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A Study to Assess the Association of Acanthosis Nigricans with Metabolic Syndrome and Its Individual Parameters: A Case-Control Descriptive Study from Tertiary Care Hospital

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ABSTRACT

Background: Acanthosis nigricans (AN) is characterised by hyperpigmented, dark, rough, velvety plaques, typically on the intertriginous areas and neck. AN could be a marker of underlying metabolic syndrome (MetS). Various parameters of MetS include hypertension, hyperglycemia, low high-density lipoprotein (HDL) cholesterol, high waist circumference (WC) and hypertriglyceridemia.

Aim: To determine the association between the acanthosis nigricans and parameters of metabolic syndrome.

Material & Methods: This study was a descriptive case-control study conducted over a period of 1 year. Fifty-five patients of AN and 55 age and sex matched controls were included to assess the association between AN and MetS parameters.

Results: Out of 55 cases of AN evaluated, 45.5% had MetS of which 58.2% were males and 41.8% females. Among the cases, 76.36% had increased WC, 36.36% had hypertension, 45.45% had elevated triglycerides, 63.63% had decreased HDL and 27.27% had increased fasting blood sugar levels. The Association of AN and MetS was found to be highly significant in the study population ($p<0.001$).

Conclusion: Our study concluded that AN patients had elevated individual components of MetS. Hence, presence of AN could be a marker of underlying MetS. Primary healthcare workers in resource poor settings should be trained to identify AN, and to asses for individual components of MetS so that, early diagnosis can be made and treatment should be started.

KEYWORDS: Acanthosis nigricans- AN, Metabolic syndrome- MetS, Fasting blood sugar- FBS, Waist circumference- WC, High density lipoprotein- HDL

INTRODUCTION

Acanthosis nigricans (AN) is characterized by symmetrical, hyperpigmented, dark, rough patches and plaques typically in the intertriginous areas, flexures, and the neck.(1) Elbows and knees, dorsal joints of hands and fingers (knuckles), external genitalia, and occasionally the face and eyelids can be involved.(2) The skin lesions begin with gray or brown pigmentation, accompanied by dryness and roughness, then become palpably thickened and covered with elevations and a velvety texture.

The prevalence of AN has been estimated to be 25% in general surveys and more than 60% in studies of overweight and obese children.(3) . In 1976, Kahn et al. published their landmark study, in which the association between AN and insulin resistance was first described.(4) In 2000, ADA established AN as a formal risk factor for the development of diabetes in children.(5)

Although AN is associated with malignancy, the recognition of its more common connection to obesity and insulin resistance allows for the diagnosis of related disorders including type 2 diabetes, the metabolic syndrome, and polycystic ovarian syndrome.(3)

Insulin at higher concentrations, can exert more potent growth-promoting effects through binding to insulin-like growth factor 1 receptors (IGF-1Rs). The binding stimulates proliferation of keratinocytes and fibroblasts, leading to AN.(6) However, the definitive cause for AN has not yet been ascertained.

AN is the most widely used cutaneous marker to identify the risk factors of non-communicable diseases, especially MetS. An Indian study by **Philip EN et al.** found MetS in 78.3% of their patients with AN.(7)

AN was found to be associated with insulin resistance and glucose metabolism in studies, but not with other defining criteria of Metabolic syndrome, such as hypertension and dyslipidemia.(8,9)Therefore, limited information on the association between AN and MetS is available at present. Hence, this study was undertaken with the aim to studying the association of AN with all individual components MetS as a whole.

MATERIALS AND METHODS

This was a descriptive case-control study conducted in 1 year on patients attending the outpatient department of dermatology at a tertiary care hospital. Ethical clearance for the study was taken from the institutional ethics committee. Informed and written consent from all participants was obtained. A total of 110 patients were included in our study. Group A included 55 cases in the age group 18-55 years of AN both male and female. Group B included 55 age and sex matched controls without ANs. Patients with a history of intake of drugs like nicotinic acid, oral contraceptives, systemic steroids, diethylstilbestrol and anti-retroviral drugs which can cause AN, and those female patients who were pregnant, lactating or in the postpartum period were excluded. The study participants were subjected to a thorough history taking and clinical examination. Age, sex, occupation, age of onset of AN, duration of AN, family history of AN, diabetes, hypertension, dyslipidemia, history of smoking, alcohol intake, and history of drug intake were noted. A Complete cutaneous and systemic examination was done for each of the study participants. The diagnosis of AN was made based on clinical findings. Histopathological examination were done in doubtful cases. Lesions of AN were described in terms of site, size, shape, color, texture, morphological appearance, and parts of the body surface involved. Measurement of height, weight, body mass index (BMI), blood pressure, and waist circumference (WC) was done.

