Original Articles

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Evaluation of histopathological changes in idiopathic cutaneous hyperchromia at the orbital region

Avaliação das alterações histopatológicas na hipercromia cutânea idiopática da região orbital

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ABSTRACT

Introduction: Identification of the underlying causes of idiopathic cutaneous hyperchromia at the orbital region (ICHOR) is crucial in selecting the best therapeutic management.

Objective: This study aims to evaluate the histopathological changes of different types of ICHOR.

Methods: Forty-nine healthy volunteers were classified into (i) hyperpigmented (ii) hypervascularised or (iii) tear trough groups. Melanin deposit, hemosiderin deposit, blood vessels dilatation, perifollicular inflammation, structures of epidermis ridges were assessed histologically. Its association with the type of ICHOR was analysed using Pearson's chi-squared test.

Results: A total of 53.1% ICHOR subjects was diagnosed as hyperpigmented, 16.3% as hypervascularised and 30.6% as tear trough and. Pearson's chi-squared test showed that hyperpigmented group associated with high level of melanin deposit ($p<0.05$), and invagination of melanin pigments into the dermal layer ($p<0.05$). Hypervascularity was associated with dilated blood vessel ($p<0.05$). Interestingly, tear trough was associated with dilated blood vessels ($p<0.05$) and perifollicular inflammation ($p<0.05$).

Conclusion: Each type of ICHOR showed distinct histopathological changes, selection of precise targeted therapy is important in treating ICHOR effectively.

Keywords: Hyperpigmentation; Histology; Melanosis

RESUMO

Introdução: *A identificação das causas da hipercromia cutânea idiopática da região orbital (HCIRO) é fundamental para o processo de seleção da melhor conduta terapêutica.*

Objetivo: *O presente estudo tem como objetivo avaliar as alterações histopatológicas de diferentes tipos de HCIRO.*

Métodos: *Quarenta e nove voluntários saudáveis foram classificados em 3 grupos: (i) hiperpigmentação, (ii) hipervascularização e (iii) sulco lacrimal. As deposições de melanina e hemossiderina, a dilatação dos vasos sanguíneos, a inflamação perifolicular e as estruturas das cristas epidérmicas foram analisadas histologicamente; a associação com o tipo de HCIRO foi analisada pelo teste do qui-quadrado de Pearson.*

Resultados: *Um total de 53,1% dos indivíduos portadores de HCIRO foram diagnosticados e classificados em hiperpigmentação, 16,3% como hipervascularização e 30,6% como sulco lacrimal. O teste qui-quadrado de Pearson mostrou que o grupo hiperpigmentação foi associado a um alto nível de depósito de melanina ($p <0,05$) e à presença de pigmentos de melanina na camada dérmica ($p <0,05$). O grupo hipervascularização foi associado a vasos sanguíneos dilatados ($p <0,05$). Curiosamente, o grupo sulco lacrimal foi associado a vasos sanguíneos dilatados ($p <0,05$) e inflamação perifolicular ($p <0,05$).*

Conclusão: *Cada tipo de HCIRO possui alterações histopatológicas distintas e a seleção de terapêutica precisamente direcionada é importante no tratamento eficaz da HCIRO.*

Palavras-chaves: *Hiperpigmentação; Histologia; Melanose*

INTRODUCTION

Idiopathic cutaneous hyperchromia in the orbital region (ICHOR) is an important, yet not clearly defined, cosmetic condition, notoriously resistant to treatment. Idiopathic cutaneous hyperchromia is characterized by by two-sided sullying of the eyelid and the orbital skin, in contrast to the adjacent facial skin, that extends towards the upper eyelids, eyebrows, malar and temporal regions, lateral nasal root. It is also known as periorbital melanosis, periorbital dusky circles, black eye circles, periocular pigmentation, periocular melanosis, infraorbital melanosis, periocular hyperpigmentation, and infraorbital discoloration.[1-4] It may arise as bilateral, rounded or semicircular, pigmented, homogenous, brownish or dark brown macules in the periocular region. In addition, it has been reported that the prevalence of ICHOR in the lower eyelid's skin is relatively higher, and typically bilateral and symmetrical.[1,2,5,6]

