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CLINICAL AND BIOCHEMICAL EVALUATION OF ACANTHOSIS NIGRICANS IN OBESE CHILDREN : A CROSS-SECTIONAL STUDY

Running title: Acanthosis nigricans in obese pediatric population

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Abstract

Lifestyle diseases are emerging epidemic of modern era, starting its pathogenesis as pre-metabolic syndrome at a younger age. Obese paediatric population is at higher risk. Acanthosis nigricans (AN) is a dermatoses which helps in identifying at risk population and aid in early intervention and lifestyle modification. The main aim of this study was to evaluate derangements in serum parameters of metabolic syndrome (serum fasting blood sugar levels and lipid profile) and their correlation with severity (grades) of AN. A total of 100 subjects of age 10-18 years were studied, 50 having obesity (OB) with AN (OB+AN) and 50 having OB without AN (OB-AN), fulfilling the set inclusion and exclusion criteria. BMI (body mass index), serum fasting blood sugar (FBS), serum cholesterol (sChol), serum triglycerides (sTG), serum low density lipoproteins (sLDL) and serum high density lipoproteins (sHDL) were measured in all subjects, along with grading of AN and its correlation with individual parameters. Compared to OB-AN group, OB+AN group had

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statistically significant higher BMI (p value 0.006), FBS (p = 0.009), sTG (p = 0.03) & lower levels for sHDL (p = 0.02). AN grades correlated positively with BMI, FBS, sTG, sChol, sLDL and negatively with sHDL levels in a statistically significant manner. The derangement in any of these parameters point towards underlying metabolic syndrome in obese subjects. Additionally, grading of AN helps in risk stratification of the obese population clinically by means of visual inspection, only.

Key words: Acanthosis nigricans, metabolic syndrome, obesity

Introduction:

Acanthosis nigricans (AN) is a dermatosis characterized by appearance of dark, coarse, thickened skin with a velvety texture. It is often symmetrically distributed on the neck, axillae, antecubital and popliteal fossae, and groin folds.(1) It is histopathologically characterized by orthokeratotic hyperkeratosis, papillomatosis of stratum spinosum, hyperpigmentation of basal cell layer without melanocytic hyperplasia and dermal inflammation.(2) Schwatrz classified AN as obesity associated, malignant AN, syndromic AN, medication associated, autoimmune AN, acral AN, naevoid AN and familial AN.(3)

Obesity in paediatric age group is also on rise due to sedentary lifestyle and is emerging as a new epidemic. Childhood obesity is associated with development of metabolic syndrome, which together raise the risk of an individual developing atherosclerotic cardiovascular disease, insulin resistance, and diabetes mellitus. Metabolic disarrangement becomes a syndrome if the patient has :

Abdominal obesity (Waist circumference >90th centile for age, gender and ethnicity) plus 2 or more of the following:

- Elevated triglycerides 150 milligrams per decilitre of blood (mg/dL) or greater
- Reduced high-density lipoprotein cholesterol less than 40 mg/dL in men or less than 50 mg/dL in women
- Elevated fasting glucose of l00 mg/dL or greater or previously diagnosed type 2 diabetes
- Blood pressure values of systolic 130 mmHg or higher and/or diastolic 85 mmHg or higher (4)

AN is increasingly seen in children and adolescents who are obese, and can serve as a cutaneous marker of underlying metabolic syndrome. Obesity associated AN is the most common AN in children and adults worldwide.(5) High body mass index (BMI) in childhood & adolescence is strongly correlated with adulthood obesity, and is a reliable way of identifying individuals at risk of weight-related morbidity and mortality.(6)

In this study we evaluated the levels of serum fasting blood sugar (FBS), serum cholesterol (sChol), serum triglycerides (sTG), serum low density lipoproteins (sLDL) and serum high density lipoproteins (sHDL) in obese paediatric patients having acanthosis nigricans were evaluated and these parameters were compared with obese children without acanthosis nigricans. These metabolic were also correlated with AN grading to know the severity of

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association of this dermatosis with metabolic syndrome and to imply this to predicting the population at higher risk by way of cutaneous examination, only.

