REVIEW ARTICLE NORTH BENGAL MEDICAL COLLEGE JOURNAL [2017], VOL., 3, No. 2 : 42-48

Acral Acanthosis Nigricans: its update and management

*Arpan Kumar Basak,[1] Joya Debnath,[2] M A Kasem Khan[3]

Received: December 20, 2016 Accepted: March 04, 2017

Abstract

Acanthosis nigricans is a skin condition that causes thick, velvety and darkened skin areas (due to increased thickness of epidermis). It commonly affects the skin of the armpits, the groin region, head and neck (back of the neck), and anal/genital region. Acral (indicating peripheral body parts) acanthosis nigricans is one among the seven types of acanthosis nigricans. It is different from the other types of acanthosis nigricans in that the lesions are present on the skin overlying the ankles, knee, fingers and toes. Acral acanthosis nigricans is usually diagnosed by a thorough clinical history and physical examination. Even though, it is a benign condition, dermatologist consultation and testing is necessary to rule out other causes of the condition. There is no definitive treatment for acral acanthosis nigricans. However, certain treatment modalities may be used for cosmetic reasons. The prognosis is typically good with no known major complications being noted.

Key words: *Acanthosis nigricans, Acral acanthosis nigricans, Obesity, Insulin resistance*

*[1.] *Assistant Professor, Department of Dermatology, Kumudini Women's Medical College, Mirzapur, Tangail*

[2.] *Assistant Professor, Department of Forensic Medicine, Kumudini Women's Medical College, Mirzapur, Tangail*

[3.] *Associate Professor, Department of Dermatology, North Bengal Medical College, Sirajganj*

Correspondence *Arpan Kumar Basak, Email: arpanbasak2010@gmail.com*

Introduction

The disease acanthosis nigricans (AN) is characterized by the presence of a thick macule with a brown velvet-like surface.[1] Lesions commonly occur in the axillary region, neck, inguinal region, anticubital fossa, and popliteal fossa. Schwartz has categorized the entity into following eight types: benign, malignant, associated with obesity, syndrome, unilateral, drug induced, mixed and acral.[2,3] Acral-type acanthosis nigricans, also called as acral acanthotic anomaly is a dermatitis characterized by velvety, papilomatous, brownish black typically affected to the dorsum of the hand and foot. It is apparently more common in persons with a dark complexion and affects acral areas without prominent affection of axilla and other flexures.[2] Acral AN usually

affects individual who are usually healthy and have no associated diseases/conditions unlike other forms of that is seen in association with an underlying condition. We accumulated several previous articles regarding this disease through internet web search, but in fact, we have a few literatures regarding this disease. In this review, we discuss with an aim to evaluate the pathogenesis of disease and its clinical implications and management.

Prevalence

A high prevalence has been observed recently due to the rising prevalence of obesity and diabetes. The prevalence varies from 7% to 74%, according to age, race, frequency of type, degree of obesity and concomitant endocrinopathy.

Clinical features

Individuals of any age group can be affected by Acral AN, but it is most commonly seen in adult population. Both males and females of all races and with ethnicities can be affected. However, it more commonly affects individuals of darker skin tones. Thus, people of African origin can be affected more than other populations. Other factors may play a role with respect to other types of AN, such as insulin resistance, cancer, medication etc. Clinically, it most commonly presents as hyperpigmented velvety, poorly-defined skin lesions as shown in clinical photograph (Figure 1). The lesions are limited to the top portion of the feet, elbows, knuckles, and knees (upper and lower extremities). The hyperpigmentation can be either brown or black. The affected individuals are usually healthy. Acanthosis nigricans is occasionally pruritic.[4]