There is limited availability of information on the prevalence of ICHOR. It is a common condition that occurs in both genders, most often in women due to endocrine factors. It occurs in young or mature populations. It is also more noticeable in certain ethnic groups, especially people with darker skin.[7] The condition's etiology remains uncertain, however several exogenous and endogenous factors have been implicated in its pathogenesis. Causal factors may be primary, such as genetic factors, excessive hyperpigmentation, shading effect due to skin flaccidity and venous congestion.[8] Idiopathic cutaneous hyperchromia in the orbital region can also occur due to post-inflammatory hyperpigmentation secondary to inflammatory lesions or skin disorders, including dermatitis and infections. The uses of vasodilator drugs, such as prostaglandins, hormone replacement therapy and contraceptives, trigger melanin production and aggravate ICHOR. In addition, exposure to the sun, the aging process, and lifestyle-related factors, such as sleeping disorders, stress, the use of alcohol, and smoking habits, are also common factors in the pathogenesis of ICHOR.[7,9]

Histologically, the severity of the darkening of the eyelids depends on (i) the amount of the melanin deposited on the epidermis and on the dermis, (ii) the thickness of the epidermis and (iii) the presence of vessels or periorbital blood flow. The thin epidermis around the eyes' areas creates a translucent appearance and leaves the structure more prominent and hyperchromic in appearance, which may be due to the deposition of melanin[1] or to the bluish hue of the veins.[2] In addition, inflammation or vasodilation / stagnant flow in the periorbital area may contribute to the darkening effect.[3]

Based on the clinical appearance, the authors of the present study proposed to classify ICHOR into: (i) *constitutional / pigmentation*, (ii) *shading effect / structural*, (iii) *postinflammatory hyperpigmentation* (PIH), (iv) *vascular*, and (v) *others*.[2,3,10,11] Hyperpigmentation type of ICHOR is defined as the presence of a brownish to black curve pigmentation band in the lower eyelids' and / or upper eyelids' skin. Hypervascular type ICHOR is characterized by the presence of erythema, predominantly in the lower eyelids, with prominent capillaries or the presence of bluish discoloration that becomes more prominent when the skin is stretched. Tear trough or shading effect ICHOR type is characterized by the presence of a dark shading corresponding to the tarsal muscle, located above the palpebral fat pads, or by the presence of a deep tear trough in the medial region of the lower orbital rim that disappear with the incidence of direct light.[2,4-6] In addition to the classification based on clinical evaluation, the identification of histological alterations caused by ICHOR is crucial for the recognition of its primary etiology, ultimately aiming at defining an effective therapeutic approach. Several limited histological studies have suggested that ICHOR is mainly characterized by epidermal and dermal hyperpigmentation,[10,12] dilated blood vessels,[13] with or without the presence of hemosiderin.[14] Graziosi *et al.* (2013) attempted to associate the severity of the darkening effect with the histological findings and concluded that the abundance of melanin and dilation of the blood vessels in the dermal layer were positively related to the ICHOR's severity.[14] However, the authors of the present article are not aware of the publication of studies on the association of ICHOR types with their respective histological changes.

There are a number of treatment options available for ICHOR, including the application of whitening agents, chemical peels, lasers, autologous fat transplantation, injection of cutaneous fillers or platelet rich plasma, as well as blepharoplasty. Despite the great number of drugs and therapies available, evidence-based studies that support the selection of treatments are scarce, in addition to the fact that the therapeutic results are often inconsistent and unsatisfactory. The authors of the present study believe that key to a successful treatment is determining the primary cause and adhere to pre-emptive and maintenance schemes. Therefore, the present study is aimed at evaluating the histological alterations underlying the different variants of ICHOR, namely the hyperpigmentation, hypervascularization and shading effect / tear trough. Although histological evaluation is less useful in recognizing tear trough, the present study intends to explore its possible histological alterations.

METHODS

Ethical compliance and free and informed consent

Previous authorization of the Research and Medical Ethics Committee (NMRR-13-1267-16770) was obtained. The free and informed written consent of all individuals were obtained after the patient had read and understood the information and instructions regarding the study that were especially prepared for the respondents.

