1 Acanthosis nigricans

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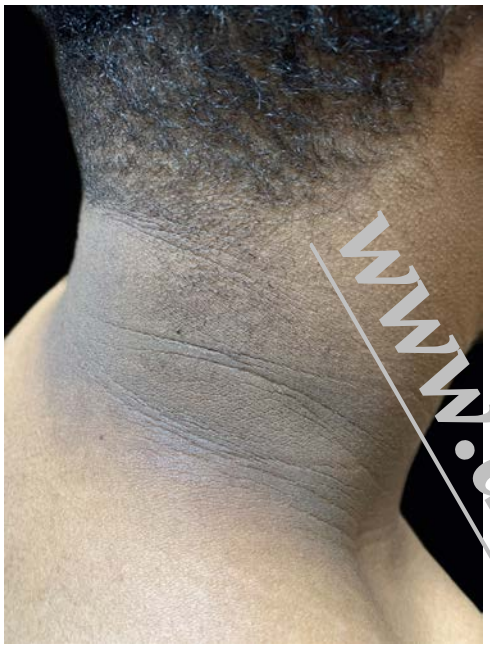


Acanthosis nigricans is characterized by hyperpigmented, verrucous or velvety plaques that usually appear on flexural surfaces and in intertriginous regions. It is most commonly seen in individuals with insulin resistance states, especially obesity and diabetes, and less frequently in association with other metabolic disorders, genetic syndromes, drugs, and malignancy. Although hyperinsulinemia, hyperandrogenemia, circulating anti-insulin receptor antibodies, tyrosine kinase receptor abnormalities (IGFR1 and EGFR), and mutations in fibroblast growth factor receptor have been implicated as causal factors, the precise pathogenesis is not yet known.

MANAGEMENT STRATEGY

The management of patients with acanthosis nigricans addresses the underlying cause, the identification of which requires a salient history, a targeted physical examination, focused diagnostic laboratory tests, and, occasionally, radiologic evaluation.

Relevant historical information includes age at onset, speed of progression from onset, presence or absence of family history, medications, transplant history, and presence or absence of symptoms related to hyperinsulinemia, hyperandrogenemia, hypercortisolism, and internal malignancy.

Drugs reported in association with acanthosis nigricans include niacin, corticosteroids, estrogens, testosterone, insulin, aripiprazole, fusidic acid, protease inhibitors, triazinate, diethylstilbestrol, palifermin, and recombinant growth hormone. Acanthosis nigricans has also been associated with renal and lung transplantation.

Physical examination should document obesity, masculinization, hirsutism, lymphadenopathy, Cushingoid features, and organomegaly. Initial laboratory screening should include fasting blood glucose and serum insulin tested concurrently to confirm or exclude insulin resistance.

Because obesity is the most common cause of both insulin resistance and acanthosis nigricans, it is the likely cause of acanthosis nigricans in overweight patients with no historical suggestion of culprit drugs or evidence of malignancy.

Rare causes of insulin resistance and acanthosis nigricans include the type A and B syndromes, the former characterized by defective insulin receptors and the latter by circulating anti-insulin receptor antibodies in association with autoimmune disorders such as lupus erythematosus. Other causes of insulin resistance and acanthosis nigricans are polycystic ovarian disease, HAIR-AN syndrome, familial lipodystrophies, and various endocrinopathies.

The most commonly associated malignancy is gastric adenocarcinoma. Less frequent associations are endocrine, genitourinary, lung, and gastrointestinal carcinomas, and, even more rarely, melanoma and cutaneous T-cell lymphomas/Sézary syndrome. Malignant acanthosis nigricans may coexist with other cutaneous markers of internal malignancy, such as tripe palms, the sign of Leser–Trélat, florid cutaneous papillomatosis, and hyperkeratosis of the palms and soles. If malignancy-associated acanthosis nigricans is suspected, age-appropriate cancer screening should be performed. Additional laboratory tests may include a complete blood count, stool test for occult blood, and chest and gastrointestinal radiographs, as well as gastrointestinal endoscopy. Referral to the appropriate specialist would be indicated.

