Original article

CED
Clinical and Experimental Dermatology

The clinicoaetiological, hormonal and histopathological characteristics of melasma in men

S. Handa,[1] D. De,[1] G. Khullar,[1] B. D. Radotra[2] and N. Sachdeva[3]

Departments of [1]Dermatology, Venereology and Leprology, [2]Histopathology, and [3]Endocrinology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

doi:10.1111/ced.13234

Summary

Background. Melasma is relatively uncommon in males, and there is a paucity of data on male melasma, including its clinical pattern, triggering factors, endocrine profile and histopathological findings.

Aim. To characterize the clinical findings and aetiological factors, including hormonal and histopathological features, of male melasma.

Methods. Male patients with melasma and age- and sex-matched healthy controls (HCs) were recruited. Demographic profile, risk factors, clinical pattern and Wood lamp findings of patients were recorded. Sera were obtained from patients and HCs to determine hormone levels. Biopsy specimens were obtained from lesional and adjacent nonlesional skin.

Results. In total, 50 male patients with melasma and 20 HCs were recruited into the study. Mean age of patients was 27.58 ± 4.51 years. The most common clinical pattern of melasma was malar, which occurred in 52% of cases. Positive family history was present in 16% of patients, while 34% had disease aggravation with sun exposure and 62% used mustard oil for hair growth and/or as an emollient. Wood lamp examination revealed epidermal-type melasma in 54% of patients. There were no significant differences in hormone levels between patients and HCs. Histologically, epidermal melanin, elastotic degeneration, vascular proliferation and mast cells were more pronounced in lesional compared with nonlesional skin. Absent to weak expression of oestrogen receptors, progesterone receptors and stem cell factor was observed in lesional skin.

Conclusion. Ultraviolet light and mustard oil are important causative factors in male melasma. Although stress and family history may contribute, hormonal factors possibly have no role. Quantitative analysis of immunohistochemical markers would provide insight in understanding the pathogenesis of melasma.

Introduction

Melasma is an acquired disorder of hypermelanosis, with a female predilection. In studies on melasma in men by Sarkar *et al.*, male patients constituted 20.5–25.83% cases,[1,2] while Pichardo *et al.* reported a prevalence rate of 14.5% in male Latino migrant workers.[3] The aetiopathogenesis of melasma includes genetic, environmental, hormonal and vascular factors. There is a paucity of data on the clinical, aetiological, endocrinological and histopathological aspects of melasma in men.[1–4] This study aimed to assess the clinical features, risk factors, hormonal profile and histopathological findings of male melasma in India.

Correspondence: Dr Sanjeev Handa, Department of Dermatology, Venereology, and Leprology, Postgraduate Institute of Medical Education and Research, Chandigarh, 160012, India
E-mail: handa_sanjeev@yahoo.com

Conflict of interest: the authors declare that they have no conflicts of interest.

Accepted for publication 25 March 2017

Methods

The study was approved by the ethics committee of the Postgraduate Institute of Medical Education and

Research, and conducted in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent.

Participants

In total, 50 consecutive male patients with melasma and 20 age- and sex-matched healthy controls (HCs) were enrolled into the study. Complete medical history including age, disease duration, risk factors such as duration of sun exposure, family history, stress, use of drugs, hormonal therapy, mustard oil or cosmetics, and Melasma Quality of Life (MELASQoL) score were recorded. Physical examination included Fitzpatrick skin phototype, clinical pattern of melasma, Wood lamp determination of the type of melasma and Melasma Area and Severity Index (MASI). A venous blood sample (5 mL) was collected from each participant for hormonal evaluation [thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), oestradiol, total testosterone, de-hydroepiandrostenone sulphate (DHEA-S), 17-hydroxy progesterone (17-OHP), α-melanocyte stimulating hormone (MSH)] and ferritin levels. Two skin biopsy specimens, one from lesional and the other from adjacent (within 10 mm) nonlesional skin, were obtained from each patient for histology and immunohistochemistry. Slides were evaluated by a dermatopathologist and findings graded on a semiquantitative scale of 0 to 3+ (0 = no staining; 1+ = weak/faint staining; 2+ = moderate staining and 3+ = diffuse staining).

Statistical analysis

Student *t*-test with SPSS software (SPSS v11.0; SPSS Inc, Chicago, IL, USA) was used to determine statistical significance. All *P*-values were two-tailed, and $P < 0.05$ was considered statistically significant. Data were expressed as mean ± standard deviation.

