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Acanthosis Nigricans as a Cause of Facial Elanosis (Clinical ndhistopathological Study)

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Abstract:
Background: *There are many causes of facial melanosis like melasma , lichen planus actinicas, frictional melanosis , post inflammatory hyperpigmentation but nthosisnigricans was not well recognized as a cause of facial pigmentation .*
Objectives: *To evaluate all cases of acanthosis nigricans of face, clinically and histopathologically and to study other associated features of acanthosis nigricans.*
Patients and Methods: *Thirty cases of acanthosis nigricans of the face were included in this case descriptive, clinical and histopathological study. This was conducted in Department of Dermatology – Baghdad Teaching Hospital, Baghdad, Iraq during the period from November 2012 to August 2014. It consisted of 29 males and one female their ages ranged from 16-58(39±4.9) years. History and examination were emphasized to all points related to the disease. Clinical grading of acanthosis nigricans of face was carried out regarding the following points: texture (thickness of acanthosis and velvety) and color changes. To assess the severity of the acanthosis nigricans of the face Sharquie's scoring system so called Acanthosis Nigricans Severity Index (ANSI) was invented to measure the severity of acanthosis nigricans and to be correlated with other manifestations of the disease. Biopsies was carried out from 2 sites, from the face for each patient and from the neck for 12 patients and processed for histopathological evaluation.*
Results*: All patients presented with facial melanosis as their main problem. Clinical assessment showed all features of acanthosis nigricans including: dark pigmentation, thickening of skin and velvety texture . Associated features of disease like skin tags, seborrhea, planter hyperkeratosis in different severity were noticed. The main other sites that were affected with acanthosis nigricans were neck, axillae and groin. Obesity was noticed in 16(53.3%) patients while overweight was seen in 10 (33.3%) patients .The third and fourth decades of life were the commonest age groups affected. The males were more affected (96.67%) than females (3.33%).Skin phototype were mainly type III and IV.*
Sharqie's grading of acanthosis nigricans of the face showed grade II in 8(26.6%) and grade III in 13 (43.3%) while grade IV in 9 (30%) patients. ***ANCI*** *score was ranged from 4–62 (29.66 ± 17.78).*
The histopathological examination of acanthosis nigricans of the face showed mainly acanthosis, with or without mild papillomatosis, basal and dermal melanosis. While the histopathological assessment of neck acanthosis nigricans showed similar features but the findings were much more exaggerated and intense.
Conclusion: *Acanthosis nigricans of the face is an important cause of facial melanosis among males where melanin deposition was detected in basal layer and dermis. The present study showed that clinical and histopathological pictures and the associated findings of acanthosis nigricans of the face were similar to acanthosis nigricans of the body especially neck and axillae. Hence acanthosis nigricans of the face especially early cases might easily mixed up with melasma, frictional melanosis and butterfly lichen planus actinicus.*
Keywords: *nthosisnigricans, face, Sharquie's ANSI scoring, facial melanosis, histopathological findings.*

I. Introduction

Facial melanosis is a major health problem among Iraqi population and often cause great disfiguring impact on effected patients and there are many etiological factors involved in its etiopathogenesis [(1)] . Recent Iraqi study showed the following causes of facial melanosis: melasma 61%, frictional melanosis 12.5%, post inflammatory hyperpigmentation 9.5%, actinic lichen planus8%, acanthosis nigricans 7.5%, nevus of Ota 1%, phytophoto dermatitis 0.5%, gazelle eye like facial melanosis 0.5% [(1)].And as we have notice from this study that acanthosis nigricans account about 7.5% of facial melanosis. This is the main reason that encouraged us to conduct the present work as the disease is not well recognized as a cause of facial melanosis in medical literatures.

Acanthosis nigricansis(AN) a skin disease characterized by hyperpigmented, thickened, verrucous plaques with a velvety texture typically symmetrical in distribution. It usually involves intertriginous areas, including: neck, axillae, groin, antecupital and popliteal fossae, knuckles and umbilicus; occasionally it involves the mucosa such as oral, esophageal, pharyngeal, laryngeal, conjunctiva, and anogenital mucosa [(2).]

Although acanthosis nigricans was initially thought to be rare[(3)], a high prevalence has been observed in several recent studies, this may be due to rising trends in the prevalence of obesity and type II diabetes mellitus. The rate of acanthosis nigricans varies among different ethnic groups, as the prevalence was lower in whites 0.5% and Hispanics 5% than in African American children 13%,[(4)]and it is found in 68.7% of females with polycystic ovaries in Iraqi patients[(5).]This finding suggests a possible genetic predisposition or increased sensitivity of the skin to hyperinsulinemia among certain populations [(6).] The incidence of acanthosis nigricansis equal for men and women [(7).]