Documentation of the lesions was done through clinical photographs taken with the patient's consent. Fasting blood sugar (FBS), high density lipoprotein (HDL) and triglycerides (TG) levels were measured in blood among the participants and corresponding values were recorded. WC was measured using a non-stretchable flexible tape in the horizontal position, just above the iliac crest, at the end of normal expiration, with the subject standing erect and looking straight forward and observer sitting in front of the subject. BMI was calculated as a ratio of weight in kilograms divided by height in square meters (kg/m^2). BMI grading was done as per the WHO criteria 2023 as follows:

Underweight: <18.5
ii. Normal weight: 18.5-24.9
iii. Overweight: 25–29.9 (pre-obesity)
iv. Class I obesity: 30–34.9
v. Class II obesity: 35–39.9
vi. Class III obesity: ≥40.

The Diagnosis of MetS as per the Joint interim statement of International Diabetes Federation, National Heart, Lung and Blood Institute, American Heart Association, World Health Federation, International Atherosclerosis Society, and International Association of the Study of Obesity was done by the presence of any three of the following five criteria(10):

- Central obesity (WC > 90cm (M) and >80cm (F)
- Hypertriglyceridemia: Triglycerides ≥ 150mg/dL or specific medication for dyslipidemia
- Low HDL cholesterol ≤40mg/dL (M) ≤50mg/dL (F) or specific medication
- Hypertension: BP systolic ≥130 or diastolic ≥85 mm Hg
- FBS ≥100mg/dL or under medication or previously diagnosed Type 2 Diabetes

STATISTICAL ANALYSIS

Descriptive and inferential statistical analysis was carried out. Results on continuous measurements were presented as mean ± standard deviation. Categorical measurements were presented in terms of frequency and percentage. Categorical data was assessed using the Chi-square test of significance. With 95% of the confidence interval, $p < 0.05$ was considered as statistically significant. A Student's t-test was used to find out the significance of the study parameters between two groups. The Chi-square test was used to find the significance of the study parameters on a categorical scale between two or more groups, the nonparametric setting for qualitative data analysis. The statistical software namely Statistical Package for the Social Sciences was used for the data analysis.

RESULTS

- The age range of the patients in our study was from 18 to 55 years with a mean age of 31.27±9.93years for the AN group and 33.84±12.23years for control group.
- Male 54% patients outnumbered females 45.5% in ratio of 1.39:1.

- Major group of patients comprised of shopkeepers, housewives and students.
- Weight and BMI were significantly higher in the study group as compared to control group.
- Age and height were comparable in both groups.
- Majority of our cases had grade 3 AN (AN) followed by grade 2 and grade 4 in neck region. Similar distribution was noted in patients having involvement of axillary region.
- In our study, most frequent sites of involvement of AN were neck 98.1%, axilla 81.5%, knuckles 44.4%.
- The proportion of subjects with abnormally high waist circumference 76.36% were significantly higher in AN group.
- Both high systolic and high diastolic blood pressure was observed in AN group in 36.36% of patients.
- A statistically significant difference was observed in HDL and triglyceride (TG) levels in the AN group as compared to the control group.
- Metabolic syndrome was seen in 45.5% of individuals in the AN group as opposed to 14.5% in control group.
- No statistically significant difference was found in fasting plasma glucose (FPG) levels among both groups.

DISCUSSION

MetS is a known risk factor for coronary artery disease; recognizing this early will help in institution of measures to prevent coronary artery disease-associated morbidity and mortality. According to **Third report of the National cholesterol Education Program (NCEP) expert panel**, patients with AN are at risk for all components of the MetS, such as obesity, hypertension, elevated triglycerides, low HDL, and impaired glucose tolerance. (11)

The age of patients in our study ranged from 18 to 55 years with a mean age of 31.27±9.93 years for the AN group and 33.84±12.23 years for the control group. **(Table:1)** In our study 54% were males and 45.5% were females. **(Table:2)** There was no significant difference between case and controls groups (p>0.566). **Choudhary S et al.**(12) reported similar age range with a mean of 32.82 ± 10.19 years for the AN group and 33.67 ± 8.09 years for comparative subjects.

