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Review Article

Role of Acanthosis Nigricans in Hidden Systemic Health

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ABSTRACT

Acanthosis Nigricans (AN), on the other hand, is known to be a benign dermatosis, which has hyperpigmented and velvet-like lesions of skin folds. However, taking AN into consideration from an aesthetic point of view may lead one to overlook essential aspects and vulnerabilities. The current paper reinterprets AN as a profound aesthetic sentinel a "cutaneous window" through which a patient's underlying asymptomatic abnormalities can be seen. Based on the common pathophysiologic principles, the article gives insight into the mechanisms of benign and malignant AN occurrence. The main feature in benign AN is hyperinsulinemia, where excess insulin in the blood cross-reacts with insulin-like growth factor-1 (IGF-1) receptors on keratinocytes and fibroblasts, resulting in cell proliferation. Such a phenomenon acts as an early indicator of metabolic syndrome, type 2 diabetes mellitus, polycystic ovary syndrome (PCOS), and many endocrinopathies. On the contrary, malignant AN, typically occurring suddenly and intensely, is caused by growth factors secreted by tumours (for example, TGF-alpha). In addition, different familial forms demonstrate links to particular genetic mutations. By distinguishing such presentations, it is possible to determine whether AN is caused by metabolic disorders or paraneoplastic phenomena. Finally, this review underlines the key role played by primary care providers and dermatologists in the process of deciphering these skin manifestations. Instead of viewing AN simply as a dermatological condition, it should be used as a diagnostic opportunity for systematic screening of the whole body. Early identification of the causative agent of AN leads to prompt treatment and helps turn the patient's fate towards the positive direction.

KEYWORDS:

• Acanthosis Nigricans • Cutaneous Sentinel • Insulin Resistance • Paraneoplastic Syndrome • Metabolic Pathologies

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INTRODUCTION

The condition acanthosis nigricans (AN) has witnessed a tremendous change in paradigms within the past century. It has been transformed from a rare clinical entity to a primary tool for detection of metabolic disorder globally. First described in 1890 by Pollitzer and Unna, AN was originally identified as a rare paraneoplastic dermatological sign invariably. associated with severe internal malignancy.[1] The current times, however, have changed the scenario altogether. As a result of a global metabolic epidemic involving obesity, type 2 diabetes mellitus and metabolic syndrome, AN has transformed from being a rare sign to a very common one.[1,2]

In terms of clinical features, this condition manifests as symmetrical, hyperpigmented, velvety, and hyperkeratotic patches due to the overgrowth of keratinocytes of the epidermis and fibroblasts of the dermis.[2,3] However, while the classical thick patches predominantly affect flexural and intertriginous areas, such as the posterior neck, axillae, and groin, modern clinical evidence shows that AN occurs in atypical areas too. Some of the atypical regions include facial regions and acral regions, such as the knuckles, elbows, and knees.[2,3]

The notion of "hidden systemic health" helps to upgrade the role of AN from a mere aesthetic complaint to an important early warning signal. The presence of high circulating insulin causes cross-reactivity at the level of IGF-1 receptors in the skin, resulting in dermatological alterations prior to the manifestation of such chronic ailments as type 2 diabetes, polycystic ovary syndrome, or metabolic syndrome[2,4] Thus, the identification of AN allows for implementing a drastic preventive measure against developing severe systemic disorders in the future.[1,4]

PATHOPHYSIOLOGY: THE MOLECULAR BRIDGE TO SYSTEMIC DISEASE

Acanthosis Nigricans (AN) acts as an extremely important skin sentinel that provides a very clear indication of pathological changes in the body via the tyrosine kinase receptor family. The molecular pathway for AN in its benign or metabolic form occurs as a result of the compensation mechanism of hyperinsulinemia in chronic insulin resistance.[4] In conditions of high physiological concentration, insulin spillover leads to the activation of IGF-1 receptors located in keratinocytes of the epidermis and dermal fibroblasts. Such a pathologic receptor-agonist combination triggers cell proliferation through mitogen pathways.[5]