Aims And Objectives:

1. To study biochemical markers of metabolic syndrome in obese children.
2. To compare levels of FBS, cholesterol, triglycerides, sLDL and sHDL in obese paediatric population with Acanthosis Nigricans And Obese without acanthosis nigricans.
3. To correlate levels of FBS, cholesterol, triglycerides, sLDL and sHDL in obese children with grades of acanthosis nigricans.

Material And Methods:

Study design

Cross-sectional study

Study setting

Out patient department of dermatology and paediatrics of tertiary care hospital in North India between April 2021 and March 2022 after approval by Institutional Ethics & Research Committee (BFUHS/2k18pTH/17416).

Sample size :

One hundered children in age group 10-18 years were included, all of whom were obese (BMI $\geq 95^{th}$ percentile for same age and gender), that had presented to OPD either with some dermatoses or acanthosis nigricans (AN). Out of 100, 50 were categorized as obese patients with AN (OB+AN group) and 50 were taken as control having obesity without AN (OB-AN group).

Case Definitions

Obese

A patient having BMI at or above the 95th percentile for children and teens of the same age and sex.(7) BMI was calculated by the formula weight (in Kg) / height^2 (in meters). Indian academy of Paediatrics (IAP) BMI charts (5-18 years) for boys and girls were plotted for each subject according to the gender.(8)

Acanthosis Nigricans

Diagnosis of AN was done by careful visual examination of each child's neck and axilla, head and neck region, armpits, breasts, elbow, groin, knees and knuckles for the presence of dark, thick, velvety and pigmented skin. Grading of AN to determine severity was done by quantitative scale devised by Burke et al.(9) Dermoscopy aided as a diagnostic tool wherever necessary.(10)

Patient Assessment

Patients attending OPD having benign acquired AN were included in OB+AN group. Detailed medical and family history was taken from all subjects. Patients on steroid therapy, endocrine disorders (such as hypothyroidism, cushing disease, etc) and having history of any malignancy were excluded from the study. The height and weight of each patient was calculated three times and mean of the three values was taken as the final reading. Presence of metabolic syndrome was assessed using criteria laid by International Diabetes Federation.(4)

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Assessment of blood parameters of metabolic syndrome

A 12 hour overnight fasting 5cc of blood samples were taken and processed. Serum fasting blood sugar levels, serum cholesterol, serum triglycerides, serum LDL & serum HDL were measured using GOD- POD method, end point (Trinder's method)(11), Allain(12), Mc Gowan's method(13), Friedewald(14) Phosphotungstic Acid Method(15) respectively.

Statistical analysis

Descriptive statistics was done for all data and were reported in terms of mean and percentages. Continuous variables were analysed with Student's *t*-test & Categorical variables were analysed with chi square test. Statistical Significance was taken as $p<0.05$ for all variables. The data was analysed using SPSS version 22 (SPSS Inc., Chicago, IL, USA) and Microsoft Excel sheet. Correlation of grades of AN with BMI, serum FBS & Lipid profile was determined using Spearman's rank correlation coefficient. Pearson's correlation coefficient was used to analyse linear correlation between continuous variables.

Results:

A total of 100 obese (OB) subjects satisfying inclusion criteria were studied and analysed on completion of study. Two study groups were matched with respect to age and gender. [Table 1] The mean age of presentation of AN in OB+AN group was 14.90 ± 2.43 years & male: female ratio in AN group is 2.125:1 with 68% of cases being males whereas in control group (without AN), it is 1.78:1 with percentage of male subjects being 63.33 percent. Family h/o obesity and family h/o diabetes was relatively more common in acanthotic group but statistically significant difference was present only with respect to family h/o diabetes (p = 0.004).

