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Clinical, Pathological and Epidemiological Aspects of *Acanthosis Nigricans*

Doshi M, Jain A*, Dilip SM, Patil S and Nadkarni N

Department of Dermatology, Dr D. Y. Patil Medical College, India

***Corresponding author:** Dr Abhinav Jain, Department of Dermatology, Dr D. Y. Patil Medical College, Sector 7, Nerul, Navi Mumbai, India, 400706, Tel: +919649254777; Email drabhinavjain7@gmail.com

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Abstract

Acanthosis Nigricans (AN) is a dermatological manifestation with systemic implications, often linked to obesity, insulin resistance, endocrinopathies, and malignancies.

Aim: This study aims to analyze its clinical, histopathological, and epidemiological features among patients attending a tertiary care center.

Methods: A cross-sectional study was conducted at a tertiary healthcare center with a total of 330 patients diagnosed with AN were enrolled. Clinical assessments included grading of lesions, body mass index (BMI) evaluation, and dermatological examinations. Laboratory investigations, including blood glucose, lipid profiles, thyroid function tests, and serum insulin levels, were performed selectively. Histopathological analysis was conducted in consenting patients.

Results: AN accounted for 4.7% of dermatology outpatient cases. The condition was most prevalent among individuals aged 31-40 years (29.7%) and was more common in females (59.09%). The neck was the most frequently affected site (81.21%), followed by the axillae (58.79%) and groin (46.67%). Obesity was the most common association (67.58%), followed by diabetes mellitus (18.79%), polycystic ovarian disease (8.79%), hypothyroidism (4.85%), drug-induced cases (2.12%), and malignancy (0.6%). Histopathology confirmed hyperkeratosis, papillomatosis, and basal layer pigmentation in most cases.

Conclusion: AN is a significant cutaneous marker of systemic conditions, particularly metabolic disorders. Its presence warrants thorough screening for underlying endocrinopathies. Clinicians should recognize AN as a potential early indicator of metabolic syndrome, facilitating timely intervention and management.

Keywords: Clinical; Pathological; Epidemiological Aspects; Dermatological Manifestation

Abbreviations

AN: *Acanthosis Nigricans*; NCDs: Non-Communicable Disease; BMI: Body Mass Index; CBC: Complete Blood Count; PCOD: Polycystic Ovarian Disease.

Introduction

The skin, recognized as an endocrine organ, often reflects various tumoral and non-tumoral diseases. Numerous skin conditions arise due to hormonal imbalances,

including hormone excess, deficiency, or resistance, as well as pathological signalling of growth factors [1]. *Acanthosis Nigricans* (AN) is not strictly defined as a standalone dermatological disease but rather as a common dermatological manifestation of systemic disorders. It is characterized by dark-brown hyperpigmentation, localized skin thickening, and a velvety texture. The lesions typically appear symmetrically in areas with skin folds, such as the neck, axillae, forehead, antecubital and popliteal fossae, groin, and umbilicus. Among children, the neck is the most commonly affected site. The high prevalence of AN in the neck and axillae may be influenced by cofactors such as friction and perspiration [2]. Mechanical factors play a significant role in the proliferation of keratinocytes, mediated by intricate cellular signalling pathways.

Other regions that may exhibit AN include the conjunctiva, lips, eyelids, flexor and extensor surfaces of the elbows and knees, knuckles (dorsal aspect), external genitalia, areolae, inner thighs, and anus. In certain cases, particularly those associated with malignancies, AN can also involve the mucosal surfaces of the oral cavity, esophagus, nose, or larynx [3-5]. Paul Gerson Unna first described AN in 1889 in a patient with "widespread pigmentation and papillary hypertrophy." The term *Acanthosis Nigricans* was later introduced in 1891 by Pollitzer and Janovsky [6]. AN is commonly associated with benign endocrine disorders, most notably obesity and insulin resistance, or it may manifest as a paraneoplastic marker of various malignancies [7,8]. *Acanthosis Nigricans* (AN) poses a significant public health burden due to its strong link with metabolic disorders, particularly obesity and type 2 diabetes. Its prevalence is rising globally, especially in rapidly urbanizing developing countries like India. Studies report AN prevalence ranging from 7% to 74% among obese individuals, with higher rates in females and those with diabetes. The economic burden of AN in India is tied to its association with non-communicable diseases (NCDs), increasing healthcare costs for screening and management. As a non-invasive marker of insulin resistance, AN can aid in early detection and intervention, potentially reducing the economic impact of metabolic disorders. Integrating AN screening into public health initiatives may enhance disease prevention and management. As a skin condition, AN is typically asymptomatic and usually occurs before the age of 40. It is most prevalent among Native Americans, followed by Africans, Hispanics, Caucasians, and rarely Asians. Hud et al. observed a higher incidence of AN in Black women compared to White women [9].