In the absence of objective evidence for a specific cause, the acanthosis nigricans may be labeled as idiopathic, which may or may not be familial. Treatment of the underlying cause, if identified, often leads to the resolution of the acanthosis nigricans. Otherwise, most published treatment modalities are symptomatic and/or cosmetic.

Specific Investigations

- Document obesity based on ideal body weight, height/weight, body mass index (BMI)
- Document blood pressure
- Determine fasting blood glucose and insulin levels in parallel. Consider ordering HbA_{1c}, alanine aminotransferase (ALT), and fasting lipoprotein profile in obese patients
- Consider screening for other endocrine and metabolic diseases
- Consider malignancy: if suspected, refer to the appropriate specialist for the best diagnostic procedure
- Consider drugs as a cause
- Consider transplantation as a cause
- Consider familial/genetic disorders as a cause

Acanthosis nigricans: a practical approach to evaluation and management. Higgins S, Freemark M, Prose N. Dermatol Online J 2008; 14: 2.

A review of the diagnosis and management of acanthosis nigricans.

Acanthosis nigricans: a fold (intertriginous) dermatosis. Kutlubay Z, Engin B, Bairamov O, et al. Clin Dermatol 2015; 33: 466–70.

A review of the classifications, etiopathogenesis, and treatment of acanthosis nigricans.

An approach to acanthosis nigricans. Phiske M. Indian Dermatol Online J 2014; 5: 239.

A review of the pertinent laboratory/radiologic investigations and treatment options of acanthosis nigricans.

Prevalence and significance of acanthosis nigricans in an adult population. Hud J, Cohen J, Wagner J, et al. Arch Dermatol 1992; 128: 941–4.

74% of obese adult patients seen at the Parkland Memorial Hospital Adult Obesity Clinic in Dallas, Texas had acanthosis nigricans. The skin disorder predicted the existence of hyperinsulinemia.

Juvenile acanthosis nigricans. Sinha S, Schwartz RA. J Am Acad Dermatol 2007; 57: 502–8.

A review of the evaluation of children presenting with acanthosis nigricans.

Cutaneous findings and systemic associations in women with polycystic ovary syndrome. Schmidt TH, Khanijow K, Cedars MI, et al. JAMA Dermatol 2013; 153: 391–8.

Among the women with polycystic ovarian syndrome, 36.9% had acanthosis nigricans.

Malignant acanthosis nigricans: a review. Rigel D, Jacobs M. J Dermatol Surg Oncol 1980; 6: 923–7.

Gastric carcinoma was reported in 55% of acanthosis nigricans cases associated with internal malignancy.

First-Line Therapy

- Treat the underlying cause — D

Acanthosis nigricans with severe obesity, insulin resistance and hypothyroidism: improvement by diet control. Kuroki R, Sasamoto Y, Imamura M, et al. Dermatology (Basel) 1999; 198: 164–6.

A 27-year-old morbidly obese man with acanthosis nigricans was treated with a low-calorie diet. A consequent decrease in weight and insulin-resistant state led to remarkable improvement of his acanthosis nigricans.

Clearance of acanthosis nigricans associated with insulinoma following surgical resection. Ghosh S, Roychowdhury B, Mukhopadhyay S, et al. QJM 2008; 101(11): 899–900.

A case report detailing the disappearance of acanthosis nigricans following surgical resection of an insulinoma.

Acanthosis nigricans in association with congenital adrenal hyperplasia: resolution after treatment. Kurtoğlu S, Atabek ME, Keskin M, et al. Pediatr 2005; 47: 183–7.

A 3-day-old girl with congenital adrenal hyperplasia presented with acanthosis nigricans of both axillae. After corticosteroid and mineralocorticoid therapy for the disease, the acanthosis nigricans resolved.

Second-Line Therapies

- Tretinoin — B
- Adapalene — B
- Tazarotene — E
- Trichloroacetic acid — C
- Metformin — C
- Ammonium lactate 12% — E
- Glycolic acid — E

Current treatment options for acanthosis nigricans. Patel NU, Roach C, Alinia H, et al. Clin Cosmet Investig Dermatol 2018; 11: 407–13.

An overview of current treatment options for acanthosis nigricans.

