Photographic, Dermoscopic and Histopathological Findings in A Case of Severe Acanthosis Nigricans and Phymatous Rosacea in A 51-Year-Old Filipino Man : A Case Report

Julius Garcia Gatmaitan[1]*, Jolene Kristine Garcia Gatmaitan-Dumlao[2], Johannes Flores Dayrit[3]

[1] Gatmaitan Medical and Skin Center, Skines Aesthetic and Laser Center
[2]Baguio General Hospital, Notre Dame De Chartres Hospital
[3]De La Salle Medical and Health Sciences Institute & Research Institute for Tropical Medicine

Abstract

Establishing a definite diagnosis for facial hyperpigmentation and pigmentary lesions in skin of color often poses challenges as they are frequently difficult to differentiate. Therefore, it becomes necessary to correlate history, clinical findings, dermoscopy, and histopathology to accurately identify and diagnose these conditions. We report a case of a 51-year-old Filipino man with a six-year history of asymptomatic pigmentation with a rough surface on forehead, cheeks, chin and neck. He also reported enlargement of the nose, earlobes, glabellar area and the chin. Dermoscopy and histopathology confirmed the diagnosis of acanthosis nigricans and phymatous rosacea. The coexistence of severe acanthosis nigricans and phymatous rosacea in skin of color has rarely been reported.

Keywords: acanthosis nigricans, rosacea, pigmentary disorders, dermoscopy

Address of corresponding author:
Gatmaitan Medical and Skin Center, Skines Aesthetic and Laser Center
Email:
juliusggatmaitan@gmail.com

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"Dark spots on the face", "dark neck" and "dark underarms" are some of the aesthetic concerns of majority of the Filipinos. Acanthosis nigricans (AN) is rarely described among Filipinos since most of them have brown to dark-brown skin color. Acanthosis nigricans presents clinically with thickened hyperpigmented leathery plaques typically on the neck, intertriginous areas and the face. Usually, AN is a common dermatological manifestation associated with obesity, insulin resistance, endocrine disorders and internal malignancy.

Previously recognized as a chronic inflammatory skin condition, rosacea is now understood to be more than just a dermatological disorder. It is considered a systemic inflammatory disease that can affect multiple systems in the body. The original standard classification of rosacea identified the most common parts observed and it classified into four subtypes: erythematotelangiectatic, papulopustular, phymatous or ocular. While this classification is well known, it offers limited considerations as to the full spectrum of signs and symptoms of this condition. Current guidelines from the 2017 National Rosacea Society (Table 1) recommend a phenotype driven approach. The presence of either fixed centrofacial erythema that may intensify periodically or phymatous changes are already diagnostic criteria for rosacea. In the absence of these features, presence of two or more major phenotypes such as papules/pustules, flushing and facial telangiectasia may be necessary to establish the diagnosis. Ocular manifestations such as lid margin telangiectasia, conjunctival injection may also be considered as major features of rosacea [1, 2]. Previous studies have highlighted the association between rosacea and various systemic conditions, including cardiovascular diseases, metabolic syndrome (MS), and insulin resistance.

Case Presentation

We present the case of a 51-year-old Filipino man with Fitzpatrick skin type IV with a six-year history of asymptomatic dark brown to black-colored macular pigmentation on forehead, cheeks, chin and neck. The lesions had ill-defined borders and a velvety surface. Few years later, the enlargement of nose, chin, glabellar and earlobe were noted. The patient was initially diagnosed as lepromatous type of leprosy due to the appearance of leonine facies and referred to us for further evaluation. Our patient denies any previous history of dermatoses, trauma, local topical application, or systemic medication that could cause discoloration and no known history of malignancy. The patient has a medical history of hypertension and diabetes which require treatment. Additionally, he has a strong family history of hypertension, diabetes, and dyslipidemia. During the physical examination, elevated BMI and blood pressure were noted. Dermatological examination revealed hyperpigmented velvety thickening of the skin on the left cheek (Figure 1a), face (Figure 1b), right cheek (Figure 1c), metophyma (Figure 1d), gnatophyma (Figure 1e), neck (Figure 1i) and knuckles (Figure 1j). Rhinophyma (Figure 1g) and otophyma (Figure 1f and 1h) were also observed. The patient also had blepharophyma.