In our study weight and BMI were significantly higher in the study group as compared to control group (p<0.05); and height were comparable in both groups (p>0.05). **(Table:3)** The significant association between BMI and AN was due to a higher proportion of obese I and obese-II patients in group A as compared to group B. **(Table:4) Ayaz T et al**(13) reported similar findings with significant positive correlation between AN and BMI.

In our study, most frequent sites of involvement of AN were neck (98.1%) and axilla (81.5%), followed by knuckles (44.4%), elbows (15.5%) and face (16.7%). **(Graph:1). Puri N et al**. has similar finding neck (93.3%) axilla (66.6%) followed by knuckles (40%).(3)

In Group A, the maximum percentage of involved sites for AN was 32.7%, observed in cases with 2 and 3 sites affected, respectively. This was followed by 21.8% of cases with involvement in four or more sites, and 12.8% with involvement in just one site **(Table:5)**. Our study marks the first instance where AN has been categorized based on the number of sites affected during examination, a novel approach not previously undertaken by any researcher.

Majority of our cases had grade 3 AN (49.1%) followed by grade 2 (30.9%) and grade 4 (20.0%) in neck region. **(Graph:2)** Similar distribution was noted in patients having involvement of axillary region. **(Graph:3) Shah NG et al.**(14) reported Grade 4 (30%), Grade 3 (24%), and Grade 2 (22%) lesions which is shows difference with our study. Difference to shah et al, our study shows earlier presentation of AN. This can be due to cosmetically aware patients which mainly consists of younger generation.

In our study, the proportion of subjects with abnormally high WC was significantly higher in AN group as compared to subjects in the comparative group for both males and females (p < 0.001). **Choudhary S et al**(12) reported similar findings with significant positive correlation between WC and AN.

A statistically significant difference was observed in systolic blood pressure (SBP) and diastolic blood pressure (DBP), HDL and triglyceride levels in the AN group as compared to the control group(p<0.05). **(Table:6) Choudhary S et al**(12) reported that the value above normal levels of HDL, TG and blood pressure was found to be significantly associated with AN.

In our study MetS was seen in 45.5% of individuals in the AN group as opposed to 14.5% in control group. There was statistically significant difference between both the groups (p<0.001). **(Table:7) Ayaz T et al.**(13) observed that prevalence of MetS was significantly higher in the group with AN**.** In our study no statistically significant difference was found in FPG levels among both groups (p =0.563). **Choudhary S et al**(12) reported no statistically significant difference was found in FBS levels among both groups.

The present study showed the proportion of subjects with severe involvement of axilla were significantly higher with MetS. In neck region, severity grade of AN was higher with MetS but, it was not significant (p < 0.05).**(Table:8)**. Our findings are similar to the study done by **Shah NG et al.**(14), who reported a statistically significant correlation between severe AN over the neck and each component of MetS.

LIMITATION

As this is a hospital-based study, small sample size, is a major limitation. More studies with a larger sample size are needed to fully establish the association between AN and MetS.

CONCLUSION

MetS is a group of health issues emerging from overnutrition, sedentary habits, and excessive fat accumulation, involving abdominal obesity, insulin resistance, dyslipidemia, and high blood pressure that confer increased risk of cardiovascular disease and diabetes mellitus. AN act as a cutaneous marker for underlying metabolic syndrome.

In our study we found strong association between different parameters of MetS and AN. In our study MetS was seen in 45.5% of individuals in the AN group as opposed to 14.5% in control group.

Majority of our cases had grade 3 AN (AN) (49.1%) followed by grade 2 (30.9%) and grade 4 (20.0%) in neck region. Similar distribution was noted in patients having involvement of axillary region.

The significant association between number of MetS components involved and AN was due to a higher proportion of more than two MetS components in AN group as compared to control group.

Primary healthcare workers in resource poor settings should be trained to identify AN, and subject these individuals for further investigations and assessment of MetS. So that early diagnosis and treatment should be given.