Results

Clinical profile and aetiological factors

Mean age of the patients was 27.58 ± 4.51 years (range 20–42 years). Fitzpatrick skin type V was present in 7 patients (14%), type IV in 33 (66%), type III in 9 (18%), and type II in 1 (2%). Disease duration ranged from 1 week to 10 years (mean 3.25 years). Eight patients (16%) had a family history of melasma. The most common clinical pattern of melasma was malar ($n = 26$; 52%), followed by centrofacial ($n = 23$; 46%) and mandibular ($n = 1$; 2%). Mean duration of sun exposure was 3.25 ± 1.92 h/day, and 17 patients (34%) reported aggravation of their melasma with sunlight. For the other risk factors, 31 patients (62%) gave a history of use of mustard oil on face and scalp hair and 10 (20%) gave a history of cosmetics use. Stress was identified as an aggravating factor in 14 patients (28%). None of the patients used hormonal therapy or other drugs known to produce melasma. Wood lamp examination identified epidermal melasma in 27 patients (54%), mixed type in 22 (44%) and dermal type in 1 (2%). Mean MASI was 7.55 ± 5.19 (range 1.2–21) and mean MELASQoL score was 30.3 ± 17.46 (range 10–70).

Hormonal evaluation

Serum samples were available for testing for 47 patients and 20 HCs. Hormone levels (mean ± SD) in patients and HCs are shown in Table 1.

Histopathological findings

Lesional and nonlesional skin biopsy specimens were evaluated for 44 patients. Fontana–Masson stain showed that in the lesional epidermis there was a normal amount of melanin in 3 patients (6.8%), while scores of 1+, 2+ and 3+ were given to 23 (52.3%), 16 (36.4%) and 1 (2.3%) respectively. In the nonlesional epidermis, the amount of melanin was normal in 10 cases (22.7%), while scores of 1+ and 2+ were given to 29 (65.9%) and 4 (9.1%) patients respectively, and no patient had a score of 3+. Positivity for c-Kit in melanocytes in lesional skin was graded as 1+ in 12 patients (27.3%), 2+ in 26 (59.1%) and 3+ in 6 (13.6%), while

Table 1 Hormonal profile in patients and HCs.

Hormone	Patients	HCs	*P*
Ferritin, ng/mL	122.59 ± 85.28	108.05 ± 73.55	0.51
TSH, μIU/mL	4.48 ± 14.3	2.77 ± 1.62	0.60
LH, mIU/mL	4.63 ± 1.82	5.28 ± 1.81	0.19
FSH, mIU/mL	4.52 ± 2.72	7.15 ± 10.56	0.28
Testosterone, nmol/L	15.58 ± 4.97	13.09 ± 5.48	0.07
Oestradiol, pg/mL	55.84 ± 17.61	49.43 ± 11.96	0.09
DHEA-S, μg/dL	279.15 ± 131.42	220. 92 ± 138.3	0.10
17-α-OH prog, ng/mL	2.29 ± 1.03	1.77 ± 0.93	0.06
α-MSH, ng/mL	2.29 ± 1.37	2.57 ± 1.10	0.42

17-α-OH prog, 17-α-hydroxy progesterone; DHEA-S, dehydroepiandrostenone sulphate; FSH, follicle-stimulating hormone; HC, healthy control; LH, luteinizing hormone; MSH, melanocyte-stimulating hormone; TSH, thyroid-stimulating hormone.

in non-lesional skin, it was 1+ in 22 patients (50%), 2+ in 20 (45.5%) and 3+ in 2 patients (4.5%) (Fig. 1). In the lesional skin, elastotic degeneration was graded as 1+ in 21 patients (47.7%), 2+ in 22 (50%) and 3+ in 1 (2.3%), whereas in nonlesional skin, elastotic degeneration was graded as absent in 4 cases (9.1%), 1+ in 36 (81.8%) and 2+ in 4 (9.1%) (Fig. 2). Toluidine blue stain for mast cells in the lesional dermis revealed positivity graded as 1+ in 28 cases (63.6%) and 2+ in 16 (36.4%) while in nonlesional dermis, staining was graded as none in 2 cases (4.5%), 1+ in 35 (79.5%) and 2+ in 6 (13.6%). Expression of c-Kit in mast cells in lesional skin showed 1+ positivity in 18 cases (40.9%), 2+ in 22 (50%) and 3+ in 4 (9.1%), while in nonlesional skin, there was 1+ positivity in 24 cases (54.5%), 2+ in 19 (43.2%) and 3+ in 1 (2.3%) (Fig. 3). Nuclear staining of oestrogen receptor (ER) and progesterone receptor (PR) was absent or very weak in both lesional and nonlesional skin. ER expression was graded as absent in 37 cases (84.1%), 1+ in 5 (11.4%) and 2+ in 2 (4.5%) in lesional skin, while in nonlesional skin it was absent in 35 (79.5%) and 1+ in 9 (20.5%). Immunoreactivity of PR in lesional skin was graded as absent in 38 (86.4%) and 1+ in 6 (13.6%), and in nonlesional skin, it was graded as absent in 37 cases (84.1%), 1+ in 4 (9.1%) and 2+ in 3 (6.8%). The endothelial cell marker CD31 in lesional dermis demonstrated 1+ positivity in 31 patients (70.5%) and 2+ in 13 (29.5%), while in nonlesional dermis it was normal in 7 cases (15.9%), 1+ in 36 (81.8%) and 2+ in 1

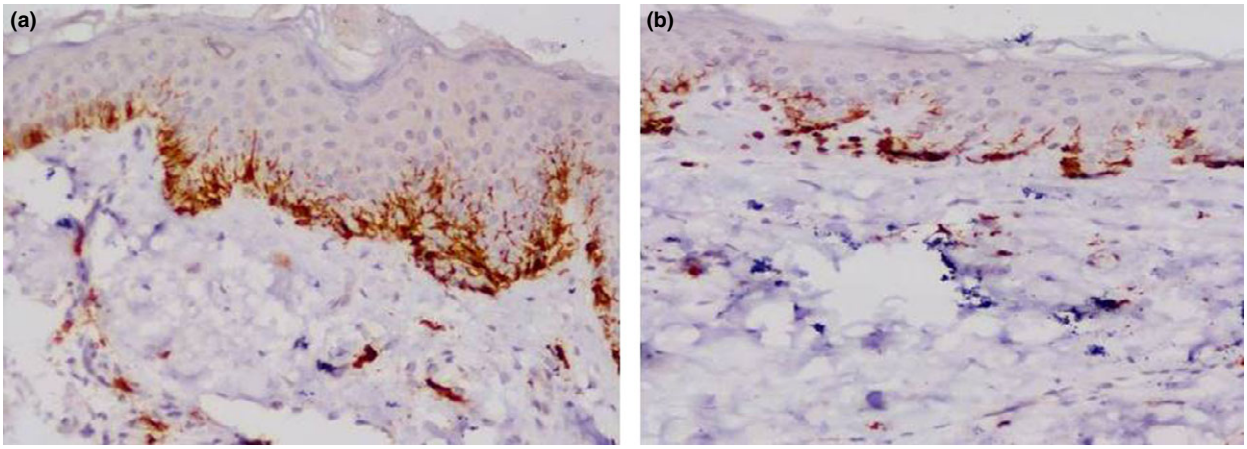

Figure 1 (a) Lesional skin demonstrating increased melanocyte dendritic processes and their dispersion in the epidermis; (b) melanocyte dendritic processes and their dispersion in the epidermis are less prominent in nonlesional skin. c-Kit, original magnification (a,b) × 200.