Aims and Objectives

This study aims to explore the clinical, pathological, and epidemiological aspects of *Acanthosis Nigricans* (AN) by analyzing its frequency among patients attending a tertiary care center. It seeks to identify patterns of AN, examine its histopathological features, and investigate potential causative factors to classify AN into its various subtypes.

Material and Methods

Study Area

The study was conducted in the Dermatology Outpatient Department of a tertiary healthcare center catering to a large patient population. This center was selected due to its pivotal role as a major healthcare provider in the region, with a high daily outpatient attendance.

Study Population

The study included all cases of *Acanthosis Nigricans* presenting to the Dermatology Outpatient Department from October 2023 to December 2024.

Sample Size and Sampling Technique

A total of 330 patients diagnosed with *Acanthosis Nigricans* were recruited consecutively over a period of 15 months.

Data Collection

Data were collected through patient interviews and clinical examinations. The purpose and benefits of the study were explained to participants, and informed consent was obtained. Detailed patient histories, including duration of symptoms, family history, and associated systemic illnesses, were recorded. A thorough dermatological examination, including the grading of lesions on the neck and axillae, was performed, along with an assessment of associated skin conditions. Body Mass Index (BMI) was documented for all participants. Routine investigations, such as complete blood count (CBC), lipid profile, blood glucose levels, thyroid function tests, and ultrasonography, were conducted for all patients. Additional tests, including serum insulin levels and LH/FSH levels, were performed selectively based on the patient's affordability, as these investigations were not available within the healthcare center. Skin biopsies were carried out only in patients who provided consent.

Data Analysis

Statistical analysis was performed using SPSS version 26 (Statistical Package for Social Sciences) on a personal computer running a Windows operating system. Proportion tests and Pearson's Chi-Square test were utilized for data analysis.

Results

Acanthosis Nigricans accounted for 4.7% of cases in this study, with the condition being most prevalent among

individuals aged 31-40 years (29.7%). It was more commonly observed in females (59.09%) compared to males (40.91%). The majority of patients (82.12%) were asymptomatic, with no complaints associated with the skin lesions. The neck emerged as the most frequently affected site (81.21%), followed by the axillae (58.79%), groin (46.67%), antecubital fossae (20.61%), and knuckles (13.64%). Additionally, two atypical sites were documented, highlighting variability in lesion distribution. Grading of lesions revealed that grade 2 lesions were most commonly observed on the neck (36.57%), while grade 3 lesions were predominant in the axillae (40.21%).

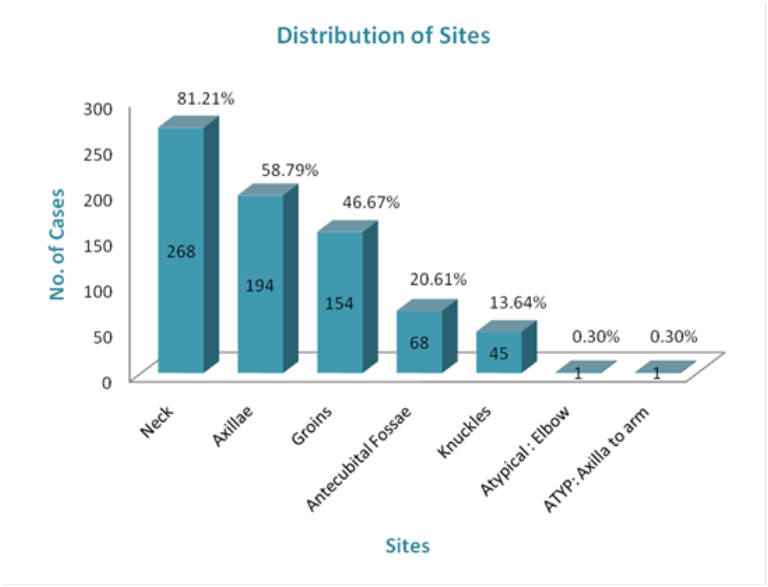

Figure 1: Distribution of sites.