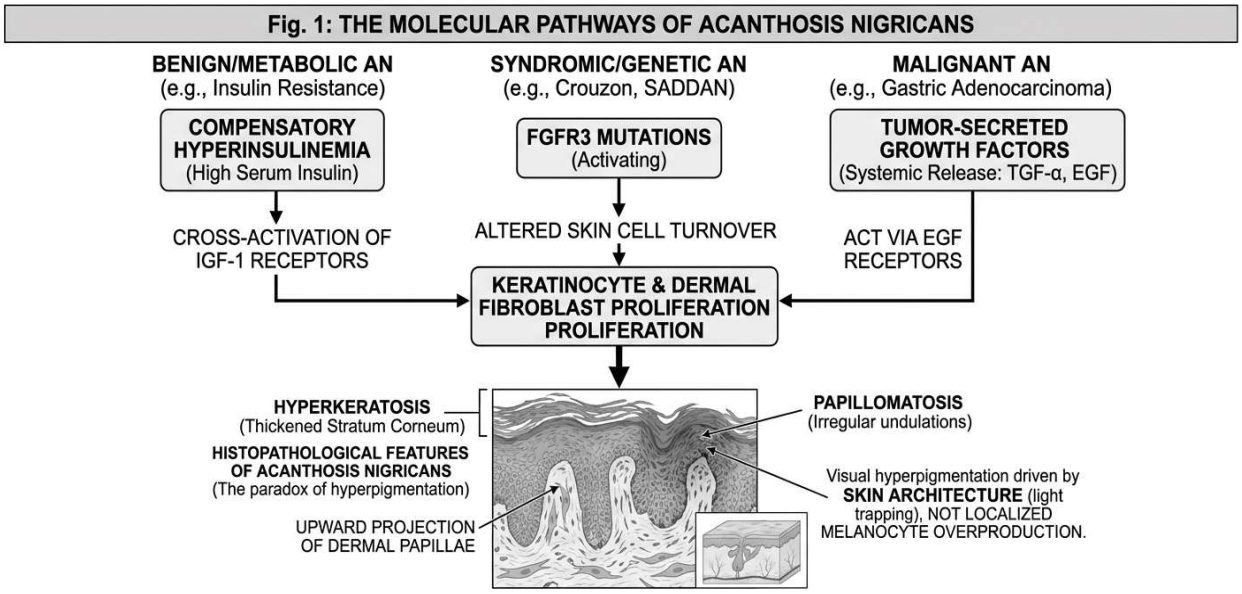

Fig. 1: Pathophysiological mechanisms linking systemic conditions to Acanthosis Nigricans. This diagram illustrates how **how distinct triggers—metabolic** compensatory hyperinsulinemia (via IGF-1 receptor cross-activation), genetic FGFR3 mutations, and paraneoplastic tumor-secreted growth factors (via EGFR)—converge on the tyrosine kinase receptor superfamily to drive dermal fibroblast and keratinocyte proliferation. The resulting histopathological features of hyperkeratosis, papillomatosis, and prominent dermal papillae upward projection collectively define the characteristic skin architecture, which produces the visual appearance of hyperpigmentation through light scattering rather than localized melanocyte overproduction.

Figure 1: Pathophysiological mechanisms linking systemic conditions to Acanthosis Nigricans

While beyond metabolism-related causes, genetic and paraneoplastic etiology focus on different members of this receptor family. Syndrome-related or genetic AN usually results from genetic changes in fibroblast growth factor receptors like FGFR3. This leads to constitutive activation of pathways responsible for epidermal cell turnover and differentiation.[6,7] On the other hand, malignant AN results from action of tumor secreted humoral agents on systemic basis. Tumors secrete high amounts of TGF-α and EGF, both of which act on EGFR of distant skin tissues leading to development of acute and progressive skin lesions Figure 1. All these molecular mechanisms eventually lead to the formation of a specific histopathological picture. In the biopsies of lesions affected by AN, one can observe such features as significant hyperkeratosis, papillomatosis, and upward displacement of dermal papillae.[4-7] Importantly, this histology helps explain the clinical "paradox" of "hyperpigmentation." The distinctive dark velvet-like pigmentation is not the result of excessive proliferation of melanocytes or melanin production. Instead, it represents an optical illusion that results from the dramatic invagination of skin architecture in which thickened keratinocytes and deep dermal papillae create shadows.[4,5]