Study design, patient recruitment and clinical evaluation

Healthy individuals were selected for blepharoplasty and randomly invited to participate in the study. Individuals diagnosed with Ota nevus, melanocytic nevus, café-au-lait macules, Hori nevus, ephelides, localized post-inflammatory hyperpigmentation related to an identifiable trauma, inflammatory diseases / skin ulceration, allergies / asthma, hyperpigmentation associated with systemic diseases (Addison disease) were excluded from the study. Based on the clinical evaluation, ICHOR was further classified into three main categories: (i) *hyperpigmentation*,

(ii) *hypervascularization*, and (iii) *tear trough*. The clinical evaluation and a case report form were completed by plastic surgeons prior to blepharoplasty. Immediately after blepharoplasty, a portion of the medial lower left eyelid was excised and maintained in 10% formalin solution for histological analysis.[14]

Histological analysis

Paraffin-embedded skin tissues were processed with the Fontana-Masson stain for evidence of melanin deposits and the distribution pattern on the eyelid specimens. The deposition of melanin in the basal layer of the epidermis was classified as: Level 1 = low, Level 2 = moderate, and Level 3 = high. The depth of melanin distribution (i.e. up until the papillary dermis or up until the reticular dermis) was also analyzed. Pearl's staining was used to observe the presence of hemosiderin. The epidermal crests were described as normal, slightly flat, from moderately to intensely flat. The vasodilatation degree of blood vessels in the dermis was classified as Level 1, Level 2 or Level 3. The perifollicular inflammation was described as Level 1, Level 2 or Level 3 (Table 1).

Statistical analysis

Statistical analysis was performed using the statistical software SPSS 18.0 (SPSS Inc., Chicago IL, USA). Categorical data, including demographic data, Fitzpatrick phototypes classification, ICHOR classification, and pathological parameters were expressed in frequencies and percentages. The associations between clinical and histological data were analyzed using the Pearson's qui-squared test.

RESULTS

A. Demographic data

Forty-nine patients (men = 20.4%, n = 10 / women = 79.6%, n = 39) with a mean age of 52.9 ± 9.2 years met the inclusion criteria and agreed to participate in the study. A total of 67.3% of the respondents were classified as Grade III according to the Fitzpatrick scale, while 22.3% were classified as Grade IV, 8% as Grade I and 2% as Grade V. A total of 85.7% of respondents ignored the factors that triggered their ICHOR, with 55.1% having reported that noticed their dark circles for the first time in adulthood. Up to 85.7% of the respondents stated that their ICHOR was not associated with family history (Table 2).

All of the recruited cases of ICHOR presented homogeneous and symmetric bilateral hyperchromia, with the present study presuming that the histological findings related to the excised medial portion of the biopsies represent the general ICHOR pattern. The most commonly observed ICHOR was of the hyperpigmentation type (53.1%), followed by the tear trough (30.6%) and hypervascularization (16.3%) types (Table 2). The Pearson's qui-squared test showed that the ICHOR score was not associated with Fitzpatrick's scales ($\chi^2 = 3.08$, $p = 0.798$), gender ($\chi^2 = 2.25$, $p = 0.324$), and age ($\chi^2 = 54.002$, $p = 0.256$).

B. Association of histological data to types of ICHOR (Table 3)

- The deposition of melanin in the basal layer of the epidermis was significantly associated with the type of ICHOR ($p < 0.001$). Of the 26 hyperpigmentation cases, 14 cases (54%) were classified with Level 3 melanin deposition.
- Dilation of blood vessels was significantly associated with the type of ICHOR ($p < 0.01$). Of the 8 cases of hypervascularization, 4 (50%) had highly dilated blood vessels; of the 15 tear trough cases, 10 (67%) were associated with highly dilated blood vessels.
- The depth of the melanin distribution was significantly associated with the type of ICHOR ($p < 0.01$). Melanin deposits were found in the reticular dermis in 15 (58%) of the 26 cases of hyperpigmentation type.
- Peripheral inflammation was associated with the type of ICHOR ($p < 0.05$). The hypervascularization and tear trough types had the highest intensity of perifollicular inflammation, with 16.3% of cases of the hypervascularization type, 30.6% of the tear trough type and 53.1% of the hyperpigmentation type.

Table 1: Definitions of Histological Classification Grades

Histological parameters	Level	Grade definition
Basal layer melanin deposit	Level 1	Melanin pigment found only in <1 of every 5 basal cells
	Level 2	Melanin pigment found only in > 1 of every 5 basal cells
	Level 3	Melanin pigment easily found in all basal cells
Epidermal crests	Normal	No evidence of atrophy, normal thickness of the epidermis > 0.3 mm
	Slightly flat	Evidence of mild atrophy, thickness of the epidermis between 0,3mm - 0,2mm
	Moderately to intensely flat	Evidence of atrophy, thickness of the epidermis < 0.2mm
Blood vessels dilation	Level 1	Dilated vessels visible under 40x magnification
	Level 2	Dilated vessels visible under 10x magnification
	Level 3	Dilated vessels easily visible under 4x magnification
Perifollicular inflammation	Level 1	Melanin perifollicular lymphocytes found under 40x magnification
	Level 2	Melanin perifollicular lymphocytes found under 10x magnification
	Level 3	Melanin perifollicular lymphocytes easily found under 4x magnification

Table 2: Clinical characteristics

Characteristics	N°. (%), N=49
Men	10 (20.4)
Women	39 (79.6)
Age	
Mean (SD)	52,9 (9.2)
Median (IQR)	55 (44.5,58)
Age of onset	
Childhood, <12 years old	3 (6.1)
Puberty, 12-18 years old	3 (6.1)
Adulthood, > 18 years	27 (55.1)
Indefinite	16 (32.7)
Skin type	
II	4 (8.2)
III	33 (67.3)
IV	11 (22.4)
V	1 (2.1)
Family history of ICHOR	
Yes	42 (85.7)
No	7 (14.3)
Knowledge of the triggers of ICHOR	
Yes	7 (14.3)
No	42 (85.7)
Types of ICHOR	
Hyperpigmentation	26 (53.1)
Hypervascularization	8 (16.3)
Tear trough	15 (30.6)
IQR: Interquartile range	

• The presence of hemosiderin and the pattern of epidermal crests were not associated with any type of ICHOR (Table 3).

DISCUSSION

In the present study, ICHOR types were classified into three main categories: hyperpigmentation, hypervascularization, and tear trough. The causes of ICHOR may be multifactorial (e.g. hyperpigmentation combined with hypervascularization). Nevertheless, the study's interviewees were grouped into a specific category based on the more prominent clinical appearance. The majority of ICHOR cases found in the present study were of the hyperpigmentation type (53.1%), followed by the tear trough (30.6%) and hypervascularization (16.3%) types. According to the findings of Sheath *et al.* (2014), among 200 indian individuals with Fitzpatrick skin type I to IV, the most common type of ICHOR was hyperpigmentation / constitutional (51.5%), followed by postinflammatory hyperpigmentation (22.50%), hypervascularization (8%) and shading effect / tear trough (2.5%).[7] In contrast, Ranu *et al.* (2011) reported that the most common type of ICHOR among Singaporeans is the hypervascularization (41.8%), followed by constitutional hyperpigmentation (38.6%), postinflammatory hyperpigmentation (12%) and shading effect / tear trough (11.4%). In Asian patients, the hypervascularization type was found in a large number of Chinese patients (those with the lower Fitzpatrick skin types), whereas the constitutional hyperpigmentation type was more prevalent in Indian and Malaysian patients (among those with higher Fitzpatrick's skin types).[3] Two separate studies –conducted in Taiwan and South America – reported that the most common type of ICHOR was of a mixed type, predominantly the combinations hypervascularization-hyperpigmentation.[11,15]

Previous studies have reported that ICHOR with predominantly vascular etiology was linked to dominant autosomal inheritance, usually arising during childhood or adolescence.[1] On the other hand, ICHOR with predominantly melanic etiology occurs more frequently in higher phototypes and elderly patients due to excessive and cumulative exposure to sunlight. The occurrence of the constitutional hyperpigmentation type is commonly linked to the age of the patient, due to the process of skin aging, which leads to palpebral flaccidity, which in turn worsens the appearance of the dark circles.[1,16] However, the data analysis performed in the present study (Pearson's qui-squared test) suggests that the ICHOR types were not associated with the Fitzpatrick's scale ($\chi^2 = 3.08$, $p = 0.798$) and to the patient's age ($\chi^2 = 54$, $p = 0.256$), with the inconsistency possibly caused by the small sample size.

It has been suggested that the ICHOR's severity is positively correlated with the abundance of melanin and the dilatation of blood vessels in the dermal layer,[14] and that the melanin abundance is greater in the hyperpigmentation variant when compared to the hypervascularization and constitutional hyperpigmentation types.[3] The present study concludes that: (i) the hyperpigmentation type of ICHOR was positively associated with deposition of melanin in the epidermal and dermal layers, (ii) the hypervascularization type was positively associated with dilated blood vessels, and (iii) the constitutional hyperpigmentation type was associated with dilated blood vessels and the severity of the perifollicular inflammation. In contrast, the presence of hemosiderin and the structure of the epidermal crest were not associated with any type of ICHOR.