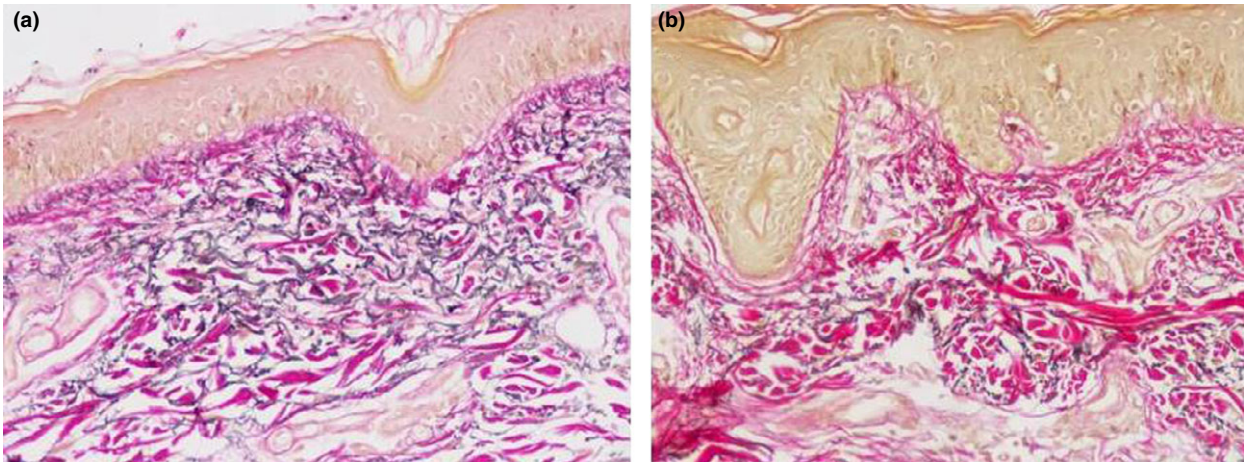

Figure 2 (a) Lesional skin showing moderate degree of elastotic degeneration; (b) no elastotic degeneration in nonlesional skin. (VVG), original magnification (a,b) × 200.

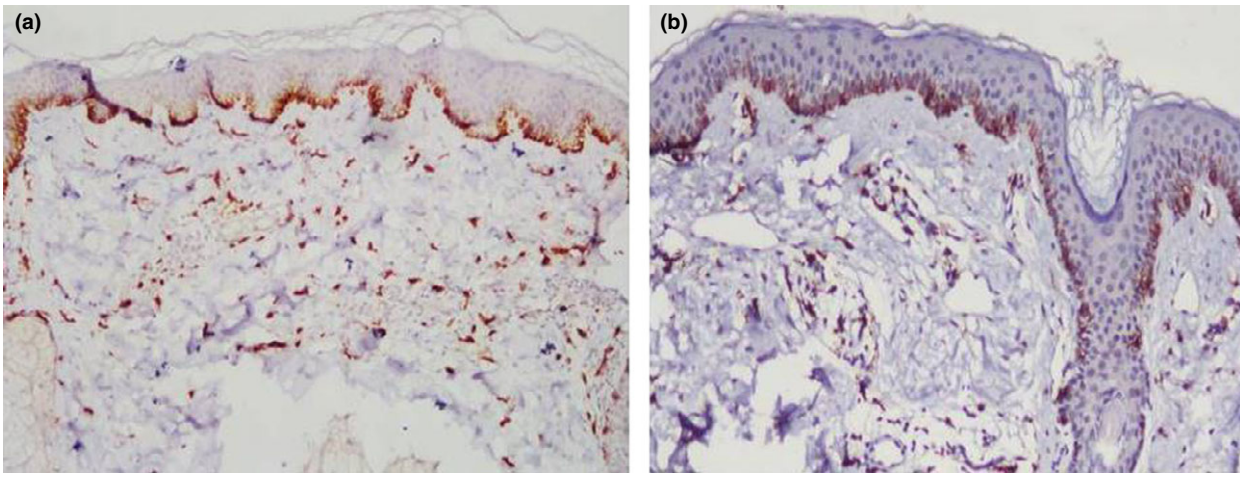

Figure 3 (a) Grade 2 positivity of c-Kit representing mast cells in the lesional skin; (b) grade 1 positivity of c-Kit in nonlesional skin. c-Kit, original magnification (a,b) × 200.

(2.3%) (Fig. 4). No or only faint positivity of stem cell factor (SCF) was observed in both lesional and nonlesional skin.

Discussion

As melasma is less prevalent in men than women, there are limited studies on its clinical features, aetiopathogenesis and histopathological characteristics in male patients.[1–4] The mean age of the patients in our study was 27.6 years and the mean disease duration was 3.25 years. This is in contrast to the study by Vazquez *et al.*, who reported a higher mean age of 38.8 years and longer mean duration of 8 years.[4]

Family history of melasma was present in 16% of our patients, in contrast to higher rates reported in other studies (39% and 70.4% respectively).[2,4]

Among the clinical patterns, the malar type was the most common in our patients, followed by centrofacial and mandibular, similar to that reported by Sarkar *et al.*[2] Anecdotal cases of extrafacial melasma on forearms and neck in men have been reported.[5] In the present study, Wood lamp examination revealed epidermal melasma to be the most common, followed by the mixed and dermal types. This is in concordance with the trend reported by Sarkar *et al.*,[2] whereas Vazquez *et al.* described the dermal type as more common than mixed melasma.[4]