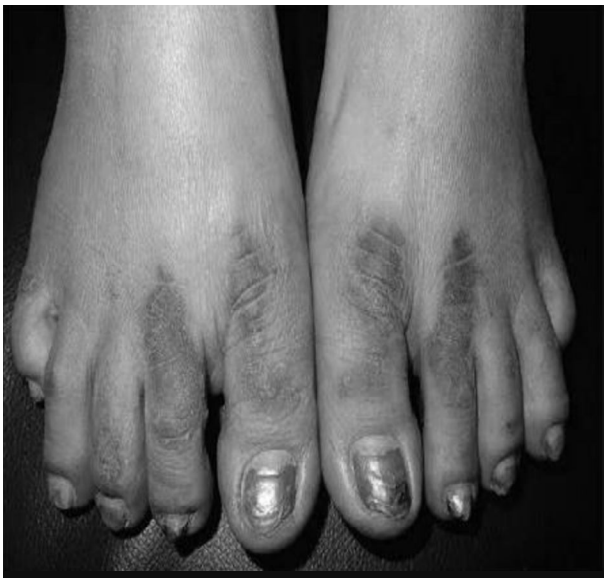

Figure 1: Bilateral hyperpigmented, hyperkeratotic skin lesions

Histopathology

Histopathology, it reveals a thickened stratum corneum with minimal involvement of the dermis except for thickened and elongated dermal projections. The thickening of stratum spinosum (acanthosis) is variable and typically mild.[5,6] The dark color of AN is likely due to hyperkeratosis rather than to a mild increase in melanin pigmentation.[2] Infiltration of lymphocytes, plasma cells or neutrophils may be present.

Association of other diseases

Acanthosis nigricans is linked to a variety of syndromes. Most are associated with insulin resistance or fibroblast growth factor receptor (FGFR). AN may also appear as an adverse effect of several medication such as glucocorticoids, niacin, insulin, oral contraceptives and protease inhibitors.[7-12] Recently, it has been reported that acral AN is associated with dermatofibrosarcoma protube-rans, non-Hodgkin's lymphoma.[13, 14]

Pathogenesis

The pathogenesis of acral type of AN is similar to acanthosis nigricans. Insulin has been demonstrated to cross dermoepidermal junction (DEJ) to reach keratinocytes. Elevated insulin concentrations result in direct and indirect activation of IGF-1 receptors on keratinocytes and fibroblasts, leading to proliferation (Figure 2). Other mediators may also contribute, including other tyrosine kinase receptors such as EGFR epidermal growth factor receptor and FGFR (fibroblast growth factor receptor). Acanthosis nigricans is commonly associated with disorders with insulin resistance, including obesity, type 2 diabetes, and the polycystic ovary syndrome.[15] At high concentrations, however, insulin can exert more potent growth-promoting effects through binding to insulin like growth factor 1 receptors (IGF-1Rs). A number of observations suggest that insulin-dependent activation of IGF-1Rs can promote cellular proliferation and facilitate the development of AN. The severity of AN in obesity correlates positively with the fasting insulin concentration.[16, 17] Thus, insulin may promote AN through direct activation of the IGF-1 signaling pathway. The true pathogenesis of AN, however, is likely to be more complex. Hyperinsulinemia may also facilitate the development of AN indirectly by increasing the levels of free IGF-1 in the circulation.

