the elongation of saturated and monounsaturated C22-C26-VLCFAs. Mutation of ELOV1 gene that encoded ELOVL fatty acid elongase-1 has been postulated as a possible factor in the development of AN in the recent studies.¹⁵
- vi) Hereditary variants of AN have been linked to the fibroblast growth factor defects.

Exogenous medications, including insulin injections have been implicated as etiologic factors and the likely mechanism is proposed to be the activation of IGF receptors.¹⁶ Kudo-Watanuki *et al.* in 2013 reported the development of AN over anterior abdomen at the insulin injection site of a 59-year-old patient with diabetes mellitus coexisting with amyloidosis.¹⁷

Agents such as palifermin (recombinant keratinocyte growth factor used to decrease mucositis with chemotherapy and stem cell transplantation) have been reported by Lane *et al.* to produce transient but dramatic acanthosis nigricans-like lesions, presumably due to activation of the fibroblast growth factor receptors (FGFR).¹⁸

Familial forms of AN have been documented in the literature. These familial forms may be isolated or syndromic forms. The syndromic forms have been subdivided into:

- (a) Insulin-resistance syndromes: these include those with mutations in the insulin receptors (i.e. leprechaunism, Rabson-Mendenhall

syndrome), peroxisome proliferator-activated receptor-gamma (i.e., type 1 diabetes with acanthosis nigricans and hypertension), 1-acylglycerol-3-phosphate O-acyl transferase-2 or seipin (primary lipodystrophy or Berardinelli-Seip syndrome), lamin A/C (Dunnigan syndrome), and Alstrom syndrome gene.¹⁹

- (b) Fibroblast growth factor defects include activating mutations in *FGFR2* (Beare-Stevenson syndrome), *FGFR3* (Crouzon syndrome with acanthosis nigricans, thanatophoric dysplasia, severe achondroplasia with developmental delay, and acanthosis nigricans [SADDAN]).

Familial cases of isolated acanthosis nigricans with no other syndromic findings have also been linked to *FGFR* mutations. Berk *et al.*²⁰ and Fu *et al.*²¹ in two independent case reports found that AN to be caused by a heterozygous mutation (c.1949A > C, p.K650 T) in fibroblast growth factor receptor 3 gene (*FGFR3*). Sequencing of the *FGFR3* gene was suggested a feasible approach to identify the etiology of AN, especially for early-onset extensive AN.

Epidemiology

AN is much more common in people with darker skin pigmentation. AN has no known sex predilection and the reported incidence is equal for men and women. AN has been reported at all ages, including at birth, although it is found more commonly in the adult population. AN has been found to be more common in Native Americans, African Americans, and Hispanics when compared to Whites or Asian origin individuals.²²⁻²³ The exact prevalence of AN is not precisely known, but due to the rising prevalence of obesity and diabetes a high prevalence of AN has been observed recently. As such, the prevalence varies widely from 7% to 74%, depending upon age, race, frequency of

type, degree of obesity and concomitant endocrinopathy. Stuart CA *et al.* in 1989 conducted a study in the sixth and eighth grades of the public schools of Galveston, Texas, USA and reported a prevalence of 7.1% in the unselected populations.²² Hud *et al.* study had reported 74% in an unselected adult obese population in Dallas, Texas, USA.²³ The prevalence of AN in an urban population in Sri Lanka was reported 17.4% in a study conducted by Dassanayake *et al.* in 2011.²⁴ The prevalence of AN in New Mexico adolescents was found to be 18.9% in a study by Mukhtar *et al.* that enrolled 233 middle school students.²⁵ Stoddart *et al.* conducted a study on a random sample of the American Indian diabetic population in Cherokee Nation members aged 5-40 years. They found that the overall prevalence rates for AN and hyperinsulinemia were 34.2 and 47.2%, respectively.²⁶ In a study conducted in China, the frequency of AN was reported as 54% in Chinese obese children.²⁷

Malignant acanthosis nigricans, in contrast to the benign form, is less common with no racial predilection and occurs more frequently in elderly persons; however, cases have been reported in children with Wilms tumor, gastric adenocarcinoma, and osteogenic sarcoma.²⁸

Classification of Acanthosis Nigricans

Multiple classifications have been proposed in literature.²⁹ The commonly cited classifications by Curth,³⁰ Hernandez-Perez³¹ and Sinha-Schwartz²⁸ are shown in **Figure 1**. Burke *et al.*⁷ have developed a scale for AN according to the severity, on a scale of 0-4 based on how many areas are affected and the scale is easy to use, has high interobserver reliability, and correlates well with fasting insulin and body mass index (BMI). This scale permits longitudinal and cross-sectional evaluation of AN and the evaluation of AN as a trait in genetic studies.