Although acanthosis nigricansis found more common in adult population; the lesion of benign acanthosis nigricans may be present at any age, including at birth, but malignant acanthosis nigricans occurs more frequently in elderly people, however cases have been reported in children with malignancies e.g. Wilm's tumour[(8).]

Acanthosis nigricans has a variety of causes, mostlikelycommon mechanism is stimulation of tyrosine kinase growthfactor receptor signaling pathways in epidermis [(9).] In insulinresistance syndromes, high levels of circulating insulin directlyor indirectly activate the insulin-like growth factor1receptor(IGF1R)[(10)].Insulin resistance due to obesity underlies the hyperinsulinaemia in obesity- associated acanthosis nigricans.[(11,12)] An elevated fasting blood insulin level confirms the presence of hyperinsulinaemia underling the diagnosis of atypical acanthosis nigricans[(13).] In malignant acanthosis nigricans, tumor deriver growth factors, in particular transforming growth factor-α, acting through the epidermal growth factor receptor (EGFR) are presumed, although anti insulin receptor antibodies have also been implicated[(14).]

The essential features are common to all forms of the disease, but often show differences in distributions, degree and extent. The earliest changes are usually dryness, pigmentation and roughness of the skin, which in affected area is gray-brown or black [(15)]. The hyperpigmentation is later accompanied by hypertrophy, increased skin marking, and papillomatosis. The most commonly involved locations are the neck, axillae, external genitalia, groin, inner thighs, antecupital and popliteal fosse, knuckles, umbilical, and perianal areain a tangible way[(16).]Histopathology of acanthosis nigricans shows hyperkeratosis, papillomatosis, slight irregular acanthosis and slight hyperpigmentation of the basal layer is present in most cases. It appears however, that the clinically observed hyperpigmentation is due to hyperkeratosis and clinical thickening rather than to melanin [(17-19)] but other studies showed melanin deposition in the epidermis and dermiswas the main causeofpigmentation [(20).] As in some early cases of acanthosis nigricans although there is no much thickening and papillomatosis on epidermis still the skin is pigmented [(21).]

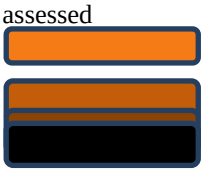
As the literature is lacking recording acanthosis nigricans as an important cause of facial melanosis, the present work wasarranged to evaluate the clinical and histopathological features of the acanthosis nigricans of the face.

II. Patients and Methods

This case descriptive, clinical and histopathological study was conducted in the Department of Dermatology –Baghdad Teaching Hospital, Baghdad, Iraq during the period from November 2012 to August 2014 . Thirty patients were involved in this study (29 males and 1 female) .The nature and aim of this study were explained for each patient. Formal consent was taken from them before taking a biopsy and photographs after full explanation about the nature of the disease. Also, the ethical approval was given by the Scientific Council of Dermatology & Venereology- Iraqi Board for Medical Specializations. History and clinical examination were done for all patients including: age, gender, onset of the disease, duration of the disease ,sites of involvement, any associated skin manifestations regarding: skin tags, bad odor, seborrhea, hyperkeratosis of palm and\ or sole, acanthosis nigricans at other sites of body like axillae, neck, groin, knuckles, umbilicus, below the breast were noticed. Past medical and surgical history, menstrual and fertility history were recorded. The height and the weight of the patients were measured and body mass index was obtained for all patients by dividing the weight of the patient in kilogram on height in square meter. The waist circumference was measured on standing subjects with a soft flexible tape measured from the narrowest part of the torso as seen from the anterior view (midway between the lowest rib and the iliac crest). Fitzpatrick's skin phototypes were determined for each patient. The diagnosis of acanthosis nigricans was made clinically and site were determined. Surface areas were measured by using transparent paper on the face and by white board pen delineated the areas affected. Then by putting the transparent paper on graph paper we can measure the surface areas involved by the disease in square centimeters. Color photographs for all patients were performed by 8 megapixels camera of mobile Samsung Galaxy Note II, in the same place and distance with fixed illumination.