Based on the World Health Organization guidelines [3], a leprosy case is a patient having one or more of the following: 1) Hypopigmented skin lesions with loss of sensation, 2) impairment or involvement of the peripheral nerves as demonstrated by; a) definite loss of sensation or b) weakness of hands/feet or face or c) autonomic function disorders such as anhidrosis or d) presence of visible deformities, and 3) signs of the disease with demonstrated presence of bacilli in skin smear or histopathological confirmation. While our patient was presented with visible deformities, his neurological examination revealed intact sensation bilaterally without motor deficits bilaterally.

In all cases, the authors performed dermoscopy using a manual polarized light device (Dermlite DL2x10; 3Gen, San Juan Capistrano, CA). Dermoscopy of the cheeks (Figure 2a) demonstrated bluish gray areas with telangiectasias. Dermoscopy of the chin (Figure 2b) revealed prominent sulci, with larger brown globules and thickened perifollicular hyperpigmentation. Dermoscopy of the nape (Figure 2c) revealed markedly depressed sulci.

A 4mm skin punch biopsy of the left cheek (Figure 3a) revealed parakeratosis of the stratum corneum. There is acanthosis of the epidermis, hypergranulosis and mild spongiosis. The dermis reveals prominent fibrosis and enlarged sebaceous lobules. Fibrosis was also seen in the lower dermis. A 3mm skin punch biopsy on the left earlobe (Figure 3b) revealed mild acanthosis of the epidermis with basal cell layer hyperpigmentation. The dermis reveals fibrosis and enlarged sebaceous lobules. Fibrosis was seen in the lower dermis. Fite-Faraco stain revealed absence of acid-fast bacilli. Based on the correlation of the clinical, dermoscopic and histopathological findings, the diagnosis of AN and phymatous rosacea were made.

Management and Outcome

Patient was co-managed with a cardiologist and an endocrinologist for control of hypertension and diabetes respectively. He was prescribed with gel cream preparation containing a combination of the following: vegetable extracts (butcher's-broom, centella asiatica, calendula offinalis, horse-chestnut, liquorice), vitamin B3, betaine and β-glycyrrhetinic acid, sunscreen and low-dose oral isotretinoin (10mgs once a day for 1 month, 10mgs every other day for the 2nd month and 10mgs twice a week for the 3rd month) for the acanthosis and rosacea. In addition to the topical and oral medications, he underwent every 2 weeks of treatment with yellow laser 577nm (Quadrostar Pro®, Germany) using the following parameters; fluence: 15 J/cm2, pulse width: 36ms, pulse duration 1.5 sec, scanner mode 80% coverage) for a total of 6 sessions with remarkable improvement (Figure 4). He was also advised with strict sun protection and avoidance of rosacea triggers.

Table 1: Updated rosacea diagnosis and classification[1]

DIAGNOSTIC PHENOTYPES (only one required)	**MAJOR PHENOTYPES (any two required)**	**SECONDARY PHENOTYPES**
1. Persistent centrofacial erythema 2. Phyma; Rhinophyma Metophyma Otophyma Gnatophyma Blepharophyma	1. Transient facial erythema 2. Inflammatory papules/ pustules 3. Telangiectasias* 4. Ocular features *Excludes solely nasal alar telangiectasias	1. Burning 2. Erythema 2. Edema 3. Dryness