On assessing parameters of metabolic syndrome, we found statistically significant difference in two groups for BMI [OB+AN (29.19 ± 3.54 kg/m^2) and OB-AN (26.99 ± 3.05 kg/m^2) (p=0.006)], fasting blood sugar (FBS) [OB+AN (90.76 ± 10.55 mg/dl) and OB-AN (84.53 ± 9.24 mg/dl) (p=0.009)], serum triglycerides (sTG) [OB+AN (149.94 ± 43.36 mg/dl) and OB-AN (129.67 ± 34.69 mg/dl) (p=0.033)] and serum high density lipoproteins (sHDL) [OB+AN (40.44 ± 6.43 mg/dl) and OB-AN (44.00 ± 7.39 mg/dl) (p=0.026)]. However we did not find any significant difference in two groups for post prandial blood sugar (PPBS), serum cholesterol (sChol) and serum low density lipoproteins (sLDL), although mean levels of these three parameters were also higher in acanthotic group than in non-acanthotic group. [Table 1]

In addition, we also correlated the grades of acanthosis nigricans with above parameters. Severity of AN (as assessed using Burke et al quantitative scale)(9) showed that out of 50 patients in OB+AN group, 100% had neck involvement and 92% had axilla involvement. Other sites of involvement were antecubital fossa (74%), knuckles (64%), groins (50%) and knees (48%). Majority of patients (54%, *n*=27) had grade 4 neck AN, grade 3 neck texture grading (54%, *n*=27) and grade 4 axilla grading (42%, *n*=21) [Table 2]. On correlating the results of study population in acanthotic group with grades of AN, all the parameters of metabolic syndrome (including sTG, sChol, sLDL, sHDL, FBS & BMI) were found to be directly proportional to AN neck grading, Neck texture grading and AN axilla grading; and each correlation being highly significant ($p<0.05$). [Table 3]

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Further interpreting the results for linear relationship between independent variables using pearson correlation matrix, positive correlation ($p<0.05$) was found between serum triglycerides, serum cholesterol, serum low density lipoproteins, fasting blood sugar, post prandial blood sugar and BMI, each showing statistically significant results with one another, except for non-significant correlation between sLDL and sTG. On the other hand, sHDL showed statistically significant ($p<0.05$) negative correlation with sTG, sChol, FBS, PPBS, BMI, but not with sLDL. [Table 4]

Discussion:

Acanthosis nigricans is characterized by dark, rough, and thickened skin with a velvety feel, symmetrically distributed on the neck, axillae, antecubital and popliteal fossae, groin folds, and face; histopathologically characterized by papillomatosis and hyperkeratosis of the skin.(1) Prevalence of AN ranges from 49.2% to 58.2% in various international studies involving children or adolescents with obesity and is higher in patients with severe obesity, in certain high-risk ethnic groups or in patients already diagnosed with type 2 diabetes mellitus (T2DM).(16) Childhood AN most commonly presents as Obesity-Associated Acanthosis Nigricans, but other forms such as Benign AN, Syndromic AN, Malignant, Acral, Unilateral Naevoid, Drug-Induced, Facial or Mixed-Type Acanthosis Nigricans do exist.(17) The pathophysiological process of obesity related AN is due to underlying metabolic disarrangements. Raised fasting blood sugar levels and dyslipidaemia contribute to reciprocal decrease in end organ sensitivity and subsequent increase in circulating insulin.(18) Higher serum insulin levels activates keratinocyte insulin-like growth factor (ILGF) receptors, particularly IGF-1. Insulin, at higher concentrations, displace IGF-1 from IGF binding proteins. Further, increased circulating IGF is related to proliferation of fibroblasts and enhanced stimulation of epidermal keratinocytes, clinically manifesting as lesions of acanthosis nigricans.(19)

Childhood benign acanthosis nigricans is firmly associated with obesity, hyperinsulinemia, insulin resistance and type 2 diabetes mellitus. Thus, can be used as a reliable index for diagnosing underlying metabolic syndrome.(20)

The prime objective of this study was to find degree of dyslipidaemia and fasting blood sugar levels in patients having acanthosis nigricans. Among the demographic characteristics, mean age and male to female ratio is 14.90 ± 2.43 and 2.125, respectively. This is in concordance with previous studies done by Ng et al(16) and Kluczynik et al.(22) An important consideration for higher male : female ratio in our study can be attributed to gender differences in child care associated with gender bias in our society.

Our observations of BMI and FBS were also consistent in relation to previous studies(16)(21)(23), where BMI and FBS both were statistically significant in obese cases with AN. This observation emphasis the fact that obese children, that too with acanthosis nigricans have relatively higher blood sugar levels, correlating with their increased preponderance to develop insulin resistance and diabetes mellitus. Further, observations of parameters of lipid profile revealed only total sTG and sHDL levels to be significantly deranged in obese acanthotic patients, whilst sLDL and sChol remained statistically insignificant. This observation highlights direct bearing of high levels of sTG and low levels

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of sHDL for development of acanthosis nigricans in obese population and independent risk factors for development of metabolic syndrome in children and adolescents, as also stated previously in literature.(25)

Secondary objective of our study also found a statistically significant correlation of lab parameters of metabolic syndrome with severity of AN (done using Burke scale of AN)(9), with respect to AN Neck grading, AN texture grading and AN axilla grading [Table 3]. These results were comparable with study done by Grandhe et al which reported statistically significant correlation of increasing severity of AN with increasing BMI.(25) A positive significant correlation between the neck severity score, axilla severity score, neck texture score, was reported with BMI, fasting insulin, total cholesterol and triglycerides, but a significant negative correlation with high-density lipoprotein by Kamel et al, also.(26) However, Patidar et al showed statistically significant correlation of fasting glucose levels with acanthosis neck severity grading only.(27) On further extrapolating results of indiviual parameters, our study showed that statistically significant results with relevance to age and sex matched controls, although was present for FBS, sTG, & sHDL only[Table 1], but sChol & sLDL indiviually also showed significant correlation with grades of AN in acanthotic group.[Table 3] This lead us to draw inference that acanthosis nigricans, in a obese patient accurately characterize underlying lipid derangement.

Limitation:

Since it was a cross sectional study, therefore follow up of patients was not done. Hence, any change in parameters happening with progress/resolution of disease could not be assessed. Study subjects were inducted in the study on voluntary basis, which might have resulted in sampling bias.

Conclusion:

Presence of AN and its grades correlated positively with high BMI, fasting glycemia & increased total serum triglycerides & decreased total serum high density lipoproteins. Derangement in any of these parameters point towards underlying metabolic syndrome. Thus, AN can serve as a simple, non-invasive, visual dermatological diagnostic tool which can be used as a screening method to identify children at risk of developing type-2 diabetes mellitus and cardiovascular morbidities in future and to warrant such obese population for early lifestyle modification and healthy living, while helping clinicians too in planning their treatment protocols.

Table 1 : Demographic and metabolic profile of study population

Variable		**Obese with AN (OB + AN) (n=50)**	**Obese without AN (OB – AN) (n=50)**	***p*-value**
Age, years, mean ± SD		14.90 ± 2.43	14.90 ± 2.56	1.00
Sex, n(%)	**Males**	34 (68%)	32 (63.33%)	0.671
	Females	16 (32%)	18 (36.67%)	
BMI (kg/m^2), mean ± SD		29.19 ± 3.54	26.99 ± 3.05	0.006*
Family h/o obesity		41 (82%)	33 (66%)	0.068

