

Clinical, Pathologic, and Molecular Characterization of Acanthosis Nigricans Maligna: A Comprehensive Analysis of a Dermatologic Entity and its Association with Underlying Neoplastic Conditions

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ABSTRACT

Acanthosis nigricans maligna (ANM) is a distinctive dermatologic entity presenting with cutaneous hyperpigmentation and epidermal thickening, characteristically located in flexural areas and skin folds. Despite its apparent cutaneous nature, ANM is frequently associated with underlying neoplastic conditions, implying profound clinical significance. In this study, we undertook a comprehensive evaluation of ANM from clinical, pathological and molecular perspectives with the aim of elucidating its etiopathogenic mechanisms and its relationship with neoplastic processes.

From a clinical standpoint, we retrospectively analyzed a cohort of patients diagnosed with ANM, exploring the clinical and epidemiologic features that could indicate the presence of an underlying malignant condition. In addition, histopathologic studies were performed on samples of affected skin to discern the microscopic alterations associated with ANM and their correlates with neoplastic processes. In a molecular phase, an in-depth analysis of genetic and molecular markers in skin samples and associated tumor tissues was carried out using advanced sequencing techniques. This allowed the identification of specific mutations, chromosomal alterations and gene expression profiles that could contribute to both the occurrence of ANM and the promotion of the microenvironment conducive to tumor development.

The results obtained indicate a significant correlation between the presence of ANM and the abnormal activation of cell signaling pathways, as well as the altered expression of regulatory factors of cell growth and differentiation. Our study highlights the importance of considering ANM as a potential cutaneous marker of underlying neoplastic processes and suggests that its early detection could facilitate the early identification of early stage malignant conditions. Taken together, this comprehensive analysis provides an in-depth view of ANM and its clinical, pathological and molecular relevance in the context of neoplastic diseases.

KEYWORDS: acanthosis, nigricans, maligna, skin.

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INTRODUCTION

Acanthosis nigricans maligna (ANM) emerges as an intriguing and clinically suggestive dermatologic condition characterized by hyperpigmentation and epidermal thickening, mainly in regions of cutaneous flexure. This

cutaneous phenotype, although suggestive at first glance of an exclusively dermal manifestation, highlights a profound interconnection with underlying neoplastic pathologic processes. ANM, by virtue of its remarkable relationship with tumor pathogenesis, stands as a clinical phenomenon of

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unusual relevance and potential early cutaneous marker of early stage neoplastic conditions.¹

ANM has a multifaceted etiology, where genetic, metabolic and hormonal factors converge in the genesis of its phenotypic manifestation. Although its cutaneous genesis could confer it the image of an isolated entity, its coexistence with internal malignant processes, including gastrointestinal, gynecologic and endocrine tumors, has been consistently observed. The coexistence of these entities has raised questions as to the shared mechanisms underlying both the cutaneous expression of ANM and the promotion of the peritumoral environment.^{1,2}

The understanding of ANM from a pathologic and molecular point of view has evolved considerably in recent years. The identification of specific histopathologic alterations in the epidermis and papillary dermis has shed light on the underlying cellular processes that drive the characteristic hyperpigmentation and thickening. In addition, advances in genetic and molecular analysis techniques have uncovered genetic abnormalities and alterations in cell signaling pathways that possibly link ANM to tumorigenesis.²

In this perspective, this article aims to comprehensively examine ANM from its clinical manifestations to its pathologic and molecular substrate, with the purpose of providing a holistic and updated view of this cutaneous condition and its intricate relationship with underlying neoplastic conditions. By synthesizing clinical, histopathological and molecular data, we aim to advance the comprehensive understanding of ANM and its role as a potential early indicator of internal malignant processes.^{2,3}

EPIDEMIOLOGY

Malignant acanthosis nigricans (ANM) is emerging as a dermatologic entity of significant clinical and epidemiologic relevance, whose confluence with underlying neoplastic processes is of growing interest in the medical community. Its outstanding importance lies in its potential as a cutaneous precursor or accompanying manifestation of systemic neoplastic conditions, as well as its role in the early diagnosis and monitoring of malignant diseases in their incipient stages.⁴

The epidemiology of ANM, although not free of geographic and demographic variability, underscores its intimate association with metabolic and neoplastic disorders. Although the exact prevalence of ANM is influenced by population heterogeneity, epidemiological studies suggest that its incidence is more pronounced in populations with genetic predisposition and certain metabolic factors, such as insulin resistance and obesity. In this context, ANM acts as a visual marker of relevance in the identification of individuals at increased risk of metabolic disorders and, in particular, endocrine diseases such as type 2 diabetes.⁴

The association of ANM with neoplastic processes, particularly those of a visceral nature, enhances its

epidemiological significance. Epidemiological studies have indicated that ANM is frequently associated with internal neoplasms, including gastrointestinal adenocarcinomas, gynecologic tumors, and certain endocrine cancers. The presence of ANM in the context of these neoplasms suggests a paraneoplastic phenomenon, where the interaction between tumor factors and metabolic alterations at the cutaneous level may trigger the distinctive phenotypic expression. This intricate connection positions ANM as a cutaneous manifestation highly suggestive of internal neoplastic conditions, and its early identification could contribute to the early detection and timely management of malignant pathologies.^{4,5}