Clinical grading of acanthosis nigricans was carried out regarding the following points: texture (thickness of acanthosis nigricans and velvety) and color changes (Table-1).To assess objectively the severity of acanthosis nigricans of the face professor Sharquie invented a scoring system so called: **Acanthosis Nigricans Severity Index(ANSI)**, in this system the face is divided into 7 areas. Forehead, right temporal, left temporal, right cheek, left cheek, right nasolabial fold and left naoslabial fold. This score was depending on the following features: color, texture and surface area:

1- Color (Darkness): Scoring from 1-4 was assessed
Score 1= Light brown.
Score 2= Brown.
Score 3 = Dark brown.
Score 4 = Black



2- Texture: Scoring from 0-3
Score 0 = No thickening.
Score 1 = Mild thickening.
Score 2 = Moderate thickening.
Score 3 = Severe thickening.

3- Percentage of the total area involved, this was measured by using transparent square paper. By this method the acanthosis nigricans and the total surface areas were measured accurately by square centimeters, then the percentage of the acanthosis nigricans area relative to the total area of the same region was measured and scoring was done as follows:

a- Forehead:
Score 1= 1-25%
Score 2= 5- 50%
Score 3= 0-75%
Score 4= 5%

b- Cheek:
Score 1= 1-25%
Score 2= 5- 50%
Score 3= 0-75%
Score 4= 5%

c- Nasolabial folds:
Score 1= 1-25%
Score 2= 5- 50
Score 3= 0-75%
Score 4= 5%

d- Temporal area:
Score 1= 1-25%
Score 2= 5- 50%
Score 3= 0-75%
Score 4= 5%

The scoring for each area were done separately including: forehead, right temporal, left temporal, right cheek, left cheek, right nasolabial fold and left nasolabial fold for all patients.
The **ANSI score** was calculated by the following equation:
ANSI= (DF+TF+AF) +(DTR+TTR+ATR) + (DTL+TTL+ATL) +(DCR+TCR+ACR) + (DCL+TCL+ACL) + (DNR+TNR+ANR) + (DNL+TNL+ANL).

Where D is darkness, T is thickness, A is area, F is forehead, TR is right temporal, TL is left temporal, CR is right cheek, CL is left cheek, NR is right nsolabial, NL is left nasolabial.

The benefit of this invented score is to measure the severity of acanthosis nigricas and to be correlated with other manifestations of the disease like: obesity, fasting blood sugar and serum cholesterol and secondly this score could be used to assess the therapeutic response to treatment of acanthosis nigricans.

Skin biopsies were done for each patients taken from darkest area on the face and processed for histopathological study using both Hematoxylin\Eosin (H&E) and Fontana Masson stains. Biopsies were taken from AN of the neck from 12 patients in order to compare the histopathological changes with that of the face. Abdominal and pelvic ultrasound was carried out for all patients to look for intra-abdominal and pelvic organs and to exclude any possible intra-abdominal organ pathology. Wood's lamp examination for face and neck for each patient was done to evaluate the level of melanin deposition in the skin whether epidermal ,dermal or in combination.

Data were statistically described in terms of range, mean, standard deviation (±SD), mode of frequencies (number of cases) and relative frequencies (percentages). Comparison between investigations of patients and controlled individuals was done using Chi square (x^2) test. A probability value (p value) less than 0.05 was considered significant. All statistical calculations were done using computer programs SPSS ver. 20 (Statistical Package for the Social Science; SPSS Inc. Chicago, IL, USA)

Table -1: Sharqie's grading of acanthosis nigricans of face depending on texture.

Grade	Thickness	Color
Grade 1	0	Light brown
Grade II	Mild	Brown
Grade III	Moderate with velvety	Dark brown
Grade IV	Severe with severe velvety	Black

III. Results

Thirty patients with acanthosis nigricans of the face were included in this study, 29 (96.6%)males and 1(3.3%)female , with a ratio of male/ female 29:1. Their age ranged from 16-58(39±4,9) years. Skin phototype were mainly type III and IV. The third and fourth decades of life were the commonest age groups affect. The duration of the disease ranged from 1–8(3.34±5.67)years. All patients had bilateral symmetrical distribution of acanthosis nigricans on the face with frequency of distribution according to the site of lesion was as follows: forehead 28 (92.3%), right and left temporal 17 (54%), Rt and Lf nasolabial folds 18 (57 %), Rt and Lf cheek 22 (66.6 %). The commonest areas that were involved in association with face were neck and axillae 30 (100%), groin 5 (16.6%) and hand knuckles 4(12.2%) patients. Positive family history of acanthosis nigricans was found in 3 (10%) patients. No patients with underling malignancy, diabetes or other important medical conditions were noted.

Regarding Sharqie's grading of AN of the face, grade II was found in 8 (26.6%) and grade III in 13 (43.3%) while grade IV in 9 (30%) patients. **Sharquie's ANSI scoring** was ranged from 4– 62 (29.66 ±17.87).