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Family h/o diabetes	27 (54%)	10 (20%)	0.004*
sChol, mg/dl, mean ± SD	183.96 ± 47.03	180.37 ± 50.89	0.749
sTG, mg/dl, mean ± SD	149.94 ± 43.36	129.67 ± 34.69	0.033*
sLDL, mg/dl, mean ± SD	104.44 ± 25.32	104.40 ± 25.13	0.749
sHDL, mg/dl, mean ± SD	40.44 ± 6.43	44.00 ± 7.39	0.026*
FBS, mg/dl, mean ± SD	90.76 ± 10.55	84.53 ± 9.24	0.009*
PPBS, mg/dl, mean ± SD	101.94 ± 10.64	98.00 ± 8.76	0.091

* represents highly significant statistical difference

OB: Obese; AN: Acanthosis Nigricans; SD: Standard deviation; BMI: Body mass index; sChol: serum cholesterol; sTG: serum triglyceride; sLDL: serum low density lipoprotein; sHDL; serum high density lipoprotein; FBS: fasting blood sugar; PPBS: post prandial blood sugar

Table 2 : Grades of AN according to AN site

Grades of AN	AN Neck, number of patients, *n* (%)	Neck texture grading, number of patients, *n* (%)	AN axilla grading, number of patients, *n*(%)
0	0 (0%)	0 (0%)	4 (8%)
1	1 (2%)	7 (14%)	10 (20%)
2	7 (14%)	16 (32%)	11 (22%)
3	15 (30%)	27 (54%)	4 (8%)
4	27 (54%)	-	21 (42%)

AN: Acanthosis nigricans

Table 3 : Correlation of AN grading with various laboratory parameters (Spearman's rank correlation coefficient)

		AN neck grading	Neck texture grading	AN axilla grading
sChol	r value	0.493	0.500	0.553
	p value	0.001*	0.001*	0.001*
sTG	r value	0.558	0.497	0.460
	p value	0.001*	0.001*	0.001*
sLDL	r value	0.465	0.460	0.613
	p value	0.001*	0.001*	0.001*
sHDL	r value	-0.619	-0.536	-0.570
	p value	0.001*	0.001*	0.001*
FBS	r value	0.553	0.434	0.571

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	p value	0.001*	0.002*	0.001*
BMI	r value	0.618	0.453	0.513
	p value	0.001*	0.001*	0.001*

* represents highly significant statistical difference

AN: Acanthosis Nigricans; sChol: serum cholesterol; sTG: serum triglyceride; sLDL: serum low density lipoprotein; sHDL; serum high density lipoprotein; FBS: fasting blood sugar; BMI: Body mass index

Table 4: Correlation matrix showing Pearson's *r* and *P* values for study variables among patients with acanthosis nigricans

		sTG	sChol	sLDL	sHDL	FBS	PPBS	BMI
sTG	r value	1						
	p value							
sChol	r value	0.598	1					
	p value	<0.001						
sLDL	r value	0.177	0.539	1				
	p value	0.218	<0.001					
sHDL	r value	-0.514	-0.425	-0.247	1			
	p value	<0.001	0.002	0.084				
FBS	r value	0.445	0.525	0.490	-0.436	1		
	p value	0.001	<0.001	<0.001	0.002			
PPBS	r value	0.620	0.530	0.404	-0.438	0.664	1	
	p value	<0.001	<0.001	0.004	0.001	<0.001		
BMI	r value	0.519	0.511	0.331	-0.400	0.468	0.605	1
	p value	<0.001	<0.001	0.019	0.004	0.001	<0.001	

sTG: serum triglyceride; sChol: serum cholesterol; sLDL: serum low density lipoprotein; sHDL; serum high density lipoprotein; FBS: fasting blood sugar; PPBS: post prandial blood sugar; BMI: Body Mass Index

Figure 1: Acanthosis Nigricans Neck Grade 1

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Figure 2: Acanthosis Nigricans Axilla Grade 4