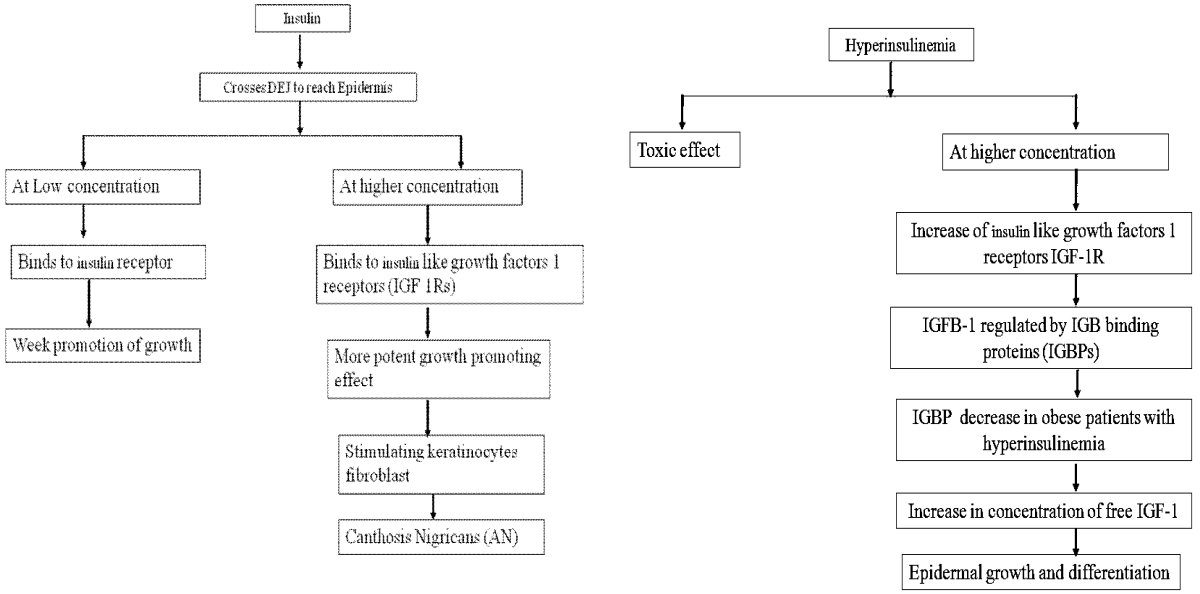

Figure 2: The flow chart showing the pathogenesis and role of IGF on signal pathways on keratinocytes and melanocytes

Diagnosis

Diagnosis is mostly clinical and can be confirmed by histopathologic observations. The lesion may demonstrate a benign epidermis with hyperkeratosis, papillomatosis, thickening of epidermis (acanthosis), increased number of melanocytes (melanocytic hyperplasia) and lymphocytic inflammation. Interestingly, there are only fewer acanthosis with no hyperpigmentation that do not fit the histologic terminology. The hyperpigmented appearance is actually due to hyperkeratosis. Microscopically, all the seven types of share similar features.

Investigations

Diagnosis is based on clinical with histopathology examination needed for confirmation. Histological findings are similar in all forms of AN. Spectroscopic and colorimetric measurements combined with chemometric analysis methods also provide sensitive and specific diagnosis of AN.[17]

Evaluation and Management

In majority of cases, improvement of the skin lesions is the primary concern of patients presenting to dermatologists. Treatment of its underlying condition often results in improvement of AN. Therapeutic approach involves treatment of underlying disease or tumor, cessation/avoidance of the inciting agent in drug-induced AN, use of topical/oral agents and cosmetic surgery.[18] Weight loss and exercise have shown to increase insulin sensitivity and reduce insulin levels causing improvement in obesity associated AN. Correction of hyperinsulinemia reduces hyperkeratotic lesions.

Topical Treatment

Retinoids

It is epidermopoietic and causes a reduction of the stratum corneum replacement time. It corrects hyperkeratosis and causes near complete reversion to normal state. Lahiri and Malakar in their study have reported that intermittent tretinoin application is needed to maintain improved status.[19]

Ammonium lactate and tretinoin

Lactic acid is an alpha-hydroxy acid that works as a peeling agent and also via release of desmogleins, indicating disintegration of desmosomes. Retinoids affect cell growth, differentiation, morphogenesis and alter cell cohesiveness. Though the exact mechanism of action of the two agents is unknown, synergistic interaction is thought to play a role.[20]

Peels

Trichloroacetic acid (TCA) is safe, easily available, cheap, and easy to prepare. It causes precipitation of proteins of epidermal cells leads to necrosis and destruction of epidermis, followed by inflammation followed by activation of wound repair mechanisms. This leads to re-epithelialization with replacement of smoother skin. The previous study have reported improvement of AN in six female patients after TCA peeling.[21] The advantages of TCA are that it is a stable product, safe and effective therapeutic modality for AN in comparison to other topical treatments. Topical tretinoin needs frequent application for long duration and improves hyperkeratosis, but not hyperpigmentation. Topical salicylic acid, podophyllin, urea, and calcipotriol need frequent application, while TCA peel is done in two to three sessions. Dermabrasion or alexandrite laser are expensive and may lead to post inflammatory hyperpigmentation.