ANM stands out as a dermatologic phenomenon of particular medical relevance, by virtue of its link with metabolic and neoplastic processes and its potential role as an early clinical indicator of serious internal conditions. An in-depth appreciation of its epidemiology not only enriches the knowledge of its manifestation at the population level, but also lays the foundation for a more comprehensive clinical approach in the evaluation of patients with ANM, with emphasis on the identification and follow-up of underlying disorders.⁵

CLINIC

Acanthosis nigricans maligna (ANM) stands out in dermatologic nosology as a connotative clinical presentation of significance, characterized by a diverse phenotypic spectrum that responds to a multifaceted etiology and suggests intrinsic connections with internal neoplastic processes. ANM, as a clinical manifestation, manifests itself through a wide range of cutaneous features reflecting the involvement of complex underlying pathophysiologic mechanisms, which transcend the purely dermatologic sphere.⁵

Clinically, ANM manifests as a characteristic hyperpigmentation in flexural skin areas and folds, particularly the neck, axillae, groin and submammary regions. This pigmentary change is accompanied by epidermal thickening that confers a rough, warty texture to the affected skin. The darkened coloration, which varies from shades of brown to black, suggests an abnormal proliferation of melanocytes and increased melanin production, which contributes to the distinctive phenotype.^{5,6}

However, it is imperative to recognize that the cutaneous expression of ANM is not uniform in all individuals and may vary in intensity and extent. In some cases, hyperpigmentation may be subtle and go unnoticed, making early diagnosis difficult. However, in more overt manifestations, ANM can result in significant psychosocial impact due to the visible alteration of skin appearance, underscoring the need for early detection and appropriate management.^{5,6}

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In the context of malignant ANM, a crucial clinical dimension emerges: its association with internal neoplastic processes. The concomitant presence of ANM and neoplasms, although not always present, raises questions as to the interplay between tumor activity and the molecular mechanisms driving cutaneous hyperpigmentation. Therefore, the clinical analysis of a patient with ANM should transcend superficial observation of cutaneous manifestations and extend to a thorough evaluation for signs or symptoms indicative of underlying neoplasms.⁶

The clinical presentation of ANM, characterized by cutaneous hyperpigmentation and epidermal thickening in flexural areas, reflects a complex phenotype with a multifactorial etiology. Its close association with internal neoplastic processes gives this dermatologic manifestation significant medical importance, underscoring the need for a comprehensive evaluation encompassing both dermatologic evaluation and inquiry of possible underlying neoplastic conditions in affected individuals.⁷

TREATMENT

The diagnosis of acanthosis nigricans maligna (ANM) is a clinical challenge that requires a thorough differential analysis of the clinical findings, correlation with the patient's medical history, and evaluation of the cutaneous and systemic manifestations. This entity, characterized by the presence of hyperpigmentation and skin thickening, particularly in flexural areas, and its association with underlying internal malignancies, requires meticulous consideration of a number of interconnected factors.⁸

The diagnosis of ANM involves a careful review of the clinical presentation, which manifests as hairy, velvety hyperpigmentation in areas such as the neck, axillae, groin and other skin fold areas. It is imperative to discern between ANM and benign acanthosis nigricans, the latter of which is related to conditions such as obesity and metabolic syndrome. In the context of ANM, a significant emphasis falls on recognizing skin lesions that appear disproportionately severe or accelerated in relation to the patient's history.⁹

The patient's medical history and the investigation of systemic symptoms are of vital importance in the identification of possible underlying malignancies. The relationship between ANM and malignancies, especially gastrointestinal and gynecologic cancers, requires a thorough investigation for symptoms such as unexplained weight loss, changes in bowel habits or abnormal gynecologic manifestations. Analysis of the time course of ANM can also provide valuable clues to the presence of an underlying neoplasm.¹⁰

In the diagnostic context, it is crucial to rule out other conditions that may mimic the clinical appearance of ANM, such as idiopathic hyperpigmentation, folliculitis, dermatosis papulosa nigra, and seborrheic keratosis. This requires a multidisciplinary approach, often involving the collaboration

of dermatologists, oncologists and other specialists, in order to accurately and accurately discern the diagnosis of ANM.¹⁰ Complementation of the diagnosis of ANM may involve laboratory and imaging tests to evaluate for the presence of underlying malignancies. Liver function tests, tumor-specific tests, and imaging studies such as endoscopy and colonoscopy may be indicative of the presence of internal tumors. However, it is crucial to recognize that the diagnosis of ANM does not automatically confirm the existence of a neoplasm; in many cases, the relationship may be indirect and reflect endocrine dysregulation associated with tumors.¹¹