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Table no. 1: Age group distribution in both groups

Age Group (Years)	Group		χ^2 value	p value
	Case (n=55)	Control (n=55)		
18-30	29 (52.7%)	29 (52.7%)	4.625	0.201
31-40	15 (27.3%)	8 (14.5%)		
41--50	8 (14.5%)	10 (18.2%)		
>50	3 (5.5%)	8 (14.5%)		

Table no. 2: Sex distribution in both groups

Sex	Groups		χ^2 value	p value
	Case (n=55)	Control (n=55)		
Male	32 (58.2%)	28 (50.9%)	0.329	0.566
Female	23 (41.8%)	27 (49.1%)		

Table no. 3: Anthropometric distribution among both groups

Anthropometric Parameters (Mean)	Group		t value	p value
	Case (n=55)	Control (n=55)		
Weight (kg)	78.38±14.99	67.67±12.31	4.095	**<0.001**
Hight (cm)	159.56±8.35	160.91±9.06	-0.810	0.420
BMI (kg/m^2)	30.78±5.38	26.25±5.06	4.547	**<0.001**

BMI- Body mass index

Table no. 4: Distribution of patients according to BMI in both groups

BMI Group	Group		χ^2 value	p value
	Case (n=55)	Control (n=55)		
Underweight (≤18.5)	0 (0.0%)	0 (0.0%)	18.478	**<0.001**
Normal (18.5 - 24.9)	7 (12.7%)	26 (47.3%)		
Pre-obese (25 - 29.9)	20 (36.4%)	18 (32.7%)		
Obese I (30 - 34.9)	17 (30.9%)	7 (12.7%)		
Obese II (35 -39.9)	11 (20.0%)	4 (7.3%)		
Obese III (40 & above)	0 (0.0%)	0 (0.0%)		

BMI- Body mass index

Table no. 5: No. of sites of acanthosis nigricans in cases

Sites	Frequency (N=55)	Percentage
1 site	7	12.8
2 sites	18	32.7
3 sites	18	32.7
≥ 4 sites	12	21.8

Table no. 6: Components of metabolic syndrome distribution in both groups

(Mean)	Group		t value	P value
	Case (n=55)	Control (n=55)		
WC	98.18±14.12	91.73±13.42	2.457	**0.016**
SBP	128.95±11.24	125.02±9.87	1.948	0.054
DBP	84.96±8.92	80.89±8.51	2.450	**0.016**
FBS	100.35±29.93	97.93±21.65	0.485	0.628
Triglycerides	160.53±61.52	137.25±55.19	2.088	**0.039**
HDL	42.75±15.16	48.33±11.59	-2.169	**0.032**

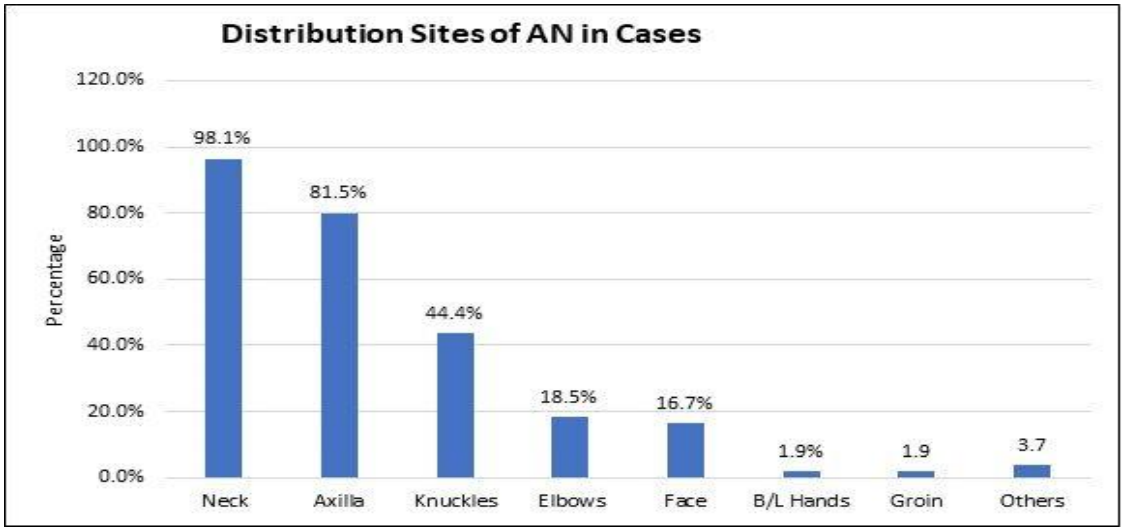
WC- waist circumference, SBP- systolic blood pressure, DBP- diastolic blood pressure, FBS- fasting blood sugar, HDL- high density lipoprotein.