CLASSIFICATION SYSTEM OF ACANTHOSIS NIGRICANS:

Acanthosis Nigricans (AN) is an important skin marker that signals underlying diseases in other systems. Classification of its manifestation into different types is of great importance for its correct diagnostics and management. The most common forms of this disease are the benign and metabolic forms. The first form is represented by the obesity-related AN that acts as a good indicator of metabolic syndrome.[6] Another type of the benign AN is idiopathic or genetic one.

On the other hand, syndromic AN is associated with profound systemic endocrine dysfunctions that are usually genetically caused. These include Type A insulin resistance syndrome (hyperinsulinemia and virilization) and Type B insulin resistance syndrome (autoimmune antibodies against insulin receptor-mediated. Moreover, syndromic AN is strongly associated with unusual congenital conditions such as Alström syndrome, Prader-Willi syndrome, and leprechaunism.

Another very significant group is paraneoplastic (malignant) AN. This type is associated with the existence of aggressive internal malignancy. Paraneoplastic AN is characterized clinically by acute onset, rapid anatomical spread, strong itching, and lesions of the mucous membrane of the mouth, palms or soles with "tripe palm" formation.

In addition, drug-induced AN is caused due to the effect of systemic drugs that affect insulin sensitivity or growth factor signaling pathway, including systemic glucocorticoids, oral contraceptive pills, high dose of nicotinic acid, and insulin therapy. Last but not least, atypical forms need to be recognized, including the nevoid AN and the facial AN, which may mimic melasma.[1,2] This will help clinicians identify underlying systemic health risk factors.[8,9]

The Sentinel Role: Decoding Hidden Systemic Pathologies

The presence of acanthosis nigricans (AN) can be considered a valuable indicator of deep-seated pathologic conditions of the body even before they develop completely. One of the first indicators of such a condition in which AN can be useful is the cardiometabolic system. In fact, AN is listed by the American Diabetes Association (ADA) as one of the risk factors for metabolic disorders. The appearance of AN strongly correlates with the presence of metabolic syndrome, atherogenic dyslipidemia, and steatosis of the liver, especially non-alcoholic fatty liver disease (NAFLD) and metabolic dysfunction-associated steatohepatitis (MASH). Moreover, AN is one of the most important predictors of other endocrine diseases. For example, in reproductive-age women, AN usually indicates polycystic ovary syndrome (PCOS), which means systemic insulin resistance. In addition, AN may indicate the presence of other endocrine disorders such as Cushing's disease, acromegaly, and hypothyroidism because hormonal disorders provoke hyperproliferation of keratinocytes.[10]

Whereas benign metabolic associations are the norm, the abrupt onset and rapid development of AN may suggest something more ominous – the paraneoplastic or malignant form of AN. The paraneoplastic or malignant form of AN shows the greatest association with the highly aggressive tumors of the abdomen, with 55–61% of these tumors

being gastric adenocarcinoma. More recent studies have shown links between malignant AN and the tumors of the pancreas, lungs, genitourinary tract, and cholangio carcinomas. Importantly, in about one third of these cancer cases, the skin lesions of AN appear before any signs or symptoms of the internal tumor.[11]

Clinical Evaluation and Diagnostic Workup

The clinical evaluation of acanthosis nigricans (AN) is started with a thorough physical examination, along with severity scoring. Dermatologists use specific standardized scoring systems, like the Acanthosis Nigricans Area and Severity Index (ANASI), to assess the lesion extent, the severity of pigmentation, and its texture.[12] If the patient presents with an unusual location of AN lesions (e.g., facial area), the differentiation of the disease from similar conditions like facial melanoses (melasma or post-inflammatory hyperpigmentation) is difficult. To solve this issue, dermatoscopy becomes the critical non-invasive diagnostic method, which shows some specific visual signs – sulcus cutis, crista cutis, and hyperpigmented dots in the cristae.[13]