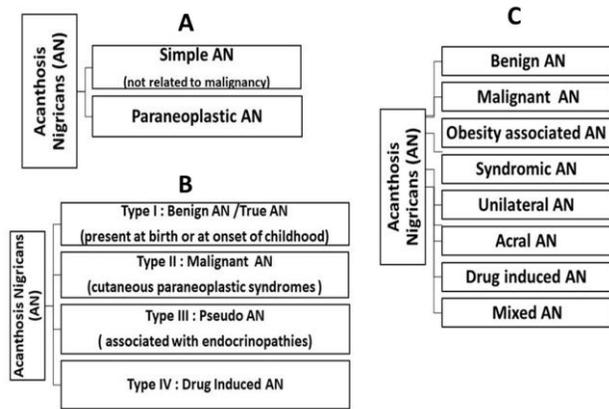


Figure 1 Classification of Acanthosis Nigricans (A) Curth, (B) Hernandez-Perez (C) Sinha-Schwartz.

Acanthosis Nigricans	Acanthosis Nigricans (AN) form
Metabolic disorders	Obesity associated AN Syndromic Type A, Type B
Genetic disorders	Unilateral acanthosis nigricans Familial acanthosis nigricans Benign genetic acanthosis nigricans
Autoimmune	AN associated with a known autoimmune disease AN associated only with autoantibodies
Paraneoplastic AN	AN associated with wide range of neoplasia
Iatrogenic AN	Medication side effects AN
Idiopathic AN	Acral AN
Mixed type AN	AN lesion with any two forms from above

Figure 2 Popa *et al.* classification of Acanthosis Nigricans.

Popa *et al.*³² in 2019, proposed a comprehensive classification system, as shown in **Figure 2**. We have adopted this classification in this review article for a greater explanation of the variants.

Metabolic disorders

Obesity-associated AN is the most common form and once termed as pseudo-acanthosis nigricans. Lesions are more common in adulthood, though it may appear at any age. The lesion's severity is related to weight excess and is often slowly reversible after weight loss. It is more common in obese patients with insulin resistance.³³ In obese women with gestational diabetes, the lesion may be a reliable marker for higher insulin needs. Similarly, in paediatric patients, AN has been shown to be a reliable early marker for metabolic syndrome.³⁴

In clinical practice, AN may be a useful morphological marker for early identification of children and adolescents, prone to insulin-resistant obese phenotype and metabolic syndrome, who could benefit from early interventions.³⁵

Syndromic AN has two types: type A (HAIR-AN) presents with hyperandrogenemia (HA), insulin resistance (IR) and AN; type B presents

with diabetes mellitus and ovarian hyperandrogenemia.

Genetic disorders

Unilateral AN is a rare inherited, autosomal dominant form that manifests at birth or during childhood or puberty and is not related to endocrinopathy. Lesions are unilateral and appear, especially in the periumbilical area, back and thighs though rarely face, scalp and chest may be involved.³⁶⁻³⁷ The salient features in the literature include localized distribution, benign course, lack of systemic and tumor associations, and occurrence due to somatic mosaicism of postzygotic gene mutation.³⁸⁻³⁹

Familial AN is a rare autosomal dominant disease. The condition is self-limiting and commonly develops from early childhood to stabilize or else recede after continuous progress till puberty. However, it may appear at any age.⁴⁰

Benign genetic AN develops from birth or early childhood, as a rare autosomal dominant form.

Autoimmune disorders

Autoimmune AN is usually determined by anti-insulin receptor antibodies that appear in

autoimmune disorders like systemic lupus erythematosus.⁴¹⁻⁴² Cases of AN accompanied by autoimmune manifestations but not type B insulin resistance, which responded to systemic immunosuppressive therapy, have been reported. Kondo *et al.*⁴¹ reported a very rare case of generalized AN with Sjogren's syndrome- and systemic lupus erythematosus-like features but without type B insulin resistance. During a 10 year clinical course, neither any internal malignancy nor other endocrinological disorders, including glucose intolerance, were detected. The lesions regressed with oral cyclosporine A, accompanied by the lowering of autoantibody titers.