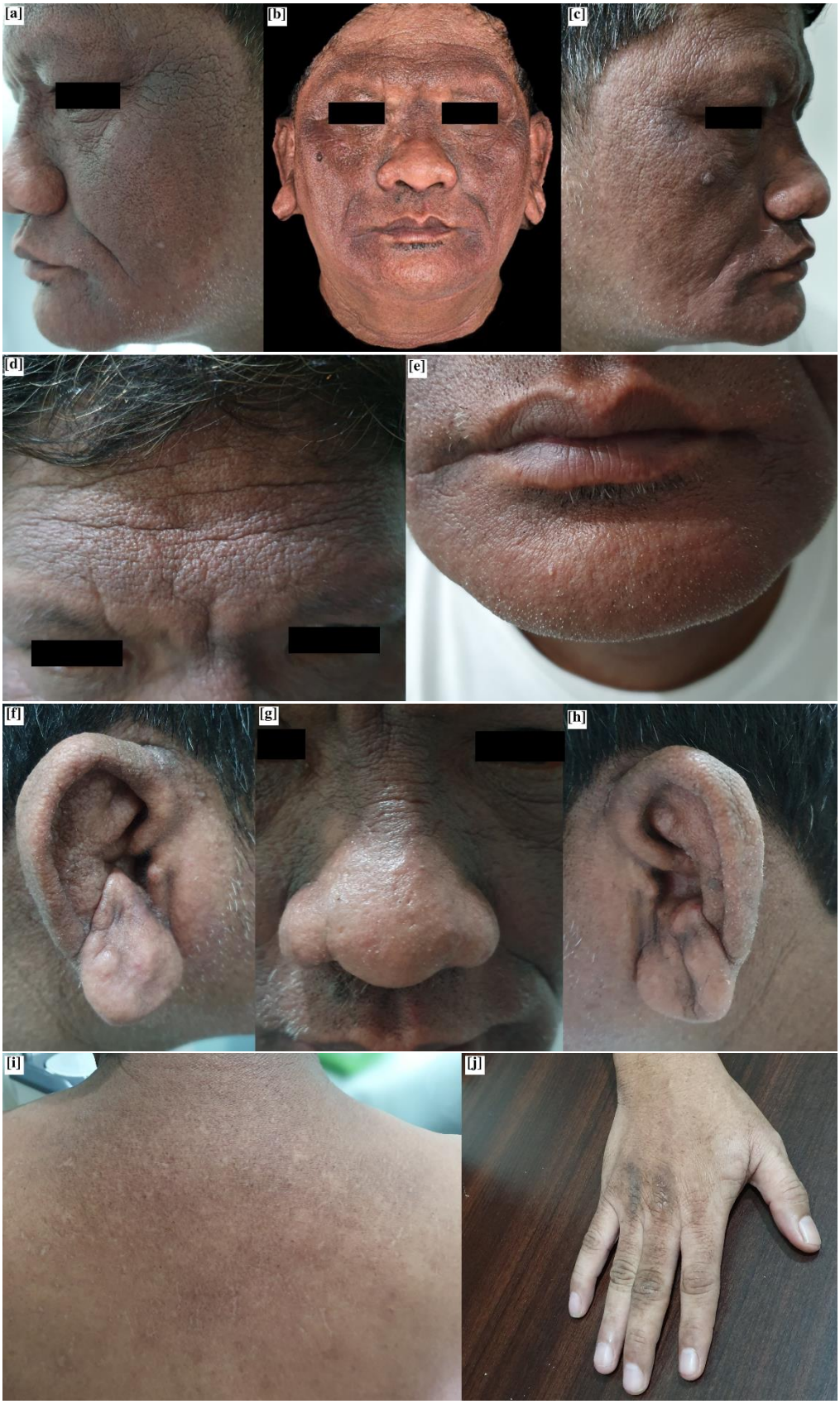

Figure 1: Hyperpigmented velvety thickening of the skin on the left cheek (a), face (b), right cheek (c), forehead (d), chin (e), neck (i) and knuckles (j). Rhinophyma (g) and otophyma (f,h) were also observed.

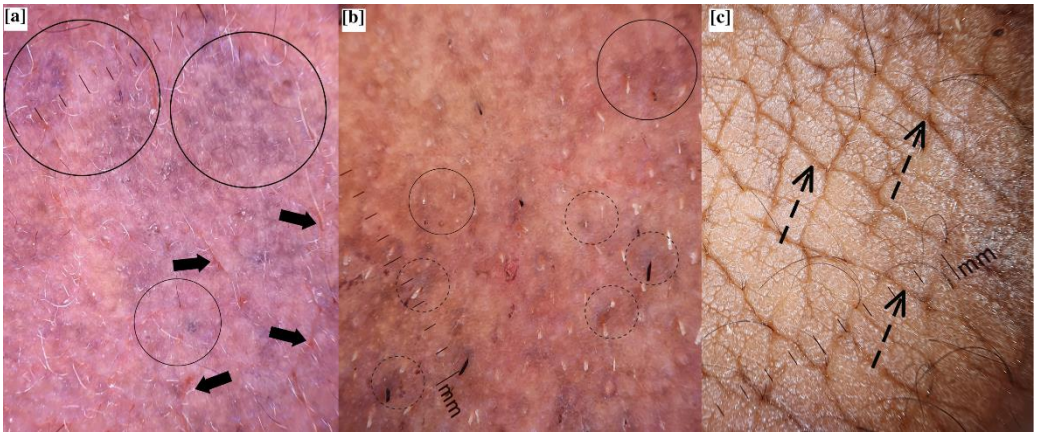

Figure 2: Dermoscopy of the cheeks demonstrated bluish gray areas (black circle) with telangiectasias (black arrow) (a) Dermoscopy of the chin bluish gray areas (black circle) and thickened perifollicular hyperpigmentation (dotted circle) (b) Dermoscopy of the nape revealed markedly depressed sulci (dotted arrow) (c) ((a-c. Dermlite DL2x10)