Comparison of the efficacy and safety of 0.1% adapalene gel and 0.025% tretinoin cream in the treatment of childhood acanthosis nigricans. Treesirichod A, Chaithirayanon S, Wongjitrat N. Pediatr Dermatol 2019; 36:330–4.

Topical 0.1% adapalene gel and 0.025% tretinoin cream applied daily for 8 weeks significantly improved neck hyperpigmentation without significant differences in efficacy or tolerability.

The efficacy of topical 0.1% adapalene gel for use in the treatment of childhood acanthosis nigricans: a pilot study. Treesirichod A, Chaithirayanon S, Wongjitrat N, et al. Indian J Dermatol 2015; 60: 103.

Topical 0.1% adapalene gel applied daily for 4 weeks led to less skin darkening in 16 patients with childhood acanthosis nigricans.

Metformin as adjunctive therapy in acanthosis nigricans treatment: two arms single blinded clinical trial. Alkhayrat A, Alshamrani N, Lama A, et al. Clin Dermatol Res J 2019; 4: 1.

Nine obese patients with acanthosis nigricans were treated with metformin 500 mg orally two times daily and topical tretinoin and hydroquinone cream for 24 weeks. Compared to the control group (topical treatment alone), the study group demonstrated greater clinical improvement in the severity of their acanthosis nigricans.

Effective treatment by glycolic acid peeling for cutaneous manifestation of familial generalized acanthosis nigricans caused by FGFR3 mutation. Ichiyama S, Funasaka Y, Otsuka Y, et al. J Eur Acad Dermatol Venereol 2016; 30: 442–5.

Glycolic acid 35% to 70% peel performed on two patients every 2 weeks led to less hyperpigmentation and keratinization. Improvement was maintained with continued peels every 2–5 months.

Third-Line Therapies

- Urea — E
- Calcipotriol — E
- Tretinoin, hydroquinone, and fluocinolone acetonide — E
- Melatonin — C
- Isotretinoin — E
- Acitretin — E
- Octreotide — E
- Dietary fish oil — E
- Sitagliptin and pioglitazone — E
- Laser long-pulsed (5 m-sec) alexandrite laser, fractional carbon dioxide laser — E

Acanthosis nigricans associated with primary hypogonadism: successful treatment with topical calcipotriol. Gregoriou S, Anyfandakis V, Kontoleon P, et al. J Dermatol Treat 2008; 19: 373–5.

Topical calcipotriol ointment 50 mcg/g applied twice daily for 8 weeks completely cleared a man's acanthosis nigricans without relapse after 6 months of observation.

Treatment of acanthosis nigricans with oral isotretinoin. Katz R. Arch Dermatol 1980; 116: 110–11.

A woman with acanthosis nigricans had skin clearance with oral isotretinoin (2 mg/kg/day) but long-term therapy was required to maintain clearance.

Generalized idiopathic acanthosis nigricans treated with acitretin. Ozdemir M, Toy H, Mevlitoğlu I, et al. J Dermatolog Treat 2006;17: 54–6.

A male with acanthosis nigricans had clearance of his acanthosis nigricans after 6 weeks of oral acitretin 25 mg taken twice daily. Improvement was maintained on acitretin 0.4 mg/kg/day.

Long-term octreotide treatment reduced hyperinsulinemia, excess body weight, and skin lesions in severe obesity with acanthosis nigricans. Lunetta M, Di Mauro M, Le Moli R, et al. Endocrinol Invest 1996;19: 699–703.

A boy affected by severe obesity was treated with octreotide for 150 days (50 mcg × three daily subcutaneous administrations).

Acanthosis nigricans. Schwartz RA. J Am Acad Dermatol 1994; 31: 1.

A woman with diabetes mellitus and acanthosis nigricans was treated with fish oil supplementation, leading to improvement despite continued hypertriglyceridemia.

Melatonin treatment improves insulin resistance and pigmentation in obese patients with acanthosis nigricans. Sun H, Wang X, Chen J, et al. Int J Endocrinol 2018; 2018: 2304746.

Seventeen obese patients with acanthosis nigricans noted improvement in skin hyperpigmentation after treatment with melatonin 3 mg/day for 12 weeks.

Regression of acanthosis nigricans with the addition of sitagliptin and pioglitazone. Adderley-Rolle EM, Peter S. West Indian Med J 2015; 64: 160–1.

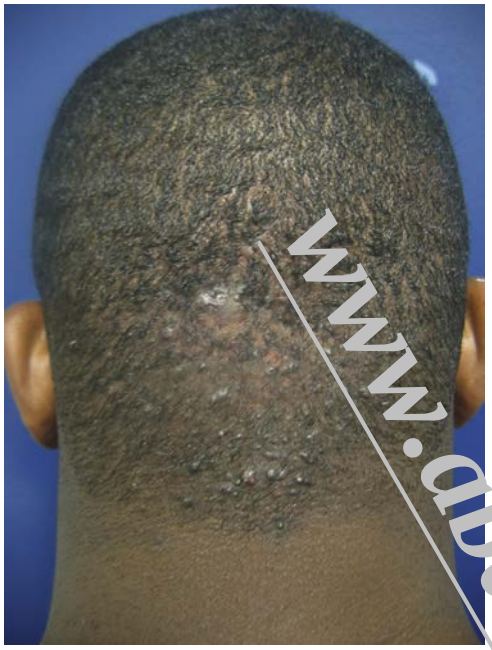
Acanthosis regressed with anti-diabetic medication.

Treatment of acanthosis nigricans of the axillae using a long-pulsed (5-msec) alexandrite laser. Rosenbach A, Ram R. Dermatol Surg 2004; 30: 1158–60.

A woman with axillary acanthosis nigricans was treated with long-pulsed alexandrite laser on one axilla, with the other axilla as an untreated control. The treated axilla showed significant improvement.

2 Acne keloidalis nuchae

Ahuva D. Cices, Andrew F. Alexis



Acne keloidalis nuchae (AKN) is a chronic disorder predominantly affecting males with Afro-textured hair characterized by inflammatory changes of hair follicles on the posterior neck and scalp that result in fibrotic papules and cicatricial alopecia. Erythematous papules and pustules are the primary inflammatory lesions of AKN. At the time of presentation, most patients will have scarring as a result of the extensive inflammation seen in AKN, manifesting as keloid-like, dome-shaped papules, plaques, or nodules, and scarring alopecia in the affected area. Tufted hairs arising from keloid-like lesions may also be present. AKN is a misnomer without true acne or keloids. The pathogenesis of AKN is poorly understood, but is likely multifactorial, including genetic, immunologic, and environmental factors.

MANAGEMENT STRATEGY

Effective management starts with an accurate diagnosis. AKN is diagnosed clinically by the presence of inflammatory papules, pustules, and scar-like lesions on the occipital scalp and posterior neck of males with Afro-textured hair. Rarely, AKN occurs in females or individuals of non-African descent. The diagnosis is made clinically, without need for biopsy in the vast majority of cases. Characteristic histopathologic features include acute and chronic folliculitis, ruptured pilosebaceous units, and dermal fibrosis. When pustules, scale, or crust is present, bacterial and fungal cultures aid to rule out bacterial folliculitis and/or superinfection, or tinea capitis, respectively. Pustules due to *Staphylococcus aureus* folliculitis can resemble early AKN, but are more superficial, lack induration or keloid-like features, and respond rapidly to appropriate antibiotics.

Treatment of AKN requires suppressing active inflammation and fibrosis as well as avoidance of exacerbating factors using a combination of medical therapies, procedural interventions, and behavioral modification. Disease management is heavily based on clinician experience due to limited evidence or controlled studies and lack of consensus guidelines.

The initial approach comprises *avoidance of close shaving, friction, and rubbing* to prevent disease exacerbations in combination with medical treatments. Mild disease is managed with a combination of topical therapies including *high-potency topical corticosteroids (group 1 or 2, e.g., clobetasol 0.05% gel or foam), antimicrobial washes (e.g., chlorhexidine wash), topical antibiotics (e.g., clindamycin phosphate 1% gel or foam), and topical retinoids (e.g., tazarotene 0.05% or 0.1% gel)*. Topical corticosteroids are applied once or twice daily and alternating in 2-week cycles to minimize effects of chronic steroid use. Twice daily application of clobetasol propionate 0.05% foam in alternating 2-week cycles was shown to be effective in a 20-subject, open-label, clinical trial. Improvement is typically achieved in 6–8 weeks and therapy is continued until signs (e.g., papules/pustules) and symptoms (e.g., pruritus, pain) have improved, with reinitiation of therapy for flares. This author (AFA) favors clobetasol propionate 0.05% foam twice daily or a *fixed combination halobetasol 0.01%-tazarotene 0.045% lotion* once daily for 2 weeks followed by application three times weekly.