Sturmer *et al.*⁴³ have speculated that some unknown autoantibodies other than the insulin-receptor antibody might generate mucocutaneous lesions found in AN. Some patients with AN who are positive for antinuclear antibodies (ANA), anti-microsomal antibodies (AMA), or show increased immunoglobulin levels might associate with disordered immunoreactivity not fitting any clinically recognizable syndromes.

Paraneoplastic AN

Paraneoplastic or malignant AN is the most worrisome of the variants of acanthosis nigricans because the underlying neoplasm is often aggressive cancer. The neoplasms usually have a rapid onset and occur concomitantly in most cases (61.3%); however, in 17.6% of cases, the lesions precede the tumor detection and in 21% of cases, appear after the tumor has become obvious.¹¹

Lesion progression mirrors the development of malignancy: efficient treatment leads to AN regression, whereas recrudescence may suggest recurrence of the malignancy. The vast majority of cases of malignant AN are secondary to

adenocarcinoma of the stomach,⁴⁴⁻⁴⁶ but cases have been reported in cancers of other organs including hepatobiliary tract,⁴⁷⁻⁵⁰ intestine,⁵¹ lungs,⁵² uterus,⁵³⁻⁵⁵ ovaries,⁵⁶ urinary tract,⁵⁷⁻⁵⁸ rectum,⁵⁹ prostate,⁶⁰ soft tissue⁶¹ and central nervous system.⁶²

Iatrogenic disorders

AN may uncommonly appear as an adverse effect of drugs that promote hyperinsulinemia. These drugs include nicotinic acid, niacin, glucocorticoids, fusidic acid, stilbestrol, methyltestosterone, estrogen, combined oral contraceptive pill, triazine, pituitary extract, growth hormone therapy and fibroblast growth factor receptor ligands such as palifermin.¹⁸

Although skin lesions are reversible when discontinuing offending treatment, the decision should be made according to the severity of the disease for which the treatment was administered.

Nicotinic acid has the most widely recognized association with acanthosis nigricans, developing on abdomen and flexor surfaces and resolving within 4-10 weeks of discontinuation.⁶³⁻⁶⁴ There are reports in the literature of the development of AN as a local cutaneous side effect of repetitive same-site insulin injections.^{18,65,66} However, it has been proven that, with the correct insulin type prescription and proper administration technique, the development of AN can be avoided.⁶⁷

Idiopathic AN

Acral AN occurs in some healthy, dark-skinned individuals, especially those of African American or sub-Saharan African descent due to yet unknown genetic factors. It is most

prominent over the dorsal surfaces of the hands and feet.⁶⁸⁻⁶⁹

Mixed-type AN

Mixed-type AN is a term applied to those situations in which a patient with one of the above types of acanthosis nigricans develops new lesions of a different etiology. An example of this would be paraneoplastic AN lesions added to older ones in an obese patient with obesity-associated AN.

Clinical features

Patients usually present with an area of darkening and thickening of the skin with no active symptoms or else with mild pruritus. On physical examination, the lesions appear symmetrical, hyperpigmented, velvety plaques that may occur in almost any location though typically locations include areas of skin folds like the groin, axilla, or posterior neck (**Figures 3-5**).

In children, the most common site of acanthosis nigricans is the posterior neck. Rarely, acanthosis nigricans may occur on the mucous membranes of the nose, oral cavity, esophagus or larynx. Eye involvement, including papillomatous lesions on the eyelids and



Figure 3 Benign AN in an obese male (Image courtesy: Prof Uwe Wollina Dresden, Germany).

conjunctiva, has been reported.⁷⁰

Nail changes, such as leukonychia and hyperkeratosis, can also occur. Females have been reported to develop lesions on the nipple.⁷¹ In some patients, they may be associated with skin tags in the same area. Nail changes like hyperkeratosis and leukonychia may be present.

Clinically, it is not possible to precisely differentiate the lesions of benign from the

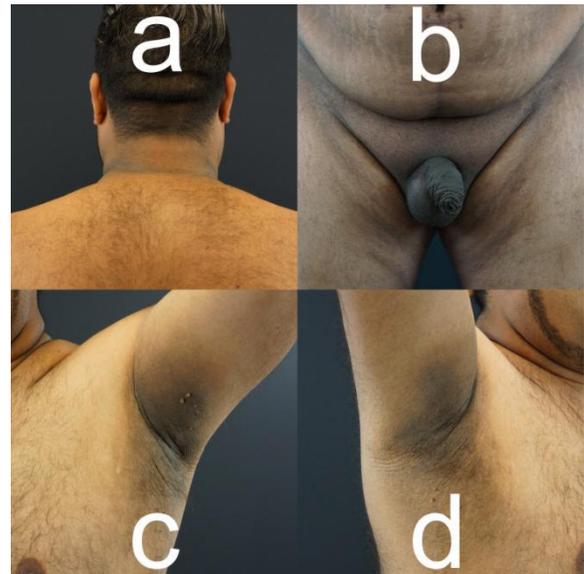


Figure 4 Relapse of AN after successful kidney cancer treatment on the neck (a), groins, scrotum and thighs (b), and axillae (c, d). In the axillae, skin tags are seen (Image courtesy: Prof Uwe Wollina, Dresden, Germany).