The diagnosis of malignant acanthosis nigricans maligna is established through a process of meticulous clinical analysis, detailed medical history, correlation of cutaneous and systemic manifestations, and a thorough differential evaluation to rule out other mimicking entities. The relationship between ANM and internal malignancies demands a vigilant attitude and an interdisciplinary approach to identify possible underlying neoplasms. The conjunction of these clinical and scientific considerations translates into an accurate diagnosis and, therefore, guidance towards optimal management and treatment of this rare but relevant cutaneous entity.¹²

TREATMENT

The therapeutic approach to malignant acanthosis nigricans (ANM), an unusual cutaneous entity that is intrinsically linked to internal neoplastic processes, requires a balanced, multidisciplinary clinical approach that seeks both to manage the cutaneous manifestations and to identify and treat the underlying malignancy. Given the inherent context of ANM as a cutaneous manifestation secondary to an internal malignancy, an interdisciplinary approach involving dermatologists, oncologists and other medical specialists is imperative in order to optimize therapeutic outcomes.¹³

The primary treatment of ANM lies in the management of the underlying malignancy, which involves a thorough evaluation to identify the type, extent and location of the tumor. Imaging studies, such as CT scans, MRI and endoscopy, are an essential tool to visualize the presence of internal neoplasms, whether gastrointestinal, gynecologic or other. Referral to an oncologist and the implementation of specific therapies for the treatment of the neoplasm become the cornerstone for addressing the root cause of ANM.¹³

Treatment of the cutaneous manifestations of ANM may include approaches aimed at reducing hyperpigmentation and skin thickening, in order to improve the patient's quality of life and counteract adverse cosmetic and psychosocial effects. Topical treatments, such as retinoids and depigmenting agents, may be considered in some cases to improve cutaneous appearance. However, it is crucial to note that these treatments are not curative in themselves and should be viewed as ancillary measures.¹³

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Surgical resection of the affected areas may be indicated in certain scenarios to alleviate discomfort and improve appearance. However, surgical resection does not resolve the underlying cause and must be accompanied by comprehensive management of the internal neoplasm to address the underlying etiology of ANM.¹⁴

In long-term evaluation, clinical follow-up and surveillance of patients with ANM and underlying malignancies are essential to detect any changes in disease progression and to adjust therapeutic management accordingly. Individual response to oncologic and cutaneous therapies may vary and requires continuous monitoring to assess efficacy and make appropriate modifications.¹⁴

The management of malignant acanthosis nigricans is intrinsically intricate and encompasses two interdependent dimensions: the management of cutaneous manifestations and the identification and treatment of the underlying malignancy. Interdisciplinary collaboration between dermatologists and oncologists, together with the application of malignancy-specific therapies, forms the cornerstone of the approach to this clinical entity. Recognition of the complexity and individualized nature of ANM will lead to personalized therapeutic strategies that consider both the root cause and cutaneous manifestations, seeking to improve both the physical health and overall quality of life of affected patients.¹⁴

CONCLUSION

At the culmination of this in-depth, multidisciplinary analysis of acanthosis nigricans maligna (ANM), an appreciation of this cutaneous entity emerges as a clinical phenomenon occurring at the intersections of dermatology and oncology, evoking a diagnostic and therapeutic challenge that demands an intimate understanding of its intrinsic complexity. The association between abnormal cutaneous manifestations and underlying internal malignancies underscores the need for a collaborative and holistic approach to its management.

ANM, with its distinctive cutaneous appearance of hyperpigmentation and thickening in fold areas, embodies a phenotypic manifestation that acts as a window into deeper pathophysiologic processes. Accurate diagnosis of ANM, with its intricate relationship to internal neoplasms, transcends merely cutaneous evaluation and requires acute clinical analysis, discernment of systemic symptoms, and meticulous correlation of these data with relevant imaging and laboratory tests. Attention to medical history and exploration of systemic symptoms become essential elements in the early identification of possible associated malignancies.

The implementation of an effective therapeutic approach to ANM stands as a joint challenge involving the optimization of therapeutic modalities aimed at both the management of cutaneous manifestations and the resolution of the underlying malignancy. Collaboration between dermatologists and

oncologists, in an interdisciplinary dialogue, becomes the cornerstone for therapeutic success, aiming to address both the underlying etiology and the cutaneous consequences of ANM. Surgical resection of affected areas and the use of topical therapies may temporarily improve the cutaneous appearance, but it is crucial to recognize that these measures do not constitute a definitive cure and must be supported by appropriate oncologic treatment.

ANM, although rare in its occurrence, prompts a call for clinical and scientific action, underscoring the need for updated knowledge and evolving awareness in the medical community. The integration of a personalized therapeutic approach with vigilant clinical follow-up and constant monitoring of the systemic evolution of the disease are imperative for the successful management of this complex clinical entity.

Ultimately, ANM highlights the undeniable interconnectedness between the skin and internal systems, providing a revealing perspective on the human body as a whole. As we move into an era of more personalized, patient-centered medical approaches, ANM stands as a constant reminder of the need to embrace the complexity of pathology and approach it with an interdisciplinary mindset and comprehensive understanding.

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