Antimicrobial washes including *chlorhexidine and povidone iodine* are used to prevent secondary infection. If superinfection is suspected, cultures and appropriate antibiotic therapy should be completed prior to initiating steroids. When pustules are present, topical antibiotics are recommended. No formal studies have been completed to evaluate the efficacy of topical antibiotics for AKN. This author (AFA) favors *topical clindamycin 1% gel or foam for treatment of mild pustules*. Efficacy of once-daily topical retinoids, including adapalene, tretinoin, and tazarotene, is unclear, though they are theorized to improve AKN through antiinflammatory effects and prevention of follicular occlusion.

Persistent inflammatory lesions as well as keloid-like scars of AKN can be effectively treated with *intralesional triamcinolone* at varying concentrations ranging from 2.5 to 40 mg/mL with higher concentrations (>20 mg/mL) reserved for large (>3 cm), keloid-like lesions. *Cryosurgery* has also been used successfully, though no studies have evaluated specific parameters for AKN, and hypopigmentation or depigmentation are risks in patients with skin of color.

Failure of the above therapies or moderate-to-severe disease warrants systemic treatments. *Oral antibiotics* are used for several weeks to months to control inflammatory flares. *Tetracyclines such as doxycycline or minocycline* are the mainstay of oral antibiotic therapy of AKN; however, published evidence is limited. This author (AFA) favors oral doxycycline for its antiinflammatory and antimicrobial effects. When *Staphylococcus aureus* superinfection is present, a course of a first-generation *cephalosporin* or doxycycline at antimicrobial doses (50–100 mg twice daily) is recommended. As an adjunct to topical and intralesional therapy, *subantimicrobial doxycycline (40 mg/day)* for 12–16 weeks is useful in this author's experience. Select cases show effective treatment of refractory inflammatory lesions with *oral retinoids* starting at 0.25–0.6 mg/kg daily followed by lower doses for maintenance.

Light and energy based therapies are effective for long-term disease control. Long-pulse, *long-wave lasers including alexandrite 755 nm, diode 800–810 nm, and neodymium:yttrium-aluminum-garnet (Nd:YAG) 1064 nm* are effective treatment for AKN due to their ability to completely destroy the hair follicle. The 1064-nm Nd:YAG laser has the most favorable profile for hair removal in darker-skinned patient populations: deepest penetration and

least absorption by melanin, thereby maximizing efficacy and minimizing risk of dyspigmentation. Its efficacy has been demonstrated in a prospective controlled trial. *Er:YAG* has been shown to have the same efficacy as Nd:YAG for papular disease as well as beneficial effects on larger plaques in a comparative trial. A 12-subject AKN trial showed targeted *ultraviolet B (UVB) phototherapy* administered three times weekly is effective and well tolerated.

Surgical excision, including scalpel, electrosurgical, or laser excision, followed by primary closure or secondary intention healing is effective for refractory and severe disease. Regardless of the surgical technique utilized, successful treatment requires complete removal of hair follicles to prevent recurrence. Horizontal ellipse excision followed by secondary intention healing is recommended for optimal cosmetic outcomes. Postsurgical adjuvant therapies have included intralesional or topical steroids and radiotherapy; however, these are not indicated given the low recurrence rate. Local radiation therapy with 3 Gy and 6 MeV × 10 sessions on alternating days was successful in treating a case of refractory AKN that recurred after therapy with topicals, oral antibiotics, isotretinoin, and partial excision.

Specific Investigations

- Pustule swab
- Punch biopsy

First-Line Therapies

• Counseling	E
• High-potency topical steroid (class I or II)	B
• Topical antibiotic	E
• Antimicrobial cleansers	E
• Oral antibiotic	E
• Topical retinoid	E

Pseudofolliculitis barbae. Chu T. Practitioner 1989; 233: 307–9.