Table no.7 : Prevalence of metabolic syndrome distribution in both groups

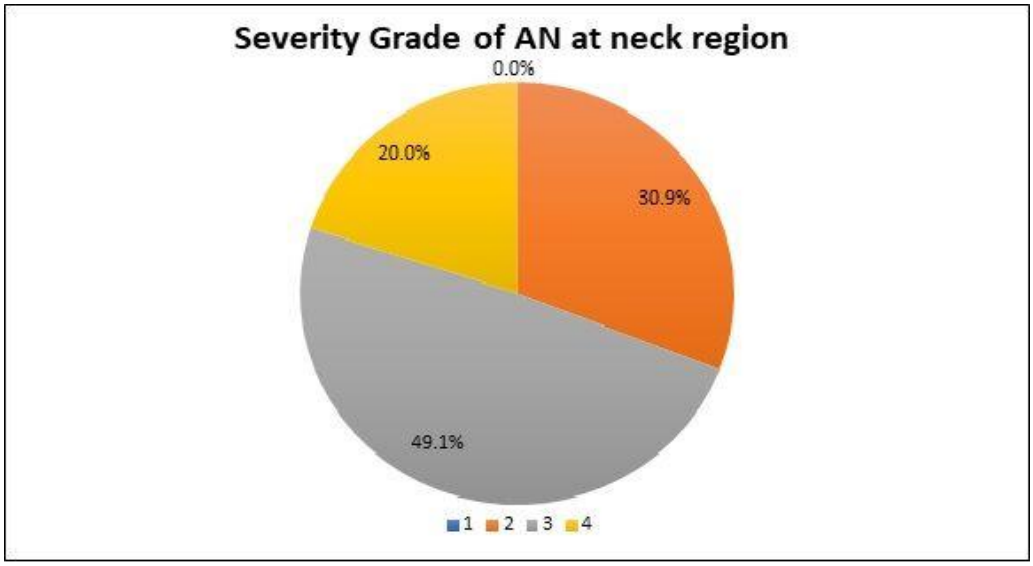
Metabolic Syndrome	Group		χ^2 value	p value
	Case (n=55)	Control (n=55)		
Present	25 (45.5%)	8 (14.5%)	12.511	**<0.001**
Absent	30 (54.5%)	47 (85.5%)		

Table no. 8: Severity Grading of AN with metabolic syndrome

Region	Severity Grade	Metabolic Syndrome		χ^2 value	p value
		Present (n=25)	Absent (n=30)		
Neck	1	0 (0.0%)	0 (0.0%)	0.938	0.626
	2	7 (28.0%)	10 (33.3%)		
	3	14 (56.0%)	13 (43.3%)		
	4	4 (16.0%)	7 (23.3%)		
Axilla	1	1 (4.8%)	1 (4.2%)	7.926	0.048
	2	5 (23.8%)	6 (25.0)		
	3	15 (71.4%)	10 (41.7%)		
	4	0 (0.0%)	7 (29.2%)		



Graph:1



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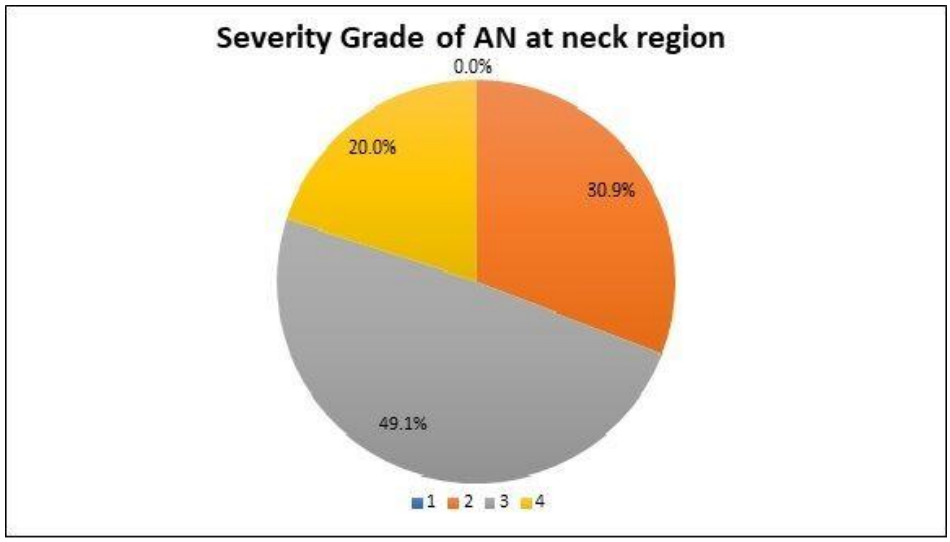

