Hyperkeratosis, Is it the sole element in Acanthosis nigricans pigmentation?
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Abstract: Acanthosis nigricans, which is characterised by diffuse velvety thickening and hyperpigmentation of mainly the flexural skin, can result from a variety of causes. The most commonly encountered one is the benign a result from little understood reaction of the skin to underlying metabolic faults and is generally seen in obese individuals or in association with endocrine disorders (diabetes mellitus, polycystic ovary syndrome), drugs, and malignancy. It also serves as a marker for Metabolic Syndrome X. Table 1 Diagnosis is usually made by the clinical appearance of affected skin. Histology when performed demonstrates basket weave pattern hyperkeratosis, papillomatosis, with mild hyperpigmentation of basal cell layer without any significant dermal changes. Although a lot is known regarding the association and pathogenesis of a but we are left with very little option when it comes to its management part. Very often we fail to provide much solace to the poor patient who is solely concerned with mitigating or at least lessening the physical disfigurement caused by hyperpigmentary changes. Pigmentation of AN has been proposed to be due to the hyperkeratosis with other factors playing little or no role. We conducted this study to find out if melanin does play any role in the pigmentary changes associated with the disorder, which will open newer prospects for management. Thus we want to establish that hyperkeratosis is not the sole element in pigmentation.

Keywords: Acanthosis nigricans; Melanosomes; Metabolic Syndrome X.

INTRODUCTION
In 1889, the first documented case of A was described by Unna and Politzer. In 1976, Kahn et al in their landmark study unveiled the association between AN and insulin resistance [1]. In our study, we are dealing with the benign (obesity related) cases of AN which are by far the commonest variant. Although, several other causes ranging from not so common to rare forms of AN are syndromic cases associated with HAIR-AN syndrome, Hashimoto thyroiditis, autoimmune disease such as systemic lupus erythematosus, scleroderma, Sjögren syndrome, and malignancies [2]. Drugs like nicotinic acid, insulin, pituitary extract, systemic corticosteroids, and diethylstilboestrol, triazine, oral contraceptives, fusidic acid, and methyl testosterone have been implicated [3]. Apart from this, Acral, Unilateral, Generalised, Familial Idiopathic and mixed variants have seldom been reported. Even though, the most common sites of affection are axillae and neck, it may also affect eyelids, lips, vulva, mucosal surfaces, dorsal hands, and flexural areas in the groin, knees, elbows and palms [4]. Degree of cutaneous involvement by the lesions of AN varied to a great extent in different patients and even at different sites of the same patient.

Proper understanding of underlying cause of hyperpigmentation in AN is the mainstay in management of gruesome pigmentary change, which is a cause of social stigma and psychological conflict in the subjects affecting their quality of life. It is well-established that hyperpigmentation in AN is due the hyperkeratotic change we encounter in histopathology with melanin playing a little or absolutely no role in pigmentary changes [5].

SUBJECTS AND METHODS:
70 patients of clinically diagnosed AN were subjected to measurement of fasting Insulin and fasting blood sugar levels. Data used in this study were obtained from fifty-seven patients of clinical AN with an elevated fasting insulin levels with normal fasting glucose levels, suggesting they were in an insulin-resistant condition. Proper History taking, physical examination and judicious investigations were carried to rule out presence of malignancy or intake of any
offending drug. In our study, female patients were only 12 in number. Our youngest subject was a 13 year old obese boy and at the opposite pole was a 62 year old overweight lady with majority between 25-45 years. Measurements made possible with the help of Mexameter® MX 18 (Courage-Khazaka Electronics GmbH, a German based enterprise. Technical Data Dimensions: 13 cm x Ø 2.4 cm Measuring surface: Ø 5 mm ≈ 19.6 mm² Probe cable: 1.3 m Weight: 85 g incl. cable Wavelengths: 3 colour measuring system green: \(\lambda = 568\) nm, red: \(\lambda = 660\) nm, infrared: \(\lambda = 870\) nm Accuracy: ± 5%) The company provides CE approved products and has been ISO 9001 and ISO 13485 approved by the TÜV Rheinland.

The Measuring Principle - The measurement is based on the phenomenon of absorption/reflection. The probe of the Mexameter® MX 18 emits 3 specific light wavelengths. A receiver measures the light reflected by the skin. The positions of emitter and receiver guarantee that only diffuse and scattered light is measured. As the quantity of emitted light is defined, the quantity of light absorbed by the skin can be calculated. Melanin is measured by specific wavelengths chosen to correspond to different absorption rates by the pigment. The result is shown within 1 second as index numbers (0-999).