Score 1- 20 in 8 (26.6%)
Score 20- 40 in 13(43.3%)
Score 40 in 9 (30%)

Normal weight was seen in 4 (13.3%) patients while overweight seen in 10 (33.3%) patients, and obese in 16 (53.3%) patients. The body mass index (BMI) ranged from 24.1–38 with a mean ±SD of 32.33± 0.72. So BMI was found to be highly significant elevated in patients with acanthosis nigricans of the face in comparison with healthy controlled individuals with P value = 0.00545.

All patients had skin tags in neck, axillae and groin. Also, seborrhea present in all patients. In addition to other associated symptoms like bad odor 21(70%) patients, Planter hyperkeratosis 9(30%) patients.

Wood's lamp examination showed mixed epidermal and dermal deposition of melanin in 30(100%) patient with acanthosis nigricans of the face and in 12(100%) patients with acanthosis nigricans of neck.

Waist circumference was greater than 102 in 25 (83.3%)patients and less than 102 in 4 (16.7%)patients. All patients had normal abdominal ultrasound.

Histopathological examination of 30 biopsies of acanthosis nigricans of face showed mainly acanthosis in different grades in 20(66.6%) patients. The epidermis was covered by melanin deposition but was more heavy in basal layer in 30(100%) patients. This melanin deposition was well demonstrated by Fontana rather than by H&E stain as there could be scanty melanin by H&E but was heavy by Fontana stain. The dermis showed no perivascular infiltrate but there were frequent melanophages in 16 (53.3%) patients in superficial and mid dermis and these melanophages were more obvious by Fontana stain rather than H&E stain. Also, mild papillomatosis was seen in 5(17.1%) patients. While the histopathological evaluation of neck acanthosis nigricans was similar to that of face but all histopathological features were more marked than those of face, in which there were acanthosis with papillomatosis in different grades, hypermelanosis of the whole epidermis but was more intense in the basal layer. This melanin deposition was well seen by Fontana rather than by H&E stain. The dermis showed frequent melaophages in superficial and mid dermis. These melanophages were well demonstrated by Fontana stain rather than by H&E stain as some time there were few melanophages by H&E while there were frequent by Fontana stain. No perivascular infiltrate was noticed.

So the histopathological findings of acanthosis nigricans of face were similar to those of neck but were more exaggerated in the later and the severity of histopathological changes was well correlated with the severity of acanthosis nigricans of the neck and of the face.

Figure-1: Fifty two years old male with acanthosis nigricans of the forehead, side of the face, temporal area and nasolabial folds.

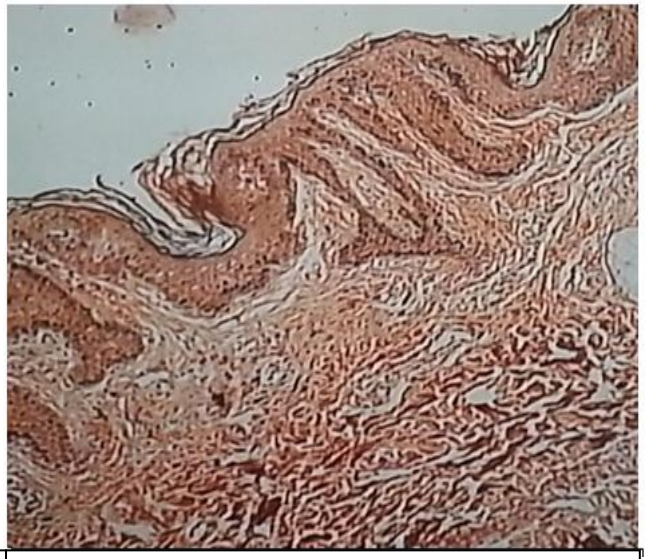


Figure -2: Biopsy from patient with acanthosis nigricans of the face stained by Fontana masson stain, showing epidermal & dermal melanosis with dermal melanophage (original magnification X 10).

Figure- 3A: Histopathology of 32 years old male with acanthosis nigricance of tempol showing papillomatosis (using Fontana stain, original magnification 40).

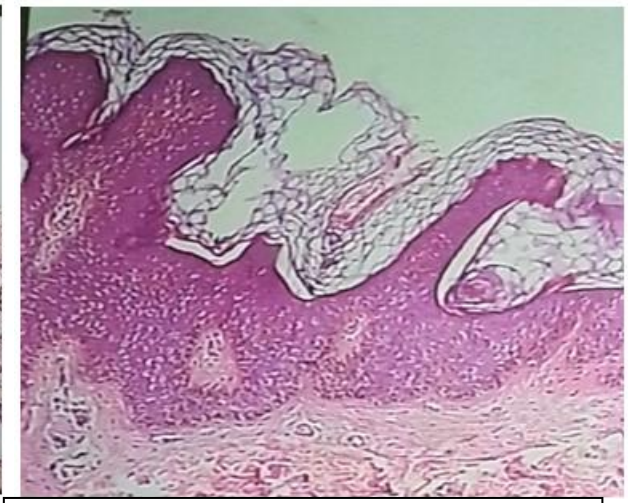


Figure- 3B: H&E stain of same patient showing epidermal and basal melanosis and papillomatosis (original magnification 40).

IV. Discussion

Acanthosis nigricans is a major health problem worldwide including Iraq especially among obese individuals[1]but unfortunately medical literatures is lacking about acanthosis nigricans of face. And as acanthosis nigricans usually present as a pigmentation of skin a recent Iraqi study showed that acanthosis nigricans of face account for 7.5% of the facial melanosis.[1] The present work was arranged to highlight to important things: first to show that acanthosis nigricans of the face is not a rare problem and secondly to report that acanthosis nigricans of the face is one of the common causes of facial melanosis.

Acanthosis nigricans was reported to be a disease of young adults and also could be seen in children younger than 10 years age[5] while in the present study, middle age males (39 years) were the commonest age

affected. Males (96.6%) were commonly involved in present study while females were mainly affected in patients with ordinary acanthosis nigricans[5]. This gender discrepancy could not be well explained but probably acanthosis nigricans of face is rare among females. Acanthosis nigricans has been reported to be common in patients with skin phenotype III and IV [21] and finding of present study was also seen among patients with skin type III and IV .

All medical literatures mentioned that the cause of pigmentation of acanthosis nigricansis related to the thickening of skin and its velvety texture but in Iraqi study showed that melanin deposition in epidermis and dermis was the main cause of pigmentation[21]. The present work confirmed this finding as melanin was found to be increased in basal layer of epidermis and superficial dermis even in mild cases of acanthosis nigricans of the face where there is no clinical and histopathological thickening of the skin. It has been noticed that the degree of pigmentation is well correlated with the severity of thickness and velvety texture of the skin in patients with acanthosis nigricans of the face. This is difficult to be explained but we can speculate that the epidermis in general could be considered as a " **store of melanin** "and this store will be increase whenever there is thickening and increase in volume of the epidermis, accordingly whenever there is increase in quantity of melanin in epidermis ,there will give more darkening and pigmentation of the skin. Also, interesting to record that in some mild cases of acanthosis nigricans of the face, the histopathology was very similar to that of melasma, accordingly melanin deposition in the skin could be one of the earliest manifestation of acanthosis nigricans.

The present work confirms that the histopathology ofacanthosis nigricans of the face were similar findings to that of the neck and axilla but in a mild form.

Forehead was the most common site involved (92.3%), followed by cheek in (66,6 %), temporal areas(54%) and nasolabial folds (57 %) of patients . The involvement of nasolabial folds is very important clinical marker of AN of the face to be differentiated from other facial melanosis especially the frictional type.

The present work is the first one to invent grading and scoring of the face **(ANSI scoring)** and grading was found to be very comparable to ANSI score:

Grade II in 8 (26.6%) and ANSI score 1-20 in 8 (26.6%) patients.

Grade III in 13 (43.3%) and ANSI score 21-40 in 13 (43.3%) patients.

Grade IV in 9 (30%) and ANSI score >40 in 9 (30%) patients.

This grading and scoring could be very useful to assess the severity of the disease and the therapeutic response to drugs, they are also could be used a good tool to be correlated with metabolic arrangement like fasting blood sugar fasting insulin and triglyceride.

The associated skin manifestations of acanthosis nigricans of the face especially seborrhea, skin tags, planter hyperkeratosis, bad odor and body mass index was significantly increased and were comparable with the result reported in patients with ordinary acanthosis nigricans[8].

In conclusion, acanthosis nigricans of face is an important cause of facial melanosis among Iraqi males where it's clinical and histopathological pictures and associated manifestations were similar to acanthosis nigricas of body in addition to the common histopathological features of the disease: melanin deposition in epidermis and dermis was an important clinical finding in the present study. Sharquie's grading and ANSI scoring of acanthosis nigricans of the face is a newly invented parameter to assess the severity of the disease. Also, this score could be used to assess the therapeutic response to treatment of acanthosis nigricans of the face.

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