



AN OVERVIEW OF ACANTHOSIS NIGRICANS

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ABSTRACT:

Acanthosis is not a disease but a symptom of disease. It is a thickened brown, velvety texture and brown patches on the skin.

It appears on the neck, axillae, appears in folds of skin, armpit, groin, antecubital fossae. papillomatosis found on cutaneous and mucosal surface also associated with malignancy.

Different categories of AN includes obesity associated, syndromic, acral, drug induced, familial, malignant, autoimmune, unilateral and mixed AN.

We are going to study in this article about AN, it's types it's management, diagnosis, clinical features and occurrence of symptom in a type 2 DM.

As a conclusion we get whole information about AN as a sign of pre-diabetes. However, AN is treatable condition. Weight reduction is the scientific and practical management strategy.

KEYWORDS: Acanthosis Nigricans, Obesity, Diabetes mellitus, Insulin resistance, Risk factor.

INTRODUCTION:

The term Acanthosis Nigricans was first introduced by Dr Paul Gerson Unna in 1889 and the first case report was published by Dr Sigmund Pollitzer in 1891.^[1]

It is a dermatological condition which is characterized by dark brown hyperpigmented patches which may occur in any location. It is a lesion affecting localized areas of skin which relates with papillomatosis and darkening due to hyperkeratosis.^{[2][3]} The skin condition is either associated with benign, endocrine disorders mostly with obesity and insulin resistance as a sign of various malignancies.^{[4][5]}

CLASSIFICATION OF ACANTHOSIS NIGRICANS:

1) **Obesity associated AN:**

It is most common type also called as “Pseudo-acanthosis nigricans”. It can occur at any age commonly in adulthood. Lesions can be managed by weight reduction, diet management. IR is most common in such patients.^{[6][7][8]}

2) **Syndromic AN:**

It is associated with syndrome, occurs as two types: Type A and Type B.

Type A [HAIR-AN] which is present with hyperandrogenemia, IR and AN.

Type B occurs with uncontrolled DM, ovarian hyperandrogenemia or autoimmune disease in women.^[9]

3) **Acral AN:**

Also referred as “acral acanthotic anomaly” Typically it occurs in healthy patients most commonly in individuals who have dark skin (African American descent), lesions being prominent to knees, elbows, knuckles, dorsal surfaces of hands and feet.^{[10][11]}

4) **Drug induced AN:**

This may manifest as an adverse effect of several medication that promote hyperinsulinemia.

Drugs include nicotinic acid lotion, fusidic acid ointment, oral corticosteroids, oral contraceptive pill, growth hormones (diethylstilbesterol, testosterone), subcutaneous insulin, protease inhibitor.^{[12][13][14]}

5) **Familial AN:**

It may arise as an autosomal dominant trait. Lesions may manifest during early childhood manifest at any age until puberty either stabilizes or regresses. It occurs due to mutations in fibroblast growth factor receptor 3.^{[15][16][17]}

6) **Malignant AN:**

It is associated with cancer, most commonly is gastrointestinal adenocarcinomas(gut) i.e tumor of gut and genitourinary cancers such as prostate, breast and ovary, lesions are present in mouth, on tongue and lips.^{[15][18][19]}

7) **Autoimmune AN:**

AN is determined by anti-insulin receptor that appears in antibodies to insulin receptor which results in conditions like SLE, scleroderma, Hashimoto’s thyroiditis.^[20]

8) **Unilateral AN:**

Also called as Nevoid AN. It is an autosomal dominant trait. Lesions occurs unilaterally along Blaschko lines which becomes evident at infancy, childhood or adulthood occurs over face, scalp, chest, abdomen especially pre-umbilical area, back, and thigh.^{[19][21][22]}

9) **Mixed AN:**

It occurs when a patient already has any of above types of AN but develops a new lesion of AN^{[19][21]}

CLINICAL FEATURES:

- Skin tags are similar on cutaneous and mucosal surfaces
- Pruritis may be present in malignant nigricans
- Hyperpigmented, velvety plaques symmetrically distributed over the neck, axillae, groin, popliteal and antecubital fossae
- Has bad odor.
- Lesions can occur on areolae, conjunctivae, lips and buccal mucosa.
- AN appears slowly, taking months or years to form if appears suddenly it can be a warning sign of cancer.
- Excessive roughness, dryness and overgrowth i.e hyperkeratosis of the skin.^{[19][21][23]}

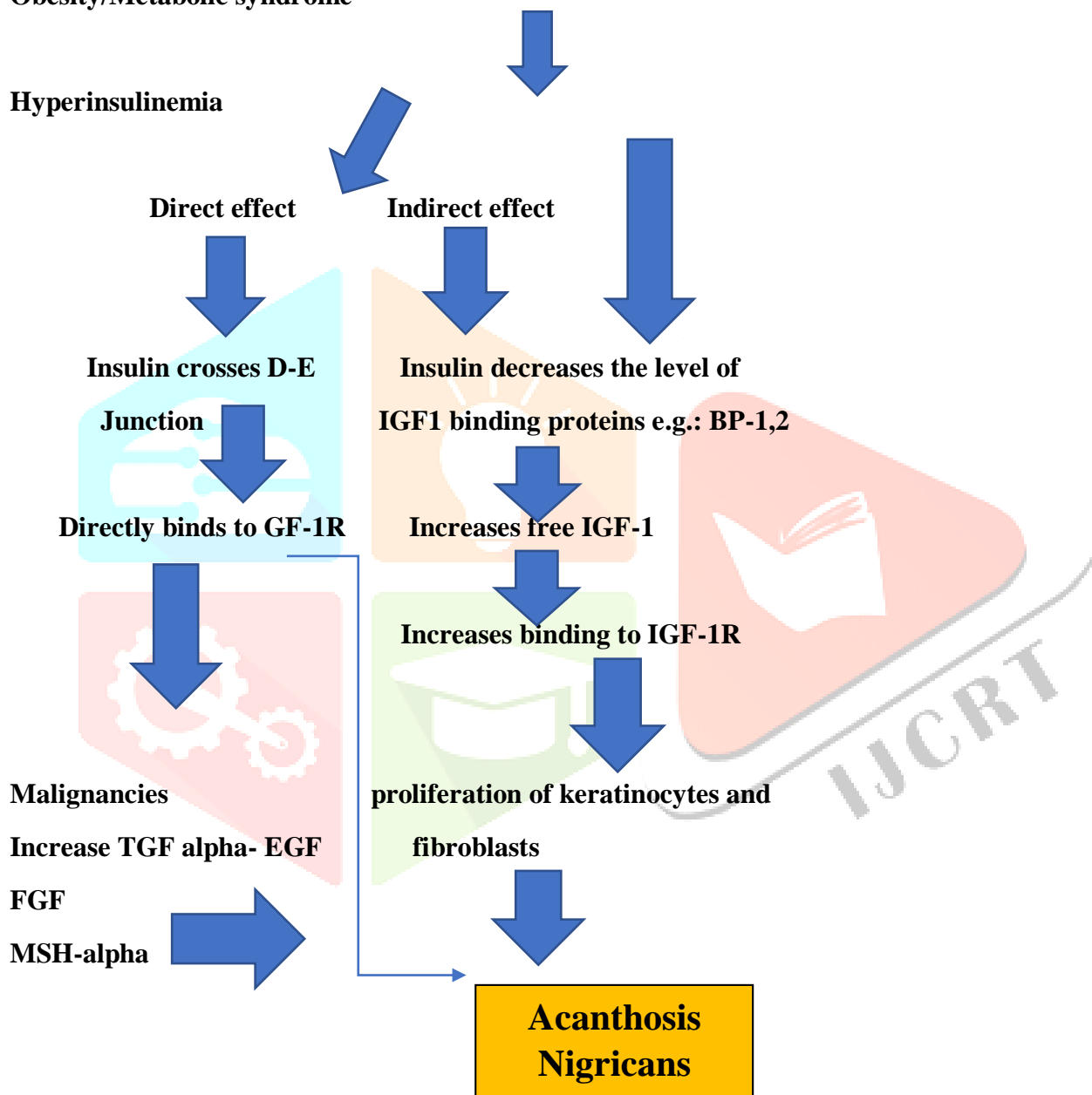
PATHOGENESIS:

The pathogenesis of AN is associated with stimulation of proliferation of epidermal keratinocytes and dermal fibroblasts.

There are several growth factors suggested as mediators include Insulin like growth factor receptor-1 (IGFR1), Fibroblast growth factor receptor (FGFR), Tyrosine kinase receptor (TGF), Epidermal growth factor receptor (EGFR).

Obesity/Metabolic syndrome

Hyperinsulinemia



Obesity is associated with hyperinsulinemia and in certain individuals have direct effect and insulin crosses the dermo-epidermal junction and then directly binds to IGF-IR present on the keratinocytes and fibroblast and leads to the proliferation. More commonly direct effect is seen only in very high insulin states more common is the indirect effect.

When there is high insulin in the blood it decreases the level of IGF-1 binding proteins eg: IGF BP-1, BP-2 since there are less binding proteins so there will be more levels of free IGF-1 and these IGF-1 will bind to these receptors which are present on keratinocytes and fibroblast and leads to proliferation ultimately results in AN.

In FGFR signaling there causes mutation which leads to hyperactivation of this receptor and again results in proliferation of keratinocytes over the dermal fibroblasts.

In malignancies mechanism of action is slightly different mainly gastric cancer they produce large amounts of TGF- α in high amounts can bind to EGFR present on keratinocytes and fibroblast leads to proliferation. Certain malignancies involves up regulation of EGF as well as melanocyte stimulating hormone (MSH) but their role is not clearly defined what is clearly defined is increase in TGF- α is responsible for AN ^{[15][24][25]}

DIAGNOSIS:

- On skin biopsy hyperkeratosis, leukocyte infiltration, epidermal folding and melanocyte proliferation may be seen.
- Histopathological findings include epidermal hyperkeratosis.
- For obesity and insulin resistance few methods are used are:
 - i. Fasting insulin level
 - ii. Glucose/Insulin ratio
 - iii. Quantitative insulin sensitivity check (QUICKI) If the QUICKI < have higher risk of IR.
 - iv. Homeostasis model assessment -IR(HOMA-IR).IR is diagnosed if HOMA-IR > 2.71.
 - If the cause of AN is not clear blood tests, X-rays can be performed
 - History of current and post medical conditions, family history and medications
 - Hemoglobin
 - Lipoprotein profile
 - Alanine aminotransferase for obesity associated AN
 - Radiological investigations (plain radiography, ultrasonography, MRI) for malignancy associated AN ^[26]

TREATMENT:

General measures:

- ✓ Most of the AN are obesity related, weight loss is the first therapy, diet, exercise.
- ✓ Blood pressure, fasting lipid profile, hemoglobin A1C and liver function test should be done

❖ Topical treatment:

I. Retinoids:

Topical retinoids is considered as the first line treatment. Retinoids correct the hyperkeratosis and corrects the epidermal thickness. It is used as a first line treatment for unilateral nevoid AN ^{[3][27]}

II. Ammonium lactate and tretinoin:

Lactic acid is alpha-hydroxy acid works as a peeling agent and releases of desmogleins which results in disintegration of desmosomes. Synergistic reaction is observed. ^[28]

III. Topical Vitamin D analogues:

It inhibits keratinocyte proliferation and promotes differentiation by increased intracellular calcium levels and cyclic GMP levels. It decreases the insulin by decreasing the number of active keratinocytes. Calcipotriol is a common vitamin D analogue which is used for multiple dermatoses. ^[29]

IV. Peels:

Trichloroacetic acid (TCA) is an agent used for chemical peeling and results in destruction of epidermis leading to repair and rejuvenation. There is necrosis of epidermal layers which leads to inflammation.

15% TCA causes coagulation of skin proteins leading to frosting. Wound repair mechanism gets activated and new skin growing appears which is smoother and less pigmented.^{[31][30]}

V. Miscellaneous treatment:

The treatment includes fish oil, 20% podophyllin in alcohol, topical calciferol and surgical excision. Triple combination depigmenting cream (tretinoin 0.05%, hydroquinone 4%, fluocinolone acetonide 0.019%). Kojic acid alone/combination used as depigmenting cream. Urea and salicylic acid are other options.^{[28][31][32][33]}

❖ *Systemic treatments:*

i. Retinoids:

Retinoids such as isotretinoin, acitretin and etretinate used for AN. They have effect on cell growth, differentiation, cohesiveness. If medicine is stopped relapses occur.^[3] The mechanism result in normalization of epidermal growth and differentiation.

Acitretin is used for benign and syndromic AN. Isotretinoin is used to treat extensive AN^[34]

ii. Insulin sensitizers:

The insulin sensitizing agents such as metformin and rosiglitazone are useful in treatment of AN associated with obesity and insulin resistance.

Rosiglitazone reduces the fasting insulin levels and improves the skin texture. Metformin decreases glucose production and increases peripheral insulin, reduces hyperinsulinemia, body weight and improves insulin sensitivity^[35]

❖ *Cosmetic treatment:*

Long-pulsed alexandrite laser was designed to target melanin in hair and hypothesized that thermal heating of epidermis and dermis results in tissue remodeling of axillae and concluded 95% clearance of AN^{[28][31][36]}

❖ *Other therapies:*

Somatostatin analogue octreotide used in AN. Psoralen and ultraviolet (PUVA) therapy is used in bronchial carcinoma and malignant AN which showed improvement in pruritis, keratosis and maceration.^[37]

CONCLUSION:

As per our study acanthosis nigricans is treatable in somewhat condition such as obesity related which will improve weight loss and drug induced is resolved when medication is stopped. This review summarizes the different categories of AN which might help with patient diagnosis, treatment protocol. As AN is treatable but complete cure and disappearance of lesions are not confirmed, therefore long-term studies and furthermore research must be done in the treatment of AN and to prevent long term consequences.

DISCUSSION:

We are going to study in this article about acanthosis nigricans as a pre-diabetes risk, so we have to pay more attention towards the lifestyle modification so that risk of diabetes is prevented. As a clinical professional we have taken the review on 37 articles that a special care is important when condition AN occurs, so therefore to cure DM the AN management must be done. Pre-condition care if taken then AN condition can be prevented.

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