Figure 5 Malignant AN in a woman with cholangiocarcinoma (Image courtesy: Prof Uwe Wollina, Dresden, Germany).

Table 1 Difference between benign and malignant acanthosis nigricans.

Features	Benign	Malignant
Onset	Birth, childhood or puberty	Mostly adulthood
Distribution		
Extent of involvement	Lesser	Widespread
Distal extremities	Spared	Affected
Mucous membrane	Rarely affected	Commonly affected
Palms & soles	Rarely affected	Commonly affected
Pigmentation	Less, limited to thickened areas	More, and extends beyond the thickened areas
Skin thickening	Mild	Marked
Skin irritation	None or less	Marked
Additional features	None	i) Tripe palms, ii) Leser-Trelat sign, iii) Florid cutaneous papillomatosis (FCP)

i) Tripe palms [46, 72-74]: a cutaneous condition characterized by ridged velvety lesions on the palms resembling the lining of a cow's stomach (tripe).
 ii) Leser-Trelat sign [73-75]: the abrupt appearance of multiple, and sometimes itchy, seborrheic keratoses that rapidly increase in their number and size.
 iii) Florid cutaneous papillomatosis (FCP) [68,75-76]: characterized by the rapid onset of numerous small warty papules on the trunk and the extremities that morphologically resemble viral warts.

malignant AN, but there are certain features that should arouse suspicion as depicted in **Table 1**.

Diagnosis

The diagnosis of AN is mainly based on clinical assessment. Confirmation is obtained by a skin biopsy. The histological pattern of the lesion is common in all forms of AN described above and comprise of hyperkeratosis, epidermal folding, the proliferation of melanocytes in the stratum basale of the epidermis with leukocytic infiltration.³² The hyperpigmentation seen on clinical examination is attributed to thickening and hyperkeratosis rather than the excess of melanin.⁷⁷ In malignant AN, the hyperkeratosis is a dominant feature and due to the proliferation of keratinocytes, while the hyperpigmentation is minimal.¹

Tristimulus colorimetry and diffuse reflectance spectroscopy (DRS) are white-light skin reflectance techniques used to measure the intensity of skin pigmentation and have been shown to provide sensitive and specific diagnosis of AN. Tristimulus colorimetry quantifies and characterizes the objective colour

change in AN, while DRS may be useful in characterizing changes in skin melanin content associated with this skin condition.⁷⁸⁻⁷⁹

Blood tests, endoscopy, or imaging studies may be required to rule out diabetes or cancer as a cause of AN. Since a significant majority of cases are associated with insulin resistance and/or obesity, screening for diabetes and measuring glycosylated haemoglobin is recommended.^{33,80}

Differential Diagnosis

Intertriginous granular parakeratosis Usually self-resolving, pruritic, red-to-brown, scaly-to-hyperkeratotic papules or plaques found most commonly in the axillae or other intertriginous areas, generally in the middle-aged women.⁸¹

Haber's Syndrome A rare genodermatosis characterised by an early onset rosacea-like eruption associated with multiple keratotic lesions on non-sun-exposed skin of the trunk.⁸²

Confluent and reticulated papillomatosis An uncommon skin condition affecting the trunk,

neck and axillae and characterized by asymptomatic, hyperpigmented papules and plaques that have a peripheral, net-like configuration.⁸³

Dowling-Degos disease A rare autosomal dominant genetic disease that presents in adult life with multiple small progressive reticular, reddish-brown to dark-brown, pigmented lesions, particularly in the folds of the skin with soft tissue fibromas and follicular hyperkeratosis.⁸⁴

Acropigmentation reticularis of Kitamura A rare, autosomal dominant disorder characterized by a slightly atrophic, angulated, hyperpigmented macules that are arranged in a reticulate pattern typically on the dorsal aspect of hands and feet. The lesions usually start in the first and second decades of life and gradually darken over time.⁸⁵