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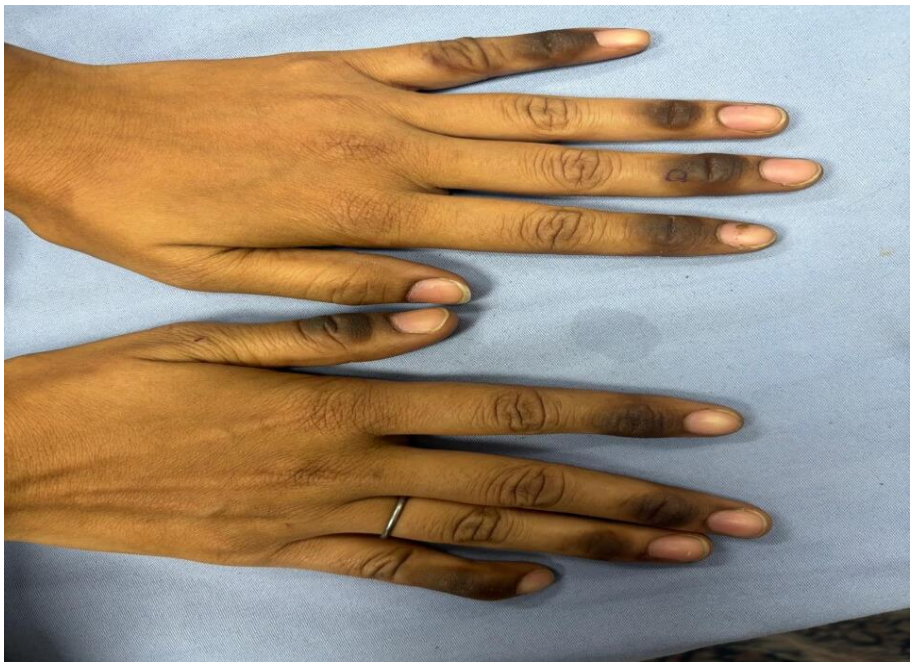

Figure:1 AN in knuckles area

Figure:2 AN in-neck region

Figure:3 AN in-axilla region

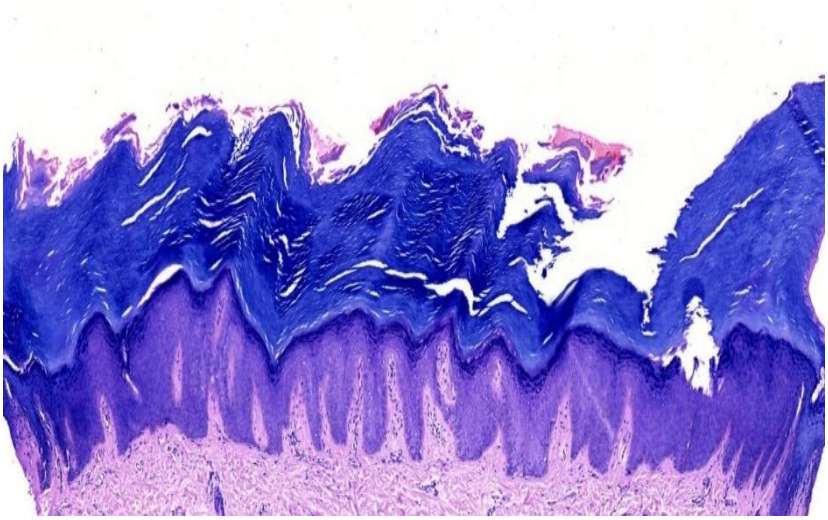

Figure:4 Histopathology of AN showing irregular acanthosis, hyperkeratosis, orthokeratosis and elongation of rete ridges and enlargement of dermal papillae (papillomatosis) (H & E x 40)