Hypopigmented macules of photodamaged skin and their treatment with topical tretinoin

ALESSANDRA PAGNONI1, ALBERT M. KLIGMAN1,2, IQBAL SADIQ2 and TRACY STOUDEMAYER1

1S.K.I.N. Incorporated, 151 East Tenth Avenue, Conshohocken and 2Department of Dermatology, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Hypopigmented macules are frequently observed in the photo-damaged skin of elderly people. We undertook to study and treat 2 types of hypomelanosis of photoaged skin. These lesions were: 1) idiopathic guttate hypomelanosis; and 2) macular hypomelanosis. Comparative studies included: 1) high-resolution photography using parallel polarized light, ultra-violet (UVA) and epiluminescence; 2) Silflo replicas for microtopography; and 3) suction device (Cutometer®) for elasticity. Macular hypomelanosis was distinguishable from idiopathic guttate hypomelanosis because the macules were less white and less well demarcated. Glyphic markings were essentially absent in macular hypomelanosis, but variably effaced in idiopathic guttate hypomelanosis. Distensibility of the macules was characteristically low in proportion to the loss of glyphic markings. The chief histologic finding was the absence of melanin in basal keratinocytes. Macular hypomelanosis and idiopathic guttate hypomelanosis are probably related disorders along a spectrum of depigmentation. Treatment with tretinoin for 4 months restored the elasticity, the glyphic markings, with a partial restoration of pigmentation.

Key words: idiopathic guttate hypomelanosis; elasticity; macular hypomelanosis; microtopography.

(Accepted January 28, 1999.)

Acta Derm Venereol 1999; 79: 305–310.

A. Pagnoni, MD, S.K.I.N. Incorporated, 151 East Tenth Avenue, Conshohocken, PA 19428, USA.

MATERIALS AND METHODS

Epidemiology

A total of 40 Caucasian women (phototypes 2 and 3), living in the Philadelphia suburban area (40° latitude) were examined. Their age range was evenly distributed, between 31 and 74 years (mean 52±13 years). The dorsal forearms and lower legs were examined. We identified MH as small macules, smooth, typically lacking glyphic markings and paler than the surrounding skin, but never as white as IGH (Fig. 1). IGH, on the other hand, was recognized as small asymptomatic, macular, sharply defined off-white lesions, with or without glyphic markings (Fig. 2A) (4, 5, 7–10). Under Wood’s light, whiteness was accentuated (7), more so in IGH.

Non-invasive methodologies

We studied 7 MH and 3 IGH lesions in 7 Caucasian women between 60 and 74 years old. The following tests were performed on selected macules: ultraviolet-A photography; parallel-polarized photography; epiluminescence photography; elasticity; and replicas (Silflo). All the macules were located on the dorsal forearm, except for 1 IGH lesion on the lower leg.

Light photography. The photographic equipment comprised a standardized table-camera unit (Faraghan Studio, Philadelphia, PA, USA). One 1200-watt xenon flash lamp (White Lightening Ultra 1200, Paul C. Buff Inc., Nashville, TN, USA) was mounted in front of the subject at a 30-degree angle from the horizontal plane. The subject placed the arm or leg in a fixed arm/leg-rest.

Black-and-white UVA photographs were used selectively to enhance the visualization of melanin pigment (11). A 315–390 nm UV-transmittance filter (18-A Kodak) was mounted on the 90-mm macro lens (Tamron) of a 35-mm camera body (Minolta X-700). We used T-Max 400 Kodak film. This was processed in a high-speed developer to increase sensitivity to approximately 1000 ASA.

Fig. 1. Macular hypomelanosis (→) is hypopigmented, but not as white as idiopathic guttate hypomelanosis. The macule also shows smoothness and lack of glyphsics.
Fig. 2. Idiopathic guttate hypomelanosis (→) (A, C, E) before and (B, D, F) after 4 months of tretinoin applications. (A–B) Flash light photography. (C–D) UVA light photography. (E–F) Epiluminescence photography. After 4 months there was (B, D) a marked rebuilt of glyphics and (B, D, F) recovery of pigmentation. Also, the epiluminescence photos showed a striking decrease in the hyperpigmentation surrounding the macule after treatment.
Parallel polarized light was used to enhance surface details. We attached a linear polarizer filter in front of the flash lamp and a linear polarizer (Tiffen filter) on the camera lens. The planes of polarization of the 2 filters were adjusted in parallel position to enhance the surface structure (12, 13). We used 100 plus Kodak Ektachrome film.

Elasticity. Skin distensibility and elasticity were measured using a vacuum device, Cutometer SEM 575 (Courage + Khazaka, Köln, Germany) (16). This consists of a hand-held cylindrical probe with an opening of 2-mm (17–19). An electrically controlled vacuum lifts the skin into the cylinder and an optical system measures the height (in millimeters) of the skin pulled inside the cylinder. For each measurement a suction of 400 mbar was applied for 3 s and then released, the skin retracts to a point of residual elevation (R1). The maximum elevation of the skin during the suction is called “distensibility” (R0), which refers to the capacity of the skin to be stretched. When the vacuum is released, the skin retracts to a point of residual elevation (R1). The ratio of retraction (R0–R1) to the maximum extension (R0) defines the biological elasticity or “gross elasticity” (R2).

Four subjects were studied. Six macules were investigated: 3 IGH and 3 MH. All were on the dorsal forearm, except for 1 IGH on the lower leg.

Skin biopsy
A 3-mm punch biopsy was obtained, fixed in formalin and stained with hematoxylin-eosin, Hale, Fontana and Luna stains.

Two typical MH were biopsied from the dorsal forearms of 2 subjects and 2 typical IGH were biopsied, 1 from the lower leg and 1 from the dorsal forearm of another 2 subjects. The nearby photodamaged skin was also biopsied in the first 2 people with MH. The samples were evaluated by image analysis (analySIS, Soft-Imaging Software GmbH, Munster, Germany) for a measure of epidermal thickness.

Tretinoin treatment
Four photodamaged women between 61 and 74 years old completed a 4-month treatment on the dorsal forearms. Three had MH and 1 had IGH. One forearm received tretinoin (Retin-A cream, Ortho Pharmaceutical Corp., Raritan, NJ, USA) once nightly. We started the treatment on the second week and, after the second week, we increased the dose to the maximum permitted by the study. A sunscreen was applied to both sides each morning to avoid further photodamage. Both types of macules were found in the same subjects in only 10% of women.

RESULTS
Epidemiology
On the lower legs, no MH were observed at any age, while IGH were found in 9% of the subjects aged 51–60 years, and in 18% in those aged 61–74 years. By contrast, on the dorsal forearms MH and IGH were found in all age groups. However, the size of the macules and the prevalence percentage increased proportionally with increasing age. In the group 31–40 years old only 2-mm-size macules were observed: these were MH in 30% of the subjects and IGH in 10%. The frequency of 2-mm MH remained the same in the entire population, but these were associated with larger ones starting around 50 years of age. Larger MH lesions were present in 9% of subjects between 51 and 60 years old and in 45% of those between 61 and 74 years old. Over 41 years of age IGH were always larger than 2 mm. These were observed in 13% of people aged 41–50 years, 18% in ages 51–60 years and 28% in ages 61–74 years.

Both types of macules were found in the same subjects in only 10% of women.

Non-invasive methodologies
Clinical photographs showed a marked loss of pigment in both types of lesions, IGH being much whiter and more sharply demarcated than MH (Figs. 1, 2C and 2E).

Parallel-polarized pictures correlated well with the glyphic patterns on Silflo replicas. The replicas, however, reproduced microtopographic details more precisely (Figs. 2A and 2A). Both showed a marked lack or absence of glyphics in both types of macules on the dorsal forearms, compared with adjacent skin. The IGH on the leg, however, had only a slightly diminished glyphic pattern.

The Cutometer readings on both MH and IGH are shown in Table I. The lesions of the dorsal forearms had 37% lower extensibility–R0 than the adjacent skin. R2, a measure of skin elasticity, was 0.20 compared with 0.02 in uninvolved skin (t-test: paired 2 sample for means).

Table I. Comparison of elastic values (R0: extensibility, R2: gross elasticity) of hypopigmented macules (IGH and MH) and adjacent uninvolved skin on 5 dorsal forearms

| Dorsal forearm | R0 (mm) | R2 |
|---------------|--------|---|
|               | Uninvolved skin | Macules | Uninvolved skin | Macules |
| A             | 0.18    | 0.07 | 0.57 | 0.86 |
| B             | 0.13    | 0.06 | 0.52 | 0.83 |
| C             | 0.26    | 0.19 | 0.58 | 0.37 |
| D             | 0.22    | 0.20 | 0.57 | 0.65 |
| E             | 0.18    | 0.09 | 0.56 | 0.56 |
| Mean (± SD)   | 0.19 (± 0.05) | 0.12 (± 0.07)* | 0.56 (± 0.02) | 0.65 (± 0.20) |

*p < 0.005 compared with uninvolved skin (t-test: paired 2 sample for means).
elasticity, did not show statistically significant differences. These same macules showed a lack of glyphics. The IGH on the leg, that displayed a more regular glyphic pattern, showed extensibility and gross elasticity similar to that of the nearby skin. The percent change for this IGH, compared with adjacent skin, was as follow: R0 = +7% and R2 = –12%.

Histology
MH and IGH could not be differentiated histologically. Dorsal forearm lesions showed a flat dermo-epidermal junction and variable epidermal thickness. In one sample, the epidermal thickness was 40 μm vs. 70 μm in adjacent skin and, in a second sample, 64 μm vs. 54 μm, as measured by image analysis. The stratum corneum showed variable thickness; thinner in some lesions, thicker than normal in others. Fontana stain revealed much fewer melanin granules in the basal layer compared with adjacent skin and only a few granules in the viable epidermis. Luna stain showed a massive increase in thick, curled, branched elastic fibers (elastosis). Hale stain showed a thicker Grenz’ zone and an increased amount of glycosaminoglycans (GAGs) compared with adjacent skin. The IGH specimen from the leg showed similar epidermal findings. However, the elastosis and GAGs were much less prominent.

Treatment
In Nivea-treated forearms, no changes in pigmentation, glyphic pattern, elastic values and histology were observed either in IGH or MH.

By contrast, the tretinoin-treated macules clinically disappeared after 4 months, with an almost complete recovery of glyphics and partial repigmentation (Figs. 2, 3A and 3B). A great improvement was already evident after 2 months of therapy.

Parallel-polarized light photos correlated with the silicon replicas in showing a dramatic reconstitution of the glyphic pattern both in IGH and MH (Figs. 2A, 2B, 3A and 3B). In Silflo replicas microtopographic details were slightly less prominent than on adjacent skin.

UVA and epiluminescence photos showed a partial repigmentation in both IGH and MH (Figs. 2C–F).

Fig. 3. Idiopathic guttate hypomelanosis (→) (A, C) before and (B, D) after 4 months of tretinoin application. (A–B) Silflo replicas. (C–D) hematoxylin-eosin stain, × 20 magnification. After 4 months there was a marked rebuilt of glyphics, as shown in (B). Tretinoin induced epidermal acanthosis along with correction of atypia (D). A modest redevelopment of rete pegs was observed.

Acta Derm Venereol 79
Interestingly, the surrounding skin showed a decrease in pigmentation. After tretinoin treatment both IGH and MH showed a statistically significant increase ($p < 0.005$) in distensibility-R0 (77%) and gross elasticity-R2 (34%) compared with the pretreatment values. Also, the values of R0 and R2 for the tretinoin-treated macules were statistically significantly higher ($p < 0.05$) compared with Nivea-treated ones.

Tretinoin induced epidermal acanthosis along with correction of atypia. A modest redevelopment of rete pegs was observed (Figs. 3C–D). Fontana stain showed an increased density of melanin, not only in the basal layer, but throughout the entire epidermis including the stratum corneum. The elastic tissue and GAGs remained unchanged.

**DISCUSSION**

From our findings both MH and IGH increase in number and size with increasing age. Sunlight clearly plays an etiologic role in MH. Indeed, MH was observed only on the dorsal forearms, a common photodamaged area, and characteristically showed loss of glyphs and histological changes of photodamage.

Previous histologic studies on IGH reported contradictory findings on stratum corneum thickness (5, 7, 9, 10). Also, the epidermis was either of normal thickness with well-developed rete ridges (4, 5, 7) or flat and atrophic (6, 9, 10). Invariably, the keratinocytes had a decreased amount of melanosomes (4 – 7, 9, 10, 20, 21). The melanocytes were fewer, smaller, with rare dendrites or normal in shape and number, but both types of cells produced immature melanosomes with sparse melanin (4 – 7, 20). The papillary dermis was either normal (4, 5, 7, 10, 20) or thickened (6).

The histologic aspect of IGH and MH on photodamaged dorsal forearms did not allow us to differentiate between the 2 types of lesions. The main epidermal feature in all macules was a lower density of melanin granules compared with the adjacent skin.

From the literature, photodamage is apparently not a prerequisite for the development of IGH (7, 9, 10). The IGH we biopsied from the lower leg did not show histologic signs of photodamage and, clinically, retained a good glyphic pattern. This suggests a pathogenesis different from MH. Additionally, MH and IGH do not frequently occur together in the same individual. Gilhar et al. (22) suggested the presence of a systemic factor in the development of IGH, because IGH epidermis transplanted into mice re-pigmented after 3 weeks. In any case, restoration of pigmentation indicates that melanocytes, though inactive, are present in hypopigmented macules. In this study, the increase in melanin pigmentation after tretinoin, could indicate an improvement in melanin transfer to keratinocytes or a stimulation of melanin synthesis. It is interesting that in photoaged hyperpigmented skin tretinoin has a bleaching effect. These apparently conflicting results could be partially explained by the capacity of tretinoin to “normalize” functions.

The absence of skin glyphs is more critically linked to solar radiation, as observed in the IGH and MH on the dorsal forearms. Indeed in the lesions described by Wilson et al. (7), where glyphs were well developed, there were virtually no actinic changes of the epidermis and dermis.

Our data support the view that the 2-mm probe we used for biomechanical measurements is sensitive to detect variations on the superficial part of the skin (17), possibly epidermis and stratum corneum. On the dorsal forearm, the elastic properties of the macules were quite different from those of the adjacent skin. The loss of skin glyphsics could alone account for lower distensibility (R0). It has been shown in cyanoacrylate biopsies that the folding of the stratum corneum into glyphsics enables the skin to conform when a force is applied (23). It is noteworthy that the IGH on the leg that had a good glyphic pattern also showed extensibility and elasticity similar to the adjacent skin. Additionally, the increased distensibility of the macules after tretinoin treatment was accompanied by the restoration of glyphsics.

The marked amelioration of both types of lesions with topical tretinoin was noteworthy. Since Nivea alone had no effect in any of the parameters studied, simple moisturization is not enough to achieve these improvements. Follow-up of 2 patients with MH a year after stopping tretinoin showed clinical regression of the macules to the original state.

We found that the frequency of IGH was much lower than reported in the literature (4 – 6). This difference can be attributed to the following factors: 1) the literature did not distinguish between MH and IGH, in which case the frequency approaches ours; 2) our subjects were recruited from a “normal” population and not from dermatologic clinic.

We conclude that tretinoin dramatically improves IGH and MH and, although these lesions are mainly cosmetic defects, this treatment can be recommended for those concerned with appearance. In addition, maintenance therapy may be required for durable effects.