Method - Measurements of A pigmentation were acquired from axillae and postero lateral aspect of neck with control measurements made from inner surface of forearm and skin over clavicle. During measurement, the mexameter probe was placed perpendicular to the skin with light pressure to avoid blanching effect; furthermore a spring in the measuring head provides constant pressure over the skin.

RESULTS:

We have made every effort to furnish the result of our study in a lucid fashion without going into much statistical complications. Mexameter readings were in terms of Melanin Value (MV), which we calculated from both lesional as well as normal sites in every subject. MV varies in a single individual over distinct lesional sites, thus the average of the measured values calculated. We have not given much emphasis to absolute MV, as melanin content depends upon an individual’s complexion. In this study, we are focussing on how many folds MV have increased in lesional skin as compared to the normal skin in a single individual which will give us a better parameter for comparison among different subjects. Majority of our patient (41 out of 57, 72%) have a 2-3 average hike in MV over lesional skin as compared to normal control skin (Figure I). Only 2 subjects have their average MV higher than 3, rest have it in between 1-2. No major differences in Melanin Value could be appreciated between sexes. Further, a brief enumeration of absolute MV done in Table1.

Fig-1: Number of folds of increase in MV in leisonal skin as compared to normal skin
Table-1: Range of Absolute MV Range

<table>
<thead>
<tr>
<th>Measurement Sites</th>
<th>Absolute MV Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axillae (L)</td>
<td>375-1170</td>
</tr>
<tr>
<td>Postero Lateral aspect of neck (L)</td>
<td>539-1095</td>
</tr>
<tr>
<td>Inner surface of forearm (C)</td>
<td>362-681</td>
</tr>
<tr>
<td>Skin over clavicle (C)</td>
<td>193-574</td>
</tr>
</tbody>
</table>

Table-2: Major types of AN

<table>
<thead>
<tr>
<th>SL. No.</th>
<th>Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Bening AN</td>
</tr>
<tr>
<td>2.</td>
<td>Obesity associated</td>
</tr>
<tr>
<td>3.</td>
<td>Syndromic</td>
</tr>
<tr>
<td>4.</td>
<td>Malignant</td>
</tr>
<tr>
<td>5.</td>
<td>Acral</td>
</tr>
<tr>
<td>6.</td>
<td>Unilateral</td>
</tr>
<tr>
<td>7.</td>
<td>Medication associated AN</td>
</tr>
<tr>
<td>8.</td>
<td>Mixed AN</td>
</tr>
</tbody>
</table>

DISCUSSION:

In our study, we used mexameter readings to get quantititative and accurate result and we found raised MV over AN lesion as compared to normal skin, which indicates that melanin do have a role in determining AN pigmentation [6]. This was done to overcome the limitation of human eye, which is very sensitive for the distinction of colours viewed side by side, but, as soon as they are separated by space or time, differences are frequently undetected. Furthermore, the impression the eye receives from colours depends on the ambient lighting. The result of our study was in sheer contradiction to histopathological findings which failed to demonstrate even with special stains for melanin any significant increase in the latter in lesional skin. This enigmatic conflicting result can be clarified by further peeping into the histopathology, where we encounter papillomatosis, which apparently increases the density of keratinocytes containing melanosomes, while keeping their absolute number almost unchanged. Thus, our old culprit, hyperkeratosis along with the new offender is responsible for unsightly appearance of AN affected skin. Our observation is further supported by a study published on vitiligo in 2006 where they raised the possibility of presence of inactive or DOPA negative melanocytes in the white macules of vitiligo which is non-identifiable by routine histopathology [7].

Till date the treatment of bening A revolves mainly around oral insulin sensitizers like metformin and topical retinoids (0.05% and 0.1%). Other less common alternatives being 0.1% Adapalene gel, oral Retinoids, topical calcipotriol, Octreotide, 12% ammonium lactate, urea, salisalic acid and Fish oils [8, 9]. Dermabrasion and chemical peeling have shown mild to moderate response in a subset of patients [10].

This understanding would surely open up newer horizons in the management of pigmentary alteration in AN. Rosenbach et al.; have safely and effectively treated hyperpigmented AN of the axillae using the long-pulsed alexandrite laser targeting melanin [11].

CONCLUSION:

Thus, we conclude that with our newer understanding of underlying cause of pigmentation in AN, we can surely open up newer horizons with enhanced treatment options. But at the same time we have to remember, even if the melanin targeting medical and Dermato surgical therapies lessen the pigmentation in AN, they are not a substitute for disease modifying insulin sensitizer drugs. Hence, we can use them as adjuvants, which will ensure better treatment response with enhanced patients’ satisfaction.

REFERENCES