Upon identification, AN becomes a skin window that necessitates a hierarchical laboratory evaluation. In the presence of common phenotypes of the metabolic kind, metabolic investigation line is put into action; these include fasting insulin levels, HbA1C test, OGTT, lipids and LFTs to look for insulin resistance/metabolic syndrome. If other syndromes such as those that cause hirsutism, menstrual abnormalities and/or severe acne are present, the second investigation line of hormonal studies is required. Here, total/free testosterone, DHEAS, LH/FSH ratio and cortisol suppression are analyzed to rule out PCOS or Cushing's syndrome.[14]

Of note, an atypical presentation necessitates prompt malignancy work-up. Acute, rapid, very severe, or systemic AN in obese or aged patients is a strong indication of a paraneoplastic etiology. The latter is a malignant disease that needs immediate diagnosis and work-up. Doctors have to check the presence of cancer markers like CEA and CA19-9, as well as conduct thorough imaging and endoscopy, including both upper and lower endoscopy and enhanced CT scanning, to exclude any internal adenocarcinomas.[12]

Therapeutic Strategies: Addressing the Root Cause vs. Symptomatic Relief:

Acanthosis Nigricans treatment requires treating the underlying root cause of the systemic disorder rather than merely alleviating the symptoms presented on the skin. As the primary factor behind benign AN is insulin resistance, changes to one's lifestyle through diet and exercise form the core of treatment and restoration of metabolic balance. In instances where pharmacological intervention is needed, drugs such as metformin are instrumental in lowering not only insulin resistance but also skin thickness.[15] Moreover, modern treatments like GLP-1 receptor agonist semaglutide hold great promise as they have the potential to offer two-in-one benefits due to their ability to correct the metabolism systemically and fight inflammation.

On the other hand, when AN appears as a manifestation of an internal malignancy, the treatment strategy is completely different. AN associated with an internal malignancy that usually comes on quickly, broadly, and aggressively is caused by growth factors secreted by a tumor. Thus, effective management of these skin lesions is dependent on timely and thorough oncological treatment. The complete removal of the tumor surgically or using chemotherapy or radiation results in quick and effective removal of the dermatological lesions due to the clearance of systemic oncological triggers.[15]

Although the focus is placed on the systemic resolution, topical and symptomatic therapy provides a very useful complementary approach that allows for the improvement of the cosmetic outcome and alleviates the distress of the patient. Localized hyperkeratosis is treated using keratolytics such as topical urea (10%-20%) and salicylic acid, whereas hyperpigmentation can be controlled with retinoids (tretinoin, 0.025%-0.05%) by increasing the rate of epidermis turnover. Furthermore, procedures such as chemical peels (glycolic acid or trichloroacetic acid) and lasers help to improve the cosmetic outcome.[16]

FUTURE PERSPECTIVES AND CONCLUSION

As we look into the future, there are several important knowledge gaps that need to be

addressed in order to harness the power of AN as a preventive diagnostic tool. First and foremost, there needs to be established a clear, standardized protocol of screening in clinical medicine for non-obese children who have a completely normal body mass index, but are likely to suffer from metabolic disorder without any noticeable symptoms.

In order to overcome these barriers, a multidisciplinary approach is needed—one that does not reinforce existing silos between different medical disciplines. This requires effective integration of dermatology, endocrinology, primary care and oncology for referrals and screening programs. Indeed, since AN is an external sign of underlying pathologic processes, from insulin resistance to latent cancer, such an approach will guarantee a holistic evaluation in case of one skin condition.

In summary, Acanthosis Nigricans goes beyond being just another cosmetic issue, to become an invaluable and non-invasive indicator of internal physiologic processes. Overall, the presence, development or resolution of these darkened, velvety plaques is a highly sensitive and immediate physiological indicator of internal metabolic balance and wellness. Identification and tracking of this sentinel sign allow for early detection of potentially life-threatening internal conditions by all healthcare practitioners.

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