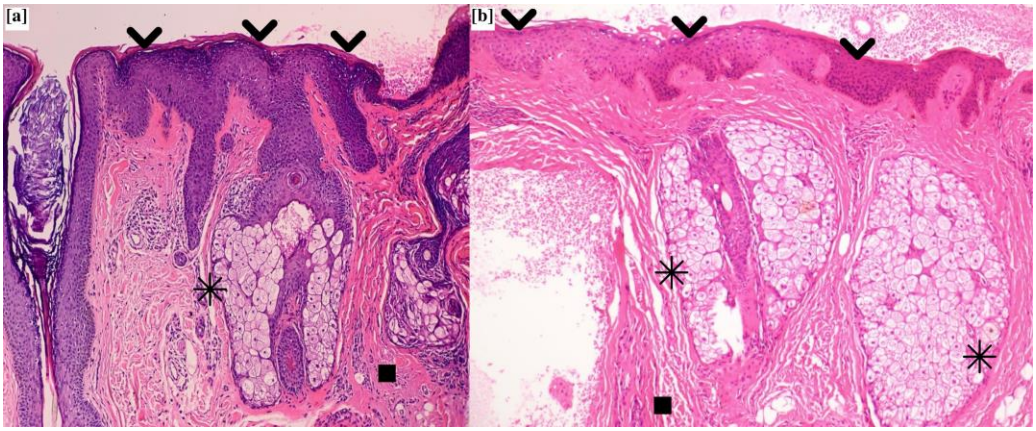

Figure 3: Histological examination of the cheek revealed parakeratosis of the stratum corneum. There is acanthosis of the epidermis, hypergranulosis (arrowheads) and mild spongiosis. The dermis reveals prominent fibrosis (black box) and enlarged sebaceous lobules (asterisk). Fibrosis is also seen in the lower dermis (black box) (a) Another biopsy on the left earlobe revealed mild acanthosis of the epidermis with basal cell layer hyperpigmentation (arrowheads). The dermis reveals fibrosis (black box) and enlarged sebaceous lobules (asterisk). Fibrosis is seen in the lower dermis (black box) (b) (a&b. H&E, 100x). The 2 biopsies are consistent with acanthosis nigricans and phymatous rosacea.

Discussion

Acanthosis nigricans clinically presents as hyperpigmented coarse thickened velvety plaques involving the intertriginous areas and, in our case, the face. Insulin has been demonstrated to cross the dermoepidermal junction and the binding of insulin to insulin-like growth factor 1 receptors stimulates proliferation of keratinocytes and fibroblasts leading to formation of AN. Hyperinsulinemia indirectly causes AN by increasing circulation of free IGF-1 levels. The increase of plasma concentration promotes cell growth and differentiation [4].

A clinico-investigative study of facial AN was done by Shah et al.[5] which investigated forty cases of facial AN and forty cases of healthy non-obese individuals. In their study, their clinic-dermoscopic-histological correlation showed that lighter brown variants of facial AN had follicular plugging and subtle sulci pattern accompanied by irregular brown globules and perifollicular pigmentation on dermoscopy and mild hyperkeratosis and basal cell layer hyperpigmentation with minimal