Calcipotriol

A beneficial agent that inhibits keratinocyte proliferation and promotes differentiation by increasing intracellular calcium levels and cyclic GMP levels in keratinocytes. It is safe, well-tolerated, alternative beneficial treatment when an etiological treatment is not possible or necessary.[22]

Miscellaneous treatment

Other therapies (case reports) are included likely fish oil, 20% podophyllin in alcohol , and surgical

excision, Urea, salicylic acid and triple combination depigmenting cream (tretinoin 0.05%, hydroquinone 4%, fluocinolone aceto-nide 0.01%) with sunscreens are other options.[20-25]

Oral Treatment

Oral retinoids

Oral retinoids (isotretinoin, acitretin) can be effective agent causing improvement, it requires large doses and extended courses, and relapses are described.[26] The mechanism of action is probably normalization of epithelial growth and differentiation.[27] Acitretin has been rarely reported for AN treatment and has showed good success in cases with syndromic and benign AN. Oral isotretinoin has been used successfully to treat extensive AN.[28]

Metformin and rosiglitazone

Oral anti diabetic agents (Metformin and rosiglitazone) are useful in reduction in fasting insulin levels with rosiglitazone when compared to metformin and modest improvement of skin texture with both.[29] Metformin reduces glucose production by increasing peripheral insulin responsiveness, reduces hyperinsulinemia, body weight and fat mass and improves insulin sensitivity.[30, 31]

Cosmetic treatment

For cosmetic purpose, long-pulsed alexandrite laser, which was designed to target melanin in hair, could improve this condition. They hypothesized that thermal heating of epidermis and dermis results in tissue remodeling and pigment reduction. They reported 95% clearance after seven sessions and concluded that long pulsed alexandrite laser can effectively and safely treat AN. [20, 23, 32]

Prognosis (Outcomes/Resolutions)

Thus, the prognosis of AN is excellent with adequate (skin) treatment. However, the overall prognosis depends upon the underlying cause of the condition. The prognosis of acral AN is excellent with no associated major complication being noted.

Conclusion

Though mainly a disease of cosmetic concern, AN can be pointer to underlying metabolic syndrome or malignancy. A thorough investigation and treatment is therefore mandatory to prevent long term consequences.

References

1. Christine AD, Lucinda SB, Stephen PS. Cutaneous manifestation of internal malignant disease. In: Wolff K, Goldsmith LA, Katz SI, Glichrest BA, Paller AS, Leffel DJ, editors. Fitzpatrick's dermatology in general medicine. 7th ed. McGraw-Hill, New York: 2008; p. 1494-1498.
2. Schwartz RA. Acanthosis nigricans. J Am Acad Dermatol. 1994; 31: 1–19.
3. Schwartz RA. Acral acanthotic anomaly (AAA). J Am Acad Dermatol. 1981; 5: 345–346.
4. Curth HO. Classification of acanthosis nigricans. Int J Dermatol.1976; 15: 592-593.
5. Rogers DL. Acanthosis nigricans. Semin Dermato. 1991; 10: 160-163
6. Schwartz RA, Janniger CK. Childhood acanthosis nigricans. Cutis. 1995; 55: 337-341.
7. Kahn SE, Beard JC, Schwartz MW, Ward WK, Ding HL, Bergman RN, et al. Increased beta-cell secretory capacity as mechanism for islet adaptation to nicotinic acid-induced insulin resistance. Diabetes. 1989; 38: 562-568.