**REFERENCES**

1. Ortonne JP. The effects of ultraviolet exposure on the skin melanin pigmentation. J Int Med Res 1990; 18 (Suppl 3): 8c – 17c.
2. Ortonne JP. Pigmentary changes of the aging skin. Br J Dermatol 1990; 122 (Suppl 35): 21 – 28.
3. Colomb D. Stellate spontaneous pseudocars. Senile and presenile forms: especially those forms caused by prolonged corticoid therapy. Arch Dermatol 1972; 105: 551 – 554.
4. Cummings KI, Cottel WI. Idiopathic guttate hypomelanosis. Arch Dermatol 1966; 93: 184 – 186.
5. Whitehead WJ, Moyer DG, Vander Ploeg DE. Idiopathic guttate hypomelanosis. Arch Dermatol 1966; 94: 279 – 281.
6. Hamada T, Saito T. Senile depigmented spots (idiopathic guttate hypomelanosis). Arch Dermatol 1967; 95: 665.
7. Wilson PD, Latker RM, Kligman AM. On the nature of idiopathic guttate hypomelanosis. Acta Derm Venereol 1982; 62: 301 – 306.
8. Falabella R. Idiopathic guttate hypomelanosis. Dermatol Clin 1988; 6: 241 – 247.
9. Falabella R, Escobar C, Giraldo N, Rovetto P, Gil J, Barona MI, Acosta F, et al. On the pathogenesis of idiopathic guttate hypomelanosis. J Am Acad Dermatol 1987; 16: 35 – 44.
10. Savall R, Fernandiz C, Ferrer I, Peyri J. Idiopathic guttate hypomelanosis. Br J Dermatol 1980; 103: 635 – 642.
11. Pagnoni A, Kligman AM. Ultraviolet photography to identify early photodamage in young children. Br J Dermatol 1997; 137: 321 – 322.
12. Philp J, Carter NJ, Lenn CP. Improved optical discrimination of skin with polarized light. J Soc Cosmet Chem 1988; 39: 121 – 132.

*Acta Derm Venereol 79*
13. Anderson RR. Polarized light examination and photography of the skin. Arch Dermatol 1991; 127: 1000–1005.
14. Steiner A, Pehamberger H, Wolff K. In vivo epiluminescence microscopy of pigmented skin lesions. II. Diagnosis of small pigmented skin lesions and early detection of malignant melanoma. J Am Acad Dermatol 1987; 17: 584–591.
15. Corcuff P, Leveque JL, Grove GL, Kligman AM. The impact of aging on the microrelief of peri-orbital and leg skin. J Soc Cosmet Chem 1987; 82: 145–152.
16. Barel AO, Courage W, Clarys P. Suction method for measurement of skin mechanical properties: the Cutometer®. In: Serup J, Jemec GBE, editors. Handbook of non-invasive methods and the skin. Boca Raton: CRC Press, Inc., 1995: 335–340.
17. Pierard GE, Nikkels-Tassoudji N, Pierard-Franchimont C. Influence of the test areas on the mechanical properties of the skin. Dermatologica 1995; 191: 9–15.
18. Elsner P, Wilhelm D, Maibach HI. Mechanical properties of human forearm and vulvar skin. Br J Dermatol 1990; 122: 607–614.
19. Cua AB, Wilhelm KP, Maibach HI. Elastic properties of human skin: relation to age, sex, and anatomical region. Arch Dermatol Res 1990; 282: 283–288.
20. Ortonne JP, Perrot H. Idiopathic guttate hypomelanosis. Arch Dermatol 1980; 116: 664–668.
21. Ploysangam T, Dee-Analap S, Suvanprakorn P. Treatment of idiopathic guttate hypomelanosis with liquid nitrogen: light and electron microscopic studies. J Am Acad Dermatol 1990; 23: 681–684.
22. Gilhar A, Pillar T, Eidelman S, Etzioni A. Vitiligo and idiopathic guttate hypomelanosis. Repigmentation of skin following engraftment onto nude mice. Arch Dermatol 1989; 125: 1363–1366.
23. Schellander FA, Headington JT. The stratum corneum: some structural and functional correlates. Br J Dermatol 1974; 91: 507–515.