Becker Melanosis A circumscribed hyperpigmented patch with an irregular outline and associated hypertrichosis. It usually develops in the second decade of life over the upper half of trunk and/or on the proximal upper extremities.⁸⁶

Erythrasma An intertriginous infection with *Corynebacterium minutissimum* that manifests as irregular but sharply margined pink or brown patches with fine scaling. It is most common in diabetics and among people living in warmer climates.⁸⁷

Seborrhea A common, chronic-recurrent disorder can affect people of any age, though it's most common in infants and adults between the ages of 30 and 60. It presents most often on the face and/ or scalp as ill-defined erythematous patches associated with fine (pityriasiform) scaling, involving mostly scalp, face and periauricular region, with the central chest,

axillae and genital region also involved in some cases.⁸⁸

Besides, the dermatological manifestations of various diseases like Addison Disease, hemochromatosis and pellagra can appear like AN. There are published reports of the "neglected nipples" condition, presenting as bilateral AN-like papules and plaques of the nipples, due to avoidance of cleansing of the nipple area, resulting in accumulation of keratotic cellular debris.⁸⁹

Complications

AN does not cause any serious complications per se. The appearance of acanthosis nigricans during childhood usually is associated with a benign condition, though in the adult-onset AN, the underlying malignancy must be ruled out. However, most cases of adult-onset acanthosis nigricans are benign and often are associated with insulin resistance.

Patient Education

There is a need to educate the patients that AN may not solely be a skin condition and hence ought to be evaluated further by multiple specialties, especially if it occurs in middle-aged to elderly patients. Patients need to be educated on identifying the risk factors and common features of the malignant conditions associated with AN. They are to be encouraged that AN per se can resolve or improve with adequate treatment of the skin condition or treatment of the underlying condition, lifestyle adjustments, including losing some weight. Depression and low self-esteem may occur in patients with AN and counselling with psychological treatment should be started early in these patients.⁹⁰⁻⁹¹

Treatment

AN is not a disease per se, but a sign of various

causes and hence, treatment of AN should focus on proper identification and correction of the underlying disease process. Simple measures like weight reduction in obesity-related AN may resolve the hyperkeratotic lesions, while correction of hyperinsulinemia can reduce the burden of AN lesions.⁷⁷ Cessation of the causative agent in idiopathic AN often results in the resolution of AN, and surgical removal of the malignant tumors is the mainstay of treatment in malignant AN.⁹²

Besides focussing on the primary goal of therapy for AN by managing the underlying cause, cosmetic resolution of AN lesions can be significant for improving the quality of life. A wide range of oral and topical treatment options have been reported.⁹³

Topical treatments

Topical retinoids Topical retinoids are one of the first-line treatment options for AN, particularly for the unilateral nevoid AN.³⁷ They act as epidermopoietic and cause a reduction of the stratum corneum replacement time, thereby leading to correction of hyperkeratosis and near-complete reversion to the normal state. Lahiri and Malakar, in their study of 30 patients, found that clinical improvement of treatment-resistant AN was seen in all patients after 14 days of 0.05% tretinoin application with 24 patients (80%) showing total clearance at 16 weeks. However, intermittent tretinoin was needed to maintain an improvement as relapse was noted within a period of 4 weeks after discontinuation of treatment.⁹⁴ There are reports of improvement, even with the use of lower concentration topical 0.1% tretinoin.⁹⁵ Studies have shown significant minimization of skin darkening by application of 0.1% adapalene gel for childhood AN.⁹⁶⁻⁹⁷ Treesirichod *et al.* in one study compared 0.1% adapalene gel and 0.025% tretinoin cream in the treatment of AN-

associated hyperpigmentation and they found that there was no statistically significant difference in the outcomes.⁹⁸

In another recent study, Treesirichod *et al.* compared the effects of 0.025% tretinoin and 10% urea. They found that both the medications significantly improved AN though the efficacy of 0.025% tretinoin was significantly better than 10% urea.⁹⁹

Combination therapy may also be used to treat AN successfully. In one case report by Blobstein, the combination of 0.05% tretinoin cream and 12% ammonium lactate cream led to the resolution of AN associated with obesity.¹⁰⁰ In another case report by Adigun and Pandya, a triple-combination depigmenting cream composed of 0.05% tretinoin, 4% hydroquinone, and 0.01% fluocinolone acetonide was applied for AN at night along with daily sunscreen and it showed successful results after one month of use.¹⁰¹