8. McKenney JM, Proctor JD, Harris S, Chinchili VM. A comparison of the efficacy and toxic effects of sustained- vs immediate-release niacin in hypercholesterolemic patients. JAMA. 1994; 271: 672-677.
9. Fleming MG, Simon SI. Cutaneous insulin reaction resembling acanthosis nigricans. Arch Dermatol.1986; 122: 1054-1056.
10. Skouby SO. Update on the metabolic effects of oral contraceptives. J Obstet Gynaecol. 1986; 6 Suppl 2: S104-109.
11. Mellor-Pita S, Yebra-Bango M, Alfaro-Martínez J, Suárez E. Acanthosis nigricans: a new manifestation of insulin resistance in patients receiving treatment with protease inhibitors. Clin Infect Dis. 2002; 34: 716-717.
12. Walli R, Herfort O, Michl GM, Demant T, Jager H, Dieterle C, et al. Treatment with protease inhibitors associated with peripheral insulin resistance and impaired oral glucose tolerance in HIV-1-infected patients. AIDS 1998; 12: F167-173.
13. Song JY, Lim JH, Kim CW, Kim HO. A case of acral type acanthosis nigricans associated with lymphoma. Korean J Dermatol 2002; 40: 841-843.
14. Lee SS, Jung NJ, Im M, Lee Y, Seo YJ, Lee JH. Acral-type malignant acanthosis nigricans associated with gastric adenocarcinoma. Ann Dermatol. 2011; 23: S208-210.
15. Cruz PD, Jr. Hud Jr. Excess insulin binding to insulin-like growth factor receptors: proposed mechanism for acanthosis nigricans. J Invest dermatol. 1992; 98: 825-856.
16. Stuart CA, Pat CJ, Peters EJ. Prevalence of aanthosis nigricansin an unselected population. Am J Med. 1989; 87: 269-272.
17. Hud JA Jr. Cohan Jb, Wagner JM. Cruz PD Jr. Prevalence and significance of acanthosis nigricans in an adult obese population. Arch Dermatol. 1992; 128: 941-944.
18. Devpura S, Pattamadilok B, Syed ZU, Vemulapalli P, Henderson M, Rehse SJ, et al. Critical comparison of diffuse reflectance spectroscopy and colorimetry as dermatological diagnostic tools for acanthosis nigricans: A chemometric approach. Biomed Opt Express. 2011; 2: 1664-1673.
19. Lahiri K, Malakar S. Topical tretinoin in acanthosis nigricans. Indian J Dermatol Venereol Leprol. 1996; 62: 159-161.
20. Higgins SP, Freemark M, Prose NS. Acanthosis nigricans: a practical approach to evaluation and management. Dermatol Online J. 2008; 14: 2.
21. Zayed A, Sobhi RM, Abdel Halim DM. Using trichloroacetic acid in the treatment of acanthosis nigricans: A pilot study. J Dermatolog Treat. 2014; 25: 223.
22. Gregoriou S, Anyfandakis V, Kontoleon P, Christofidou E, Rigopoulos D, Kontoch-ristopoulos G. Acanthosis nigricans associated with primary hypogonadism: Successful treatment with topical calcipotriol. J Dermatolog Treat. 2008; 19: 373-375.
23. Kapoor S. Diagnosis and treatment of acanthosis nigricans. Skin Med. 2010; 8: 161-164.
24. Epstein E. Podophyllin therapy in acanthosis nigricans. J Invest Dermatol. 1951; 17: 7.

25. Puri N. A study of pathogenesis of acanthosis nigricans and its clinical implications. Indian J Dermatol. 2011; 56: 678-683.

26. Hermanns-Lê T, Scheen A, Piérard GE. Acanthosis nigricans associated with insulin resistance: Pathophysiology and management. Am J Clin Dermatol. 2004; 5: 199-203.

27. Katz RA. Treatment of acanthosis nigricans with oral isotretinoin. Arch Dermatol. 1980;116: 110-111.

28. Jeong KH, Oh SJ, Chon S, Lee MH. Generalized acanthosis nigricans related to type B insulin resistance syndrome: A case report. Cutis. 2010; 86: 299-302.

29. Bellot-Rojas P, Posadas-Sanchez R, Caracas-Portilla N, Zamora-Gonzalez J, Cardoso-Saldaña G, Jurado-Santacruz F, et al. Comparison of metformin versus rosiglitazone in patients with acanthosis nigricans: A pilot study. J Drugs Dermatol. 2006; 5: 884-889.

30. Atabek ME, Pirgon O. Use of metformin in obese adolescents with hyperinsulinemia: a 6-month, randomized, double-blind, placebo -controlled clinical trial. J Pediatr Endocrinol Metab. 2008; 21: 339-348.

31. Tankova T, Koev D, Dakovska L, Kirilov G. Therapeutic approach in insulin resistance with acanthosis nigricans. Int J Clin Pract. 2002; 56: 578-581.

32. Rosenbach A, Ram R. Treatment of Acanthosis nigricans of the axillae using a long-pulsed (5-msec) alexandrite laser. Dermatol Surg. 2004; 30: 1158-1160.