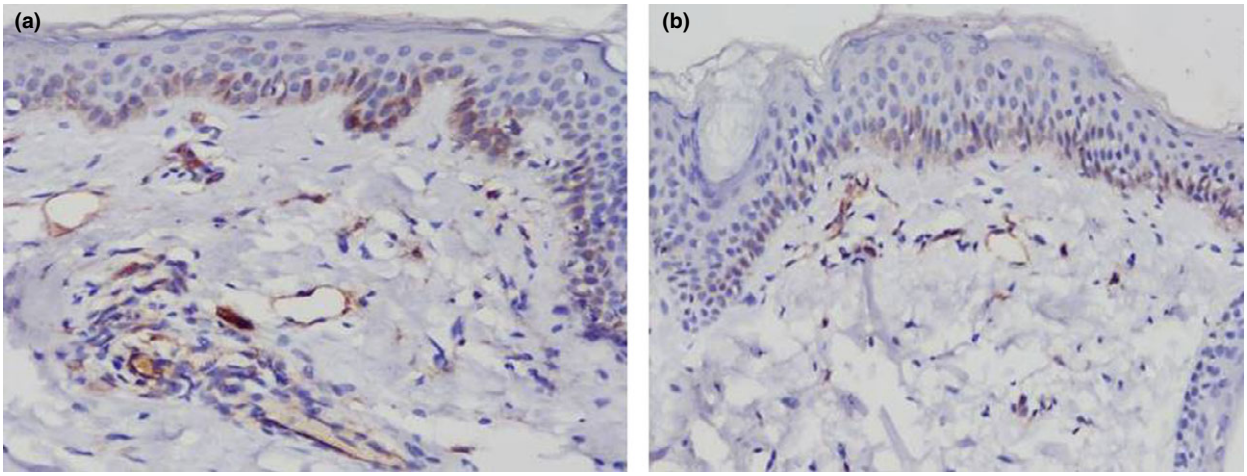

Figure 4 (a) Moderate increase in vascularity in lesional skin; (b) normal vascularity in nonlesional skin (CD31, original magnification (a,b) × 200.

We found sun exposure to be an aggravating factor in 34% of cases, which was lower than that reported by Sarkar *et al.* (48.8%)[2] and Vazquez *et al.* (66.6%).[4] Sun exposure as an exacerbating factor was more prevalent in males (48.8%) compared with females (23.9%) in a previous Indian study.[2] Ultraviolet radiation (UVR) stimulates melanocyte migration and proliferation through cytokines such as α-MSH, endothelin-1, interleukin-1 and adrenocorticotropic hormone.

Mustard oil use was noted in 62% patients in the present study and in 43.9% by Sarkar *et al.*[2] Mustard oil is used by people in northern India for hair growth and as an emollient. As it is a photosensitizer, its use on the face and hair is possibly important in causing melasma in Indian men. Although cosmetics were used by 20% of the men, they were not found to play a role in hyperpigmentation. Stress was identified as a triggering factor in 28% of cases.

The role of hormonal factors in the pathogenesis of melasma is not clearly defined. Pregnancy and oral contraceptive use have been linked with the onset or aggravation of melasma in females. Maeda *et al.* observed that melanocytes from normal skin increase in size and produce more tyrosinase after incubation with α- MSH, FSH, LH and ACTH, whereas oestradiol, oestriol and progesterone lead to cell proliferation to a lesser extent but do not increase tyrosinase activity.[6] In the present study, we did not observe any significant difference in circulating hormone levels between patients and HCs. However, a subtle level of testicular resistance has been implicated in the pathogenesis of male melasma. High LH and low testosterone levels were noted in 9.7% of patients by Sarkar *et al.*[2] Similar results were also reported in another Indian study.[7] However, these findings need to be substantiated in studies with larger sample sizes.

A knowledge of the expression of various immunohistochemical markers in melasma is essential for understanding its pathogenesis. However, the histopathological features in male melasma are not well-characterized. We observed a moderate degree of solar elastosis in lesional skin compared with mild elastosis in nonlesional skin. Melanin content in the epidermal layers of lesional skin was more pronounced than in nonlesional skin. These findings are similar to those reported by Jang *et al.* in men with melasma.[8] Increased solar elastosis suggests that chronic sun exposure is essential for development of melasma in males. This is associated with activation of fibroblasts that may stimulate the melanocytes in the overlying epidermis. In another study on male patients, epidermal melasma with melanin pigment in the suprabasal and basal layers was observed in 50% of cases, mixed type with epidermal melanin and melanophages in 45%, and only melanophages and dendritic melanocytes in the dermis in 5%.[2] Other features included solar elastosis in 85% of cases, flattening of rete ridges in 45% and chronic inflammatory infiltrate in 30%.[2] In the present study, we found moderately increased mast cells and vascularity in the lesional dermis compared with a slight increase in the nonlesional dermis. Increased vessel area in lesional versus nonlesional skin has also been described by Jang *et al.*,[8] and it has been suggested that increased vascularity in melasma may be attributable to long-standing exposure to UVR. Both lesional and nonlesional skin demonstrated absent to weak immunoreactivity of SCF in our study. However c-Kit positivity was higher in lesional compared with nonlesional epidermis. Jang *et al.* described significantly increased expression of SCF and c-Kit in lesional compared with nonlesional epidermis in male melasma,[8] and in the dermis, SCF expression was significantly increased around the fibroblasts.[8] SCF is produced by keratinocytes and fibroblasts in response to UVR, and acts on c-Kit receptors on melanocytes, thereby causing hyperpigmentation.

Oestrogen has been implicated in the pathogenesis of melasma in females. *In vitro* studies have shown that oestradiol upregulates the transcription of tyrosinase and, tyrosinase-related proteins 1 and 2 in human melanocytes.[9] However, the role of progesterone in producing cutaneous hyperpigmentation is unclear. In a study investigating ER and PR expression in female patients with melasma, epidermis in lesional skin showed significantly increased PR expression,[9] whereas nuclear staining of ERβ was increased around blood vessels and fibroblasts in lesional dermis. Nuclear positivity of ER and PR did not differ between lesional and nonlesional skin in the present study. Jang *et al.* also observed that expression of ERβ and PR was not significantly different between lesional and nonlesional skin in male melasma.[8] Hence, the role of sex hormones and their receptors in male melasma is probably not significant.

The limitations of our study were that we could not perform quantitative analysis of immunohistochemical markers, and the study had low statistical power for the variables that were tested.

Conclusion

Sun exposure and mustard oil use are important aetiological factors for melasma in Indian men. Histopathological features such as solar elastosis and vascular

proliferation in melasma also point to UVR as a causative factor for melasma. Hormonal influences possibly do not have a role in the pathogenesis of melasma in males. Quantitative evaluation of markers may add to the pathogenesis of male melasma.

What's already known about this topic?

- Chronic sun exposure, mustard oil use and genetic predisposition are important risk factors associated with male melasma.
- Among hormonal factors, subtle testicular resistance may play a role.
- Histologically, solar elastosis, increased vascularity, and expression of SCF and c-Kit are prominent in affected skin.

What does this study add?

- Stress and positive family history are less significant contributing factors in male melasma.
- Circulating hormonal levels do not play a role in the pathogenesis of melasma in men.
- Histopathologically, although mast cells are significantly increased in lesional skin, expression of SCF is almost absent.
- Absent expression of ER and PR in lesional skin possibly excludes sex hormone influences in male melasma.

Acknowledgements

This study was supported by a IADVL-L'oreal Indian Hair and Skin Research Grant.

References

1 Sarkar R, Jain RK, Puri P. Melasma in Indian males. *Dermatol Surg* 2003; **29**: 204.
2 Sarkar R, Puri P, Jain RK *et al.* Melasma in men: a clinical, etiological and histological study. *J Eur Acad Dermatol Venereol* 2010; **24**: 768–72.
3 Pichardo R, Vallejos Q, Feldman SR *et al.* The prevalence of melasma and its association with quality of life in adult male Latino migrant workers. *Int J Dermatol* 2009; **48**: 22–6.
4 Vazquez M, Maldonado H, Benmaman C, Sanchez JL. Melasma in men: a clinical and histologic study. *Int J Dermatol* 1988; **27**: 25–7.
5 Vachiramon V, Suchonwanit P, Thadanipon K. Melasma in men. *J Cosmet Dermatol* 2012; **11**: 151–7.
6 Maeda K, Naganuma M, Fukuda M *et al.* Effect of pituitary and ovarian hormones on human melanocytes in vitro. *Pigment Cell Res* 1996; **9**: 204–12.
7 Sialy R, Hassan I, Kaur I, Dash RJ. Melasma in men: a hormonal profile. *J Dermatol* 2000; **27**: 64–5.
8 Jang YH, Sim JH, Kang HY *et al.* The histopathological characteristics of male melasma: comparison with female melasma and lentigo. *J Am Acad Dermatol* 2012; **66**: 642–9.
9 Jang YH, Lee JY, Kang HY *et al.* Oestrogen and progesterone receptor expression in melasma: an immunohistochemical analysis. *J Eur Acad Dermatol Venereol* 2010; **24**: 1312–16.