Acrochordons (skin tags) were identified in over half of the patients (58.18%), serving as a notable dermatological association with *Acanthosis Nigricans*. Among the systemic associations, obesity was the most common underlying factor, present in 67.58% of cases. Other significant associations included diabetes mellitus (18.79%), polycystic ovarian disease (PCOD, 8.79%), hypothyroidism (4.85%), drug-induced cases (2.12%), and malignancy (0.6%).

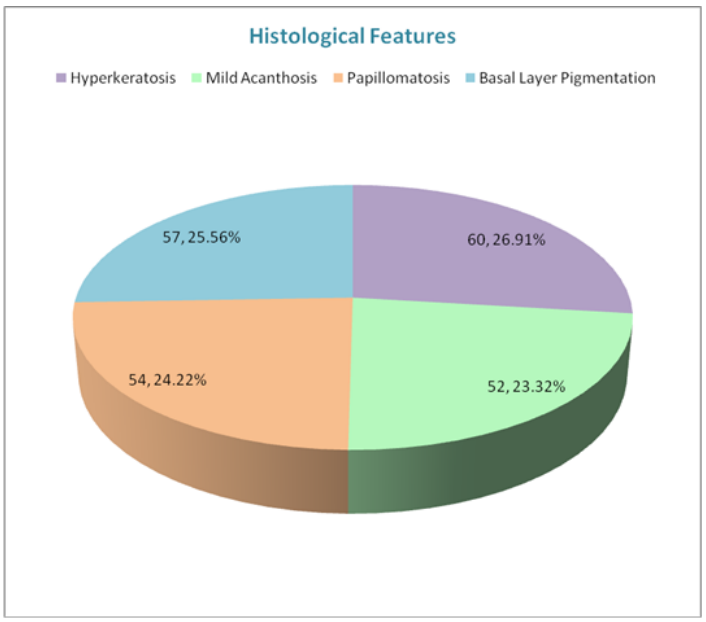

Figure 2: Histological features of *Acanthosis Nigricans*.

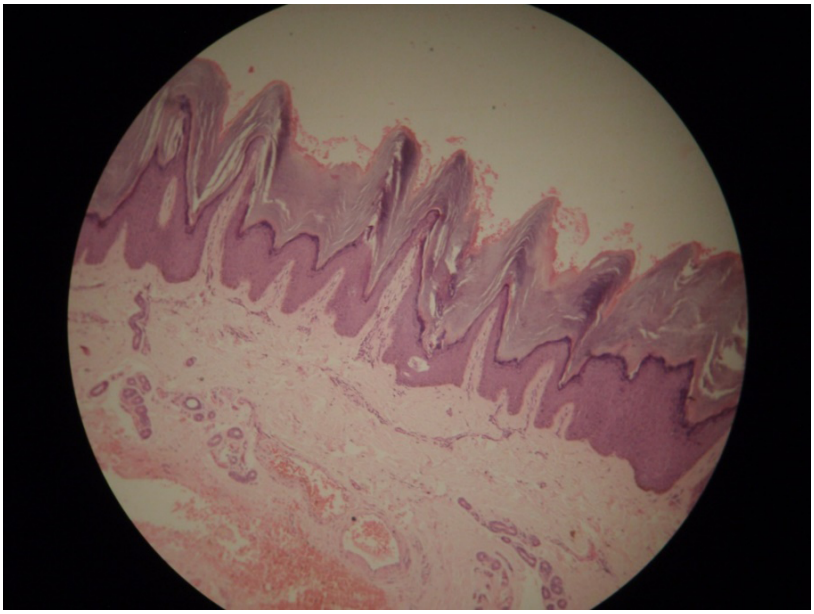

Figure 3: Classical histological picture showing characteristic hyperkeratosis (1) and papillomatosis (2).