Topical vitamin D analogs Topical Vitamin D analogs like Calcipotriene and calcipotriol are believed to inhibit keratinocyte proliferation and promote differentiation by increasing keratinocyte intracellular calcium and cyclic GMP levels, thereby reducing the number of keratinocytes resulting in minimization of the cutaneous effects of insulin¹⁰². Bom *et al.* demonstrated improvement of a mixed-type AN in the flexural areas of an obese man after 3 months of 0.005% calcipotriol cream application twice daily.¹⁰³

Lee H W *et al.* also demonstrated improvement in the lesions of an obese patient who used calcipotriol ointment twice daily for a period of 3 months.¹⁰⁴ Gregoriou *et al.* also reported calcipotriol to be a safe, effective, and well-tolerated treatment for AN, particularly in cases

where definite etiological treatment is not possible due to any reason.¹⁰⁵

Chemical peels Superficial chemical peels have been reported to be a relatively safe and effective treatment option for AN. Trichloroacetic acid (TCA) is a caustic chemical substance and causes coagulation and precipitation of skin proteins, leading to necrosis of epidermis. This destruction is followed by inflammation and the activation of wound repair, resulting in re-epithelialization with smoother skin.¹⁰⁶ Zayed *et al.* in a pilot study, documented improvement in AN in six female patients who used TCA peels. Improvement was seen with regards to hyperpigmentation, thickening, and overall appearance.¹⁰⁷ TCA is safe, easily accessible, inexpensive, and can be easily prepared and since it is a stable compound with known precipitation, absorption, and peel depth, judging its endpoint exfoliation is relatively simple.¹⁰⁶

Oral treatment

Oral retinoids (isotretinoin and acitretin) Large doses and extended courses of oral retinoids such as isotretinoin and acitretin have been found to be effective in the treatment of AN.^{95,108} The proposed mechanism of action for these drugs is the normalization of epithelial growth and differentiation. Katz reported successful treatment of an extensive AN associated with obesity with isotretinoin (3 mg/kg/day).¹⁰⁸ However, discontinuation of the treatment resulted in relapse. Walling *et al.* reported a 90% improvement of palmar AN and 50% improvement of axillary AN within 2 months of taking isotretinoin 80 mg/day. However, after gradually tapering this dose over more than a year and receiving over a total of 30 g, the patient experienced recurrence of his skin lesions that improved on taking 1000 mg metformin twice daily.¹⁰⁹ For the treatment of

AN with acitretin, some reports point towards success in cases of syndromic and benign AN.¹⁰⁶ Ozdemir *et al.* reported complete recovery of an 18-year-old male with generalized idiopathic AN experienced after 45 days of acitretin 0.8 mg/kg (50 mg) divided into two daily doses. After starting maintenance therapy of 25 mg acitretin daily for 2 months, lesions recurred that subsequently resolved with topical application of 0.1% retinoic acid¹¹⁰. Because of acitretin's longer terminal elimination half-life and fewer lipophilic properties, its use may, however, be limited with greater potential for early recurrence after discontinuation.

Metformin and rosiglitazone Metformin and rosiglitazone are useful in AN characterized by insulin resistance (IR). They are believed to increase peripheral insulin responsiveness, resulting in a reduction of glucose production, hyperinsulinemia, body weight, and fat mass, as well as an increase in insulin sensitivity in patients with insulin resistance and AN.¹¹⁰

Giri *et al.* reported an adolescent Caucasian boy with IR and extensive AN who showed complete resolution of AN after two years of metformin, despite the persistence of IR, whereas Wasniewska reported recovery of acanthosis nigricans under prolonged metformin treatment in an adolescent with normal weight¹¹²⁻¹¹³. Bellot-Rojas *et al.* observed a reduction in fasting insulin levels with rosiglitazone when compared to metformin and modest improvement of skin texture with both.¹¹⁴

Miscellaneous treatment

Other beneficial therapies (case reports) include fish oil,¹¹⁵ 20% podophyllin in alcohol (for benign AN),¹¹⁶ topical cholecalciferol and surgical excision.¹¹⁷ Urea, salicylic acid and triple-combination depigmenting cream

(tretinoin 0.05%, hydroquinone 4%, fluocinolone acetonide 0.01%) with sunscreens are other options⁷⁷.

Conclusion

Though mainly a disease of cosmetic concern by itself and most often asymptomatic without a significant impairment, AN can be of great importance to identify a wide range of underlying pathologies, including metabolic syndrome and malignancy. A thorough investigation and treatment are, therefore, warranted to prevent long term consequences.

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