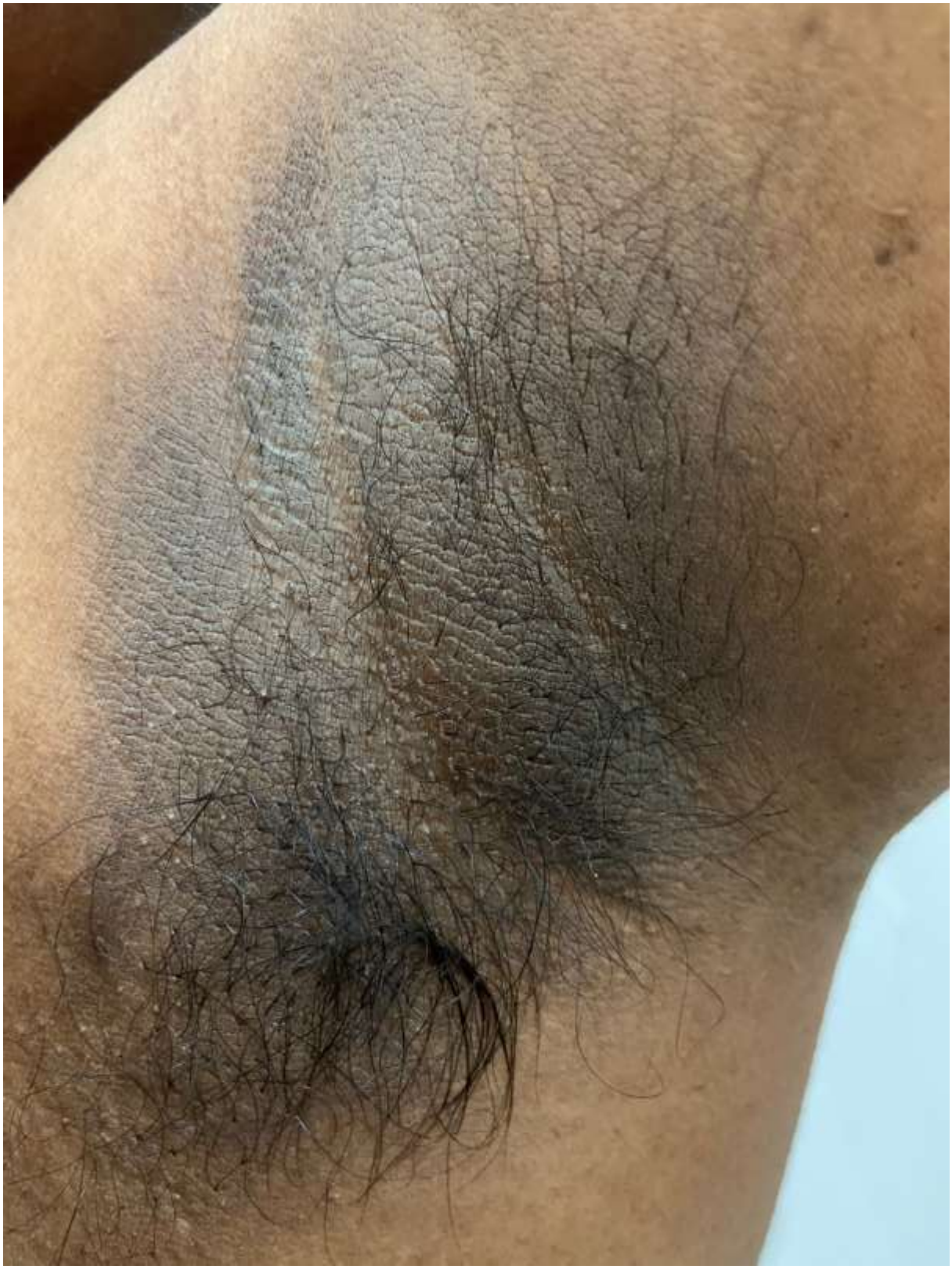

Figure 3: Acanthosis Nigricans Neck Grade 2

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