Topical clindamycin 1% was effective for pseudofolliculitis and acne keloidalis in a limited open-label study.

An open label study of clobetasol propionate 0.05% and betamethasone valerate 0.12% foams in the treatment of mild to moderate acne keloidalis. Callender VD, Young CM, Haverstock CL, et al. Cutis 2005; 75(6): 317–21.

Open-label study in 20 African American patients that showed efficacy and tolerability of topical steroids for treatment of mild-to-moderate scalp AKN. Clobetasol propionate ointment 0.05% foam used twice daily alternating 2 weeks on and 2 weeks off for a total of 8 weeks showed statistically significant improvement of papule/pustule count and pruritus scores. In the second phase, subjects with residual disease ($n = 11$) were treated with betamethasone valerate 0.12% foam twice daily from weeks 8–12 with no statistically significant change in lesion count from weeks 8–12.

Folliculitis keloidalis nuchae and pseudofolliculitis barbae: are prevention and effective treatment within reach? Alexis A, Heath CR, Halder RM. Dermatol Clin 2014; 32(2): 183–91.

Review of treatment options for AKN, which include counseling on preventative measures to avoid disease exacerbations (e.g., avoiding mechanical irritation and manipulation) and medical treatments including antimicrobial cleansers (e.g., chlorohexidine), topical and oral antibiotics, topical steroids, and topical retinoic acid. Additionally, surgical and laser therapies are also addressed.

Second-Line Therapies

• Alexandrite laser	C
• Targeted UVB	C
• Nd:YAG	C
• Er:YAG	C
• Oral retinoid	E
• Diode laser	E
• Intralesional steroids	E
• Cryosurgery	E
• Imiquimod	E
• Pimecrolimus	E

Improving acne keloidalis nuchae with targeted ultraviolet B treatment: a prospective, randomized, split-scalp comparison study. Okoye GA, Rainer BM, Leung SG, et al. Br J Dermatol 2014; 171(5): 1156–63.

Split-scalp study in 11 patients with AKN treated with targeted UVB (290–320 nm) up to three times weekly for 8 weeks, followed by 8 weeks of full scalp treatment with statistically significant decreased lesion count on treated side at 8 weeks. Authors also noted improvement in clinical appearance and patient satisfaction without tolerability limitations.

Successful treatment of acne keloidalis nuchae with erbium:YAG laser: a comparative study. Gamil HD, Khater EM, Shattab FM, et al. J Cosmet Laser Ther 2018; 20(7–8): 419–23.

In this comparative study, 30 male subjects with AKN were randomly assigned to six sessions Er:YAG 2490 nm, 3-mm spot size, pulse duration 300 msec, frequency 5 Hz, and pulse 800–900 mJ in partially overlapping mode or Nd:YAG 1064 nm, 13-mm spot size, pulse duration of 35 msec, and a fluence of 30–35 J/cm² in partially overlapping mode. Following treatment, both groups received ice compresses, and topical fusidic acid and betamethasone topically for 3 days posttreatment. Both groups had improvement in papular disease (91.8% vs. 88%). Significant improvement in plaques only in the Er:YAG-treated group.

Nd:YAG and Er:YAG can be used to treat early popular lesions of AKN. Er:YAG is more effective than Nd:YAG for the treatment of more advanced disease.

Keratosis follicularis spinulosa decalvans and acne keloidalis nuchae. Goh MS, Magee J, Chong AH. Australas J Dermatol 2005; 46(4): 257–60.

Rapid improvement of inflammatory lesions in biopsy-confirmed concomitant suppurative AKN and keratosis follicularis spinulosa in a 27-year-old Caucasian male with oral isotretinoin 20 mg (0.25 mg/kg) daily for 12 months. Maintenance of response with 20 mg every 2–3 days at 1 year.

Use of imiquimod and pimecrolimus cream in the treatment of acne keloidalis nuchae. Barr J, Friedman A, Balwin H. J Am Acad Dermatol 2005; 52(3 Suppl): 64.

Small open-label study with five subjects randomized to topical imiquimod applied once daily or pimecrolimus twice daily for 8 weeks. All five patients had significant improvement in pruritus and decreased lesion counts.