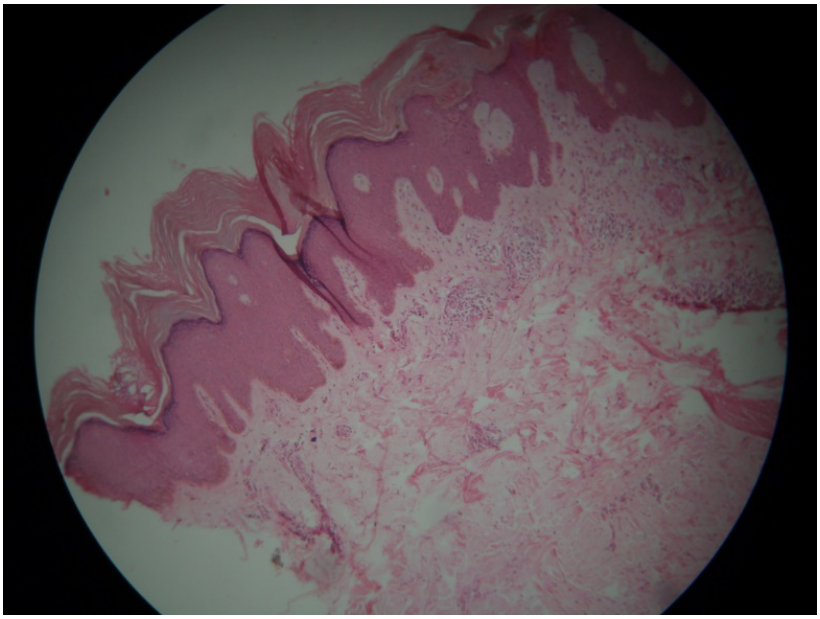

Figure 4: Histological picture showing presence of mild acanthosis.

When classified into subtypes, the obesity-related subtype was the most prevalent, accounting for 60.91% of cases. This was followed by benign (32.42%), familial (3.83%), drug-induced (2.12%), malignant (0.61%), unilateral (0.3%), and unclassified subtypes (0.3%). The findings underscore the diverse clinical presentation and systemic associations of *Acanthosis Nigricans*, emphasizing its multifactorial etiology and the need for a thorough evaluation to identify underlying causes.

Discussion

Patient Demographics and Clinical Characteristics

The study included 300 patients aged 5-65 years, with the most common age group being 31-40 years (29.7%), followed by 41-50 years (27.27%). Cases were least common in the 5-10 years (2.42%) and >60 years (2.12%) age groups. These findings align with previous studies showing peak

prevalence in the 3049 -40 years age range. In a study by Stuart et al prevalence of *Acanthosis Nigricans* was 40% in the age group 10 to years, low in more than 50 years age group and 13% in more than 70 years age group [10]. In a south Indian study, prevalence was highest in the age group 30 to 40 years [11]. Our findings are thus consistent with the findings of the other studies.

Of the total, 135 (40.91%) were male and 195 (59.01%) were female, with a male-to-female ratio of 1:1.44. This gender difference was statistically significant ($P < 0.01$) and consistent with other studies reporting higher prevalence among females. In a south Indian study, women were more affected than men [11]. In another study by Varthakavi PK, et al. [12] of all the patients affected 77.8% of them were women and only 22.2% were men [12]. In a study by Brickman et al 51% of the total affected people were females [13]. In a study by Hud, et al. 17 out of 25 patients were female [9]. Our findings were consistent with other studies.

Symptom Duration and Clinical Presentation

Many patients (34.54%) were unsure of the disease duration, while 36.06% reported lesions for 1-5 years, 25.75% for 6 months to 1 year, and 3.64% for 5-10 years. *Acanthosis Nigricans* was asymptomatic in 82.12% of cases, with pruritus reported in 17.88%, predominantly mild and non-disruptive. Pruritus was most common in groin involvement (69.5% of pruritic cases, $P < 0.01$), while neck involvement was predominantly asymptomatic (86.7%, $P < 0.01$). Literature says that *Acanthosis Nigricans* is a chronic disease [14]. None of the studies mention about the duration of the lesions.

Treatment History and Family History

Only 15.45% of patients had sought treatment, primarily using steroid creams or self-remedies, with no significant improvement. Positive family history was reported in 24.48% of cases, while 71.52% had no such history.

Obesity and BMI Analysis

Of the patients, 223 (74.33%) were obese, categorized as Class 1 (45.76%), Class 2 (19.09%), and Class 3 (2.73%). Additionally, 21.21% were overweight, 10.61% had normal weight, and 0.61% were underweight. A high waist-hip ratio was observed in 70.9% of patients. In one study *Acanthosis Nigricans* was more common in obese population. Its prevalence was reported to be 66% (19). In a south Indian study patients with higher BMI had prevalence rate of 23%.11 In a study by Brickman et al prevalence of *Acanthosis Nigricans* increased with increasing BMI, 46% in more than 95th percentile, 62% in more than 98th percentile and 70% in more than 99th percentile [13].

Site Involvement and Grading

The neck was the most commonly affected site (268 cases, 81.21%), followed by axillae (194 cases, 58.79%), and groin (154 cases, 46.67%). Less frequent sites included antecubital fossae (68 cases, 20.61%) and knuckles (45 cases, 13.64%). Two atypical cases were noted, one with a linear lesion from the right axilla to the mid-arm and another on the extensor surfaces of both elbows. Previous studies reported neck involvement in 99% and 33% of cases, and axillary involvement in 73% and 30% [15,16]. Multifocal involvement was noted in 248 cases (75.15%), while 82 cases (24.84%) had unifocal involvement, predominantly affecting the neck (57 cases).

Grading of lesions was based on Burke's scale. Grade 2 neck lesions were most common (36.57%), followed by grade 3 (27.99%), grade 1 (21.27%), and grade 4 (14.18%). Severity increased with BMI, with 100% of grade 3 and 4 cases occurring in obese individuals ($P < 0.01$). This pattern was consistent with other studies, where grade 2 was most prevalent, followed by grades 1 and 3 [17]. Grading of neck texture showed grade 1 in 38.43% and grade 3 in only 1.87%. To our knowledge, no prior studies have graded neck texture. Axillary grading revealed grade 3 as most common (40.21%), followed by grades 4 (31.96%), 2 (15.98%), and 1 (11.86%). No comparable studies on axillary grading were found. Literature suggests grading has limited clinical utility in estimating insulin resistance severity [18].

Associated Conditions

Acrochordons were the most frequent cutaneous association (192 cases, 58.18%), followed by alopecia (22.42%), hirsutism (10.91%), and acne (19.7%). Systemically, obesity was the leading association (223 cases, 67.58%), of which 22 cases also had conditions like diabetes, PCOS, hypothyroidism, or drug-induced acanthosis. High serum insulin levels were found in 68.02% of tested patients (104/153), while lipid abnormalities included elevated cholesterol (59 cases), triglycerides (35 cases), or both (16 cases). Comparative studies align with these findings, demonstrating a strong association between *Acanthosis Nigricans* and obesity. Hud, et al. reported 74% of obese individuals with acanthosis, while Brickman, et al. noted a prevalence increasing parallel to obesity [13,14]. In children, 90% of cases were linked to obesity in one study, consistent with 21.42% of obese children in our cohort [10].

Associated Conditions and Atypical Presentations

In our study, 62 cases (18.78%) were associated with type 2 diabetes mellitus (T2DM). Among these, 6 patients were obese, 45 were overweight, and 8 had normal weight. High serum insulin levels were observed in 4 patients. Comparative studies showed the prevalence of *Acanthosis Nigricans* (AN) in diabetic patients to be 11% in a Kashmir-

based study, 17% in another study, and as high as 62.6% in a North Indian study [19-21].