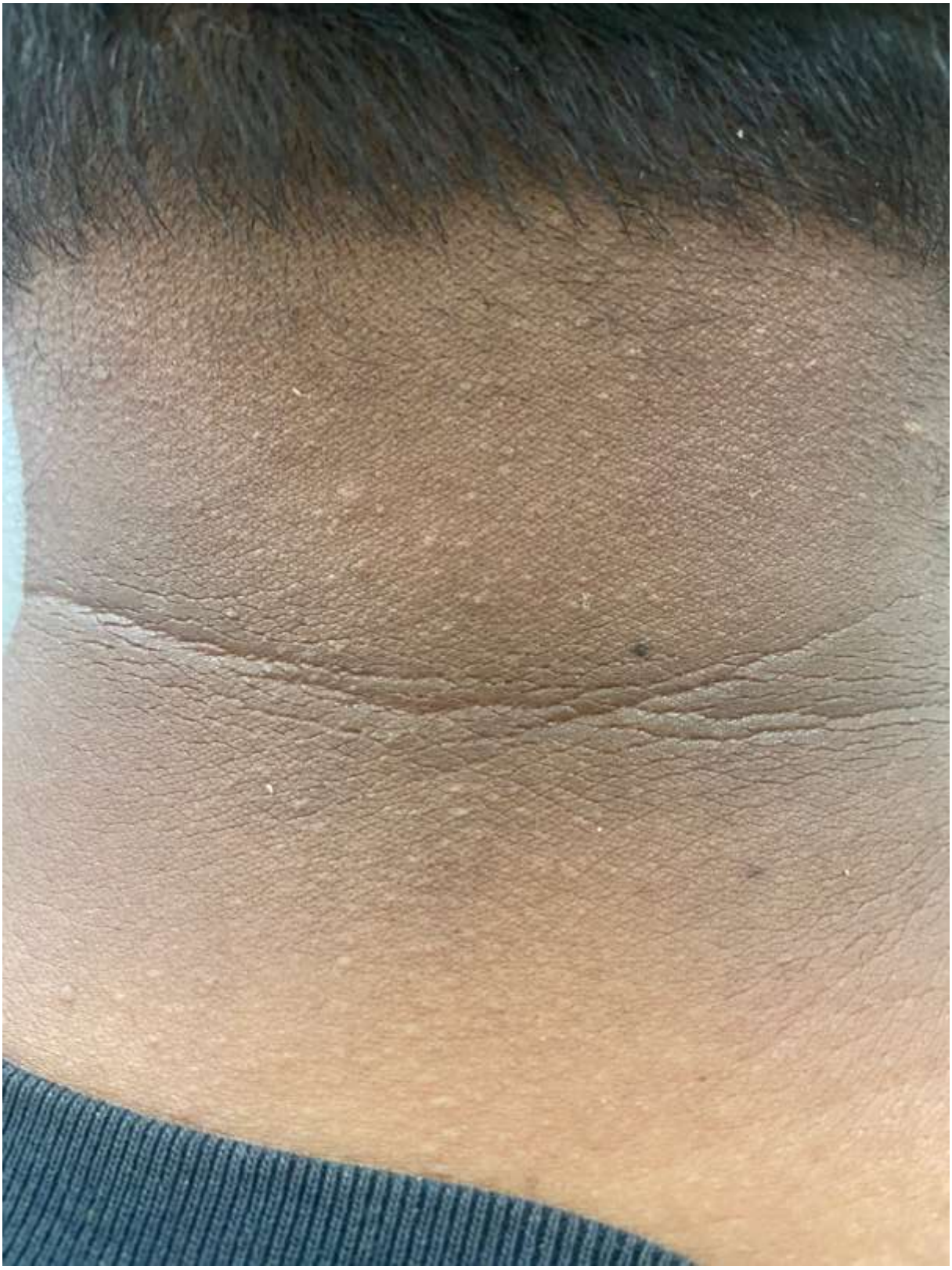

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