The determination of the histological changes induced by ICHOR are important for the verification of the clinical evaluation's precision and, consequently, for an accurate recommendation of a personalized treatment modality. The melanin associated with ICHOR may possibly respond to depigmenting agents, chemical peels, laser therapy (IPL, lasers for pigmentation, fractional lasers). Yet, according to the findings of the present study, increasing evidence has shown that pigmentation around the eyelids is not restricted to the epidermal layer and also profoundly affects the dermal layer, in addition to being resistant to treatments.[2,3,11,14] The melanin that enters the reticular dermis is normally phagocytized by macrophages to form melanophages,

Table 3: Summary of histological data and associations with ICHOR types

Parameter	Hyperpigmentation	Hypervascularization	Tear trough	Total (N)	Pearson's chi-squared test
Melanin deposit					
Level 1	1	4	6	11	x^2=21.766
Level 2	11	4	9	24	P=0.000
Level 3	14	0	0	14	
Total (n)	26	8	15	49	
Hemosiderin					
Positive	0	1	0	1	X^2=5.232
Negative	26	8	15	49	P=0.073
Total (n)	26	8	15	49	
Dilation of blood vessels					
Level 1	8	1	0	9	X^2=8.633
Level 2	11	3	5	19	P=0.003
Level 3	7	4	10	21	
Total (n)	26	8	15	49	
Depth of melanin distribution					
Papillary	11	8	11	30	X^2=9.912
Reticular	15	0	4	19	P=0.007
Total (n)	26	8	15	49	
Epidermal crests					
Normal	19	6	11	36	X^2=0.647
Slightly flat	6	2	3	11	P=0.958
Moderately flat	1	0	1	2	
Total (n)	26	8	15	49	
Perifollicular inflammation					
Light	18	3	2	23	X^2=12.955
Moderate	2	2	3	7	P=0.011
Severe	6	3	10	19	
Total (n)	26	8	15	49	

which give rise to the bluish appearance. In addition, damage to the basal membrane can lead to a decrease or migration of active melanocytes and melanin to the dermis, which ultimately lead to persistent dermal hyperpigmentation.[19,20] The high melanin content found in the dermal layer by the present study is improbable due to basal membrane damage, since the epidermal crests of 74% of the biopsies were normal. Dermal hyperpigmentation has a weaker response to common depigmenting agents partly due to the fact that most depigmenting therapies are focused on epidermal hyperpigmentation and are not effective in eliminating dermal melanophages. The present study suggests that the incorporation of topical depigmenting agents via transdermal drug delivery may be beneficial in reducing dermal hyperpigmentation.

Ranu *et al*. (2011) have suggested that depigmenting agents are ineffective in the treatment of the hypervascularization type of ICHOR.[3] They suggested that topical agents that could enhance dermal thickness, vasoconstrictors, or vascular lasers might be more effective in treating the vascular type of ICHOR. On the other hand, creams containing steroids can worsen the condition.[3] In a Japanese study, Mistsuishi *et al*. (2004) demonstrated that topical application of 2% fitonadione, 0.1% retinol, 0.1% vitamin C, and 0.1% vitamin E was effective in cases of hypervascularization type of ICHOR – but not in cases of the hyperpigmentation type.[21]

Unexpectedly, despite all cases of ICHOR linked to postinflammatory hyperpigmentation were excluded from this study, up to 67% (10 out of 15 biopsies) of constitutional hyperpigmentation cases had severe perifollicular inflammation, in addition to a high degree of dilation of the blood vessels (Table 3). The tear trough type is frequently associated with facial structural deformity, with several studies proposing that blood stasis

/ venous congestion may contribute to the appearance of the tear trough / shading effect type.[22] Inflammatory mediators (i.e. prostaglandins E1, prostaglandins E2, and histamine) are known to increase melanogenesis by triggering melanocyte proliferation and melanin production, thereby making the hyperchromic appearance of the tear trough type worse.[23] However, further studies are fundamentally needed in order to identify the causes of inflammatory reactions and their consequences in cases of tear trough type. Since the tear trough is closely related to perifollicular inflammation and dilated vessels, the authors of the present study suggest that the combination of the existing therapies with anti-inflammatory vasoconstricting agents may be useful in the treatment of these cases.

The present study therefore concludes that the hyperpigmentation type of ICHOR is closely associated with melanin deposition in the epidermis and dermis, whereas the hypervascularization type may be caused by dilated blood vessels, while the constitutional hyperpigmentation type is associated with dilated blood vessels and melanin perifollicular lymphocyte infiltration. In summary, each type of ICHOR presented diverse histological changes, and the selection of a targeted therapy is crucial for the effective treatment of ICHOR. ●

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