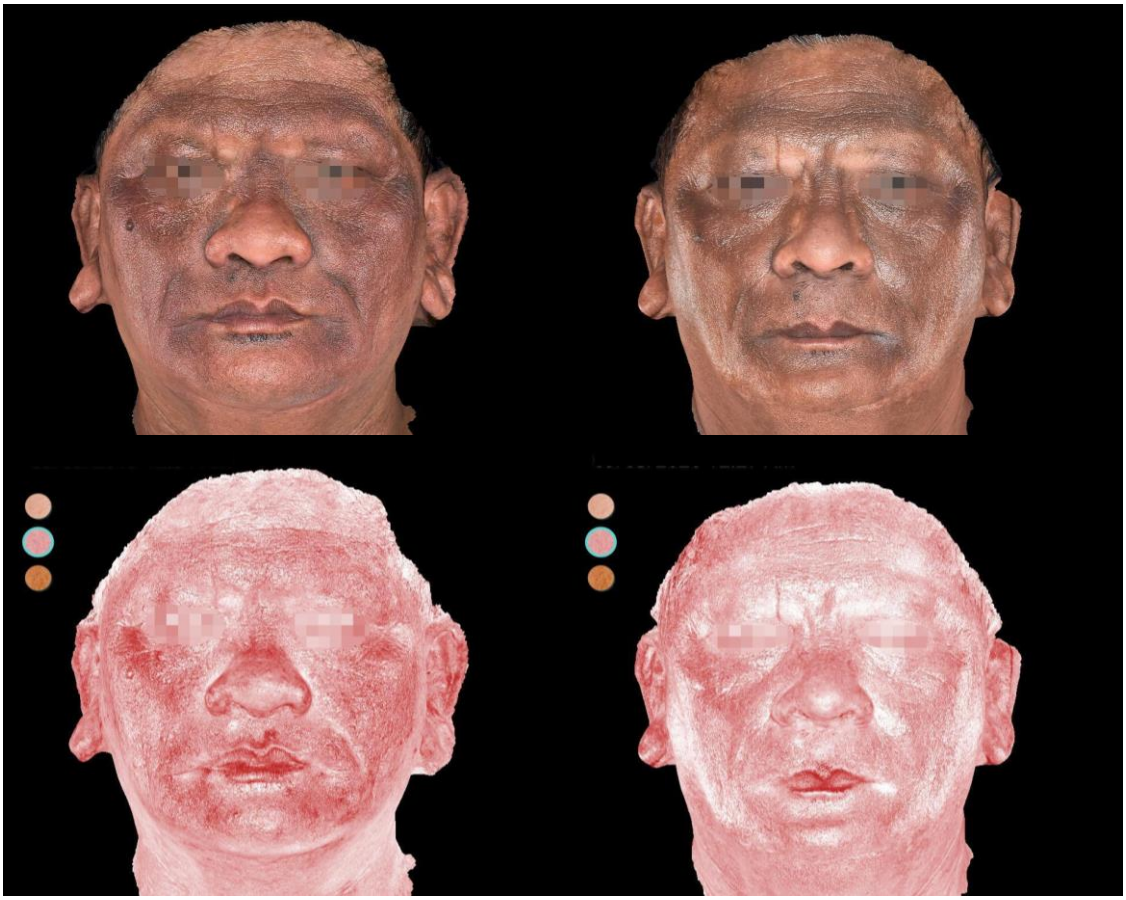

Figure 4: Decreased of phyma, hyperpigmentation and redness after three months of topical and oral medications with every 2 weeks session of pro-yellow laser 577nm.

acanthosis and papillomatosis on histopathology. On the other hand, dark-brown to black facial AN (chronic variants) showed prominent sulci, bigger brown globules, and perifollicular hyperpigmentation on dermoscopy and moderate hyperkeratosis and hypermelanization of the basal layer with moderate to severe acanthosis and papillomatosis on histopathology [5]. Our dermoscopy and histopathology findings of epidermal acanthosis, papillomatosis and hyperekeratosis were similar to the study of Shah et al. and Hermanns et al.7 where they found out that AN occur due to the acanthosis, papillomatosis, and hyperkeratosis of the epidermis. The hyperpigmentation seen in AN may be attributed to the activation of insulin-like growth factor-1 receptors (IGF-1) on the keratinocytes leading to its proliferation resulting to hyperkeratotic plaques clinically appearing as velvety hyperpigmented plaques [6,7].

The strong association between rosacea and metabolic disorder has already been established in previous studies. In a case-control study among 47 age-, gender-, and body mass indexed (BMI)-matched rosacea patients and 50 healthy controls, the rate of insulin resistance was significantly higher in rosacea group versus control suggesting a positive correlation between the two conditions [8]. Aside from this significant positive correlation with insulin resistance, cardiovascular disease risk factors, such as fasting blood glucose, lower density lipoprotein, total cholesterol, triglyceride, and systolic blood pressure and diastolic blood pressure levels, were significantly higher in patients with rosacea compared with the control group. Furthermore, results from a multi-institutional case-control study among systemic comorbidities in Korean

patients, Woo et al.[10] found a strong correlation between rosacea and metabolic syndrome (diabetes melitus, obesity and dyslipidemia). Casas et al.[9] analyzed the skin of rosacea patients and found higher expression of genes encoding pro-inflammatory cytokines (Il-8, Il-1b, TNF-a) and inflammasome-related genes (NALP-3 and CASP-1). In addition to their study, elevated levels of LL-37, VEGF, CD45RO, MPO, and CD163 were also found indicating widespread activation of the immune system [9,10]. Clinical findings in our patient include phyma, transient facial erythema and symptoms of burning, erythema, edema and dryness. Although patient complains of persistent warmth, skin redness cannot be thoroughly evaluated because of his dark skin phototype. While it is evident that the presence of erythema and telangiectasia are difficult to identify in patients with skin of color, having great awareness on other clinical signs such appearance of xerosis, scales, edema, acneiform papules and pustules is essential for the correct diagnosis and management.

Both the pathogenesis of rosacea and diabetes involves systemic inflammatory factors. While the relationship between rosacea and diabetes has not been fully elucidated yet, oxidative stress and systemic inflammation are hypothesized to contribute to the development of rosacea, insulin resistance, and complications associated with diabetes. In a study by Hua et al.[11], systemic inflammation associated with rosacea leads to structural alterations in lipoproteins, resulting in derangement in lipid profile contributing to the metabolic syndrome [11]. In addition to the systemic inflammation caused by rosacea, numerous inflammatory skin conditions have oxidative stress as their underlying cause and has been suggested to be involved in the pathophysiology in rosacea. In a case-control study by Karabay et al.[12], the group were compared with the total antioxidant status (TAC) and total oxidant status (TOC) between healthy controls and patients with rosacea. It was found that patient with rosacea have increase of oxidative stress level which manifested through higher levels of TOC [12]. Paraoxonase-1 (PON1) is an antioxidant enzyme associated with high-density lipoprotein (HDL) and plays a crucial role in the protection against atherosclerosis through serum lipoproteins oxidative modification and lipid peroxides hydrolysis. PON has demonstrated its activity in reducing the risk of metabolic syndrome, atherosclerosis, and diabetes mellitus and was found to be decreased in patients with rosacea [13].

To address the normalization of epithelial growth and differentiation, the patient was prescribed with an oral retinoid such as isotretinoin. A 33-year-old woman who had extensive AN including the axillae, groins, antecubital fossae, dorsa of the hands, angles of the mouth and areas under the breasts was treated with oral isotretinoin in a case report by Katz[14]. In the study, the patient began a regimen of 0.5mg/kg/day and was eventually increased to 1.5mg/kg/day with flattening and lightening of color on the lesions on the neck with other areas unchanged. Three weeks later, the dosage was increased to 3mg/kg/day, with flattening and returning of normal skin color. However, side effects such as severe cheilitis and dose-related elevation of serum triglyceride levels were observed prompting to decrease the dosage to 2mg/kg/day. After 16 weeks, the drug was discontinued with the darkening and thickening of the lesions recurring. The patient was eventually maintained at a dosage of 2mg/kg/day with good clinical response and minimal side effects [14]. In our study, patient was prescribed a low-dose oral isotretinoin due to the concomitant co-morbidities and the surface area involved.

Currently, there is no superior treatment for AN. However, treatment modalities such as topical tretinoin, topical vitamin D analogs, chemical peels and other tyrosinase inhibitors. Chemical peels, oral retinoids and use of 755 nm lasers may provide

benefit in some studies (15). Surgery and ablative laser treatment were recommended for local treatment of phymatous rosacea in the four guidelines/consensus, and isotretinoin was recommended for systemic drug use. The Global Rosacea treatment guidelines and expert require oral doxycycline or isotretinoin in cases of inflammatory type of phymatous rosacea. In severe cases, CO2, Erbium:yag laser or surgical excision and resection may provide therapeutic effects [16].

Conclusion

It can be challenging to describe AN and rosacea in individuals with skin of color. Increase awareness of both entities might aid in the timely diagnosis and effective treatment of this condition. Clinical presentation, dermoscopy and histopathology still remains to be the gold standard in the diagnosis. While cosmetic resolution is recommended for patients with this condition to improve their quality of life, healthcare professionals should first and foremost make an effort to identify and manage any potential underlying conditions, such as metabolic syndrome, diabetes mellitus and cancer.

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