Polycystic Ovarian Disease (PCOD) was associated in 29 cases (8.78%), with 6 obese (20.68%), 15 overweight (51.72%), and 8 normal-weight patients (27.58%). Menstrual irregularities were observed in 16 patients, including oligomenorrhea (48.27%) and amenorrhea (6.8%), while 2 patients had infertility. High LH/FSH ratios were found in 68.96% of PCOD cases (20/29), and polycystic ovaries were confirmed on ultrasonography. Skin biopsy in 6 patients showed histological features of AN in 5. Studies have reported varying prevalence rates of AN in PCOD: 15.19% (143), 2.5%, <1%, while Bhattacharya, et al. [22] noted overweight prevalence in 70% of PCOD cases and high LH/FSH ratios in 46%. Zargar, et al. [23] reported primary infertility in 15% of PCOD cases [22-25].

Hypothyroidism was noted in 16 cases, with 6 obese, 7 overweight, and 3 normal-weight patients. Alopecia with hirsutism (9 cases) and alopecia with acne (2 cases) were associated findings. Skin biopsy in 6 patients revealed specific AN feature in 4.

Drug-induced AN was observed in 7 cases: 4 patients were on systemic corticosteroids, and 3 were on oral contraceptive pills (OCPs). Among these, 2 corticosteroid users and 2 OCP users were obese. The remaining cases showed no significant associations or abnormal investigations.

Atypical Presentations included two cases. The first involved a 16-year-old female with a linear hyperpigmented plaque extending from the right axilla to the mid-arm, with normal weight and no associations. The second case was a 19-year-old female with velvety plaques on the extensor elbows, bilateral but more prominent on the left, also with no associations. Both cases showed histological features of AN on biopsy. A similar nevoid AN case localized to the umbilicus has been reported [26].

Malignancy-associated AN was observed in two cases (0.6%). The first was a 51-year-old female with AN on the neck following cervical cancer. The second was a 45-year-old female with AN on the neck and axillae after breast cancer. Both cases developed lesions post-malignancy, had normal weight, and no oral lesions. No biopsies were performed. Malignant AN is rare; one study reported only two cases out of 12,000 cancer patients over 10 years [27].

Familial Type and Histological Findings

In our study, 94 cases had a positive family history of *Acanthosis Nigricans* (AN). However, only 11 cases (3.33%) were classified as pure familial type, as the remaining 83 cases had additional associations such as obesity or diabetes mellitus. The familial cases were observed in children with a strong history in one or both parents, with no other associations and normal weight. Familial AN is considered rare in the literature [14].

Biopsy was performed in 98 cases, with 52 cases (53.06%) showing specific histological features such as hyperkeratosis, papillomatosis, mild acanthosis, and basal layer pigmentation. The remaining 46 cases (46.94%) exhibited nonspecific histological changes. Detailed findings included:

- Hyperkeratosis: 60 cases (61.22%)
- Mild acanthosis: 52 cases (53.06%)
- Papillomatosis: 54 cases (55.10%)
- Basal layer pigmentation: 57 cases (58.16%)

Conclusion

Among the 330 patients studied, the majority were females, with the neck being the most affected site. Grade 2 was the most frequently observed severity grade in neck lesions. The severity of *Acanthosis Nigricans* showed a positive correlation with increasing body mass index (BMI), reinforcing obesity as the primary associated factor. Given its strong association with metabolic dysfunction, *Acanthosis Nigricans* should not be regarded merely as a cosmetic concern but as a clinical marker warranting further systemic evaluation. Physicians should adopt a proactive approach by assessing patients for underlying conditions such as obesity, insulin resistance, diabetes mellitus, polycystic ovarian disease (PCOD), and hypothyroidism. Routine BMI assessment and metabolic screening should be considered, particularly in patients with extensive or severe lesions, to facilitate early intervention. A multidisciplinary approach involving dermatologists, endocrinologists, and primary care physicians is essential for comprehensive management. Emphasizing patient education and lifestyle modifications can further aid in mitigating disease progression and improving overall metabolic health.

Limitations

This study has several limitations that may impact the generalizability of its findings.

- **Recall Bias:** The reliance on self-reported data introduces the possibility of recall bias, as patients may not accurately remember or report past information.
- **Selection Bias:** Recruitment of participants from a single healthcare center limits the diversity of the study population, potentially affecting the applicability of the results to broader populations.
- **Unaccounted Risk Factors:** Key epidemiological factors, such as dietary habits and genetic predispositions, were not thoroughly assessed, leaving potential risk factors unaccounted for.

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