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REVIEW ARTICLE

Idiopathic Guttate Hypomelanosis: A Review of its Etiology, Pathogenesis, Findings, and Treatments

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Abstract Idiopathic guttate hypomelanosis is a common acquired leukoderma characterized by multiple, discrete round or oval, porcelain-white macules on sun-exposed areas, especially on the extensor surface of forearms and pretibial areas. It usually affects individuals aged over 40 years and the likelihood of acquiring it increases with age. The exact pathogenesis remains controversial. However, there are several factors that are believed to be involved such as aging, ultraviolet exposure, trauma, genetic factors, autoimmunity, and local inhibition of melanogenesis. Despite the benign course of progression, many patients visit medical centers owing to cosmetic concerns and to confirm the natural course of idiopathic guttate hypomelanosis. Because there is no standard therapy for this condition, numerous medical and surgical treatments including intralesional corticosteroids, topical retinoids, topical calcineurin inhibitors, phenol peeling, cryotherapy, superficial dermabrasion, skin grafting, and ablative and non-ablative lasers have been tested with mixed results. This article will thoroughly review the etiology, pathogenesis, clinical presentations, histologic, dermoscopic, and ultrastructural findings, and the treatment of idiopathic guttate hypomelanosis.

Key points

Senile degeneration, chronic ultraviolet exposure, genetics, trauma, autoimmunity, and local inhibition of melanogenesis have been proposed in the pathogenesis of idiopathic guttate hypomelanosis.

Intralesional corticosteroids, topical retinoids, topical calcineurin inhibitors, phenol peeling, cryotherapy, superficial dermabrasion, and ablative and non-ablative lasers have shown some efficacy in the treatment of idiopathic guttate hypomelanosis.

1 Introduction

Idiopathic guttate hypomelanosis (IGH) is a common acquired leukoderma, characterized by multiple, discrete round or oval, porcelain-white macules on sun-exposed areas, especially on pretibial areas and extensor surfaces of forearms. It usually affects the older population and the prevalence increases with age [1]. The exact pathogenesis remains controversial. However, there are some factors that have been believed to be involved such as aging [2], ultraviolet (UV) exposure [2, 3], trauma [4], genetic factors [5], and autoimmunity.

Despite its benign course of disease progression, many patients visit medical care owing to cosmetic concerns and to confirm its natural course. At the present time, the treatment of choice for IGH is still controversial. However, some studies reported improvements with several medical and surgical options.

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2 Literature Search Methods

We searched PubMed and MEDLINE databases from inception to October 2015. Our search terms included 'idiopathic guttate hypomelanosis', 'acquired leukoderma', 'leukopathy', and 'senile depigmented spots'. All prospective and retrospective studies available in English were included in our review, with priority given to prospective randomized controlled trials. The articles in non-English language were excluded.

The abstracts of the recognized studies were scanned to exclude those that were not clearly relevant. Additional relevant articles were identified by searching through the reference lists of numerous articles. The full articles were analyzed to determine whether they were related to the review title. We summarize the etiology, pathogenesis, clinical features, histologic, dermoscopic, and ultrastructural findings, and all treatment options for this condition.

3 Epidemiology

IGH was first described by Costa in 1951 as "symmetric progressive leukopathy of the extremities". It was subsequently confirmed on a larger group of patients reported by Cummings and Cottel [4] under the new name 'idiopathic guttate hypomelanosis'. In 1966 [6], the prevalence of IGH among adults was around 68 %. Later, Hamada and Saito [7] reported depigmented spots in 70 % of the population in their 50 s and called this entity 'senile depigmented spots'. Subsequently, Shin et al. [1] demonstrated that the prevalence of IGH among people aged over 40 years was 87 %. The probability of acquiring IGH increases with age, as it was found in 47 % of subjects aged 31–40 years, 80 % of subjects aged 41–50 years, and 97 % of subjects aged 81–90 years. However, there was a study reporting 7.0–29.8 % of patients have primary IGH lesions before the age of 20 years [2, 8]. Interestingly, the earliest occurrence was found at the age of 3 years.

The number of cases amongst women and men was almost equal at 56 and 54 %, respectively [1]; however, it seemed to be found earlier in young women than in young men [8]. This may be owing to the fact that women are more concerned with their looks than men and more likely to seek consultation from cosmetic doctors than men.

IGH occurs in all races and skin types; nonetheless, it is more prominent in darker-skinned individuals. Amongst Caucasians, IGH preferentially affects those with brown eyes and brown hair.

4 Etiology and Pathogenesis

The exact etiology remains unclear. However, several factors have been proposed such as senile degeneration, chronic UV exposure, genetics, trauma, autoimmunity, and local inhibition of melanogenesis.

4.1 Normal Aging Process

Because the prevalence of IGH increases with age on both sun-protected and sun-exposed areas [9], it can be assumed that it is a result of senile degeneration. Studies have found that the number of enzymatically active melanocytes gradually decreases by 10–20 % per decade [2]. Moreover, some reports described that skin aging might correlate with the somatic mutation of melanocytes. Nevertheless, this had not been clearly demonstrated [5]. In terms of dermatopathology findings, IGH lesions on non-exposed areas also showed signs of aging such as epidermal atrophy, rete ridge flattening, and reduced epidermal keratosis. Additionally, these findings may suggest that senile degeneration is another important factor beyond chronic UV exposure in the pathogenesis of IGH especially on sun-protected areas [8]. Ultrastructural studies [10] demonstrated the progressive loss of epidermal melanocytes in IGH lesions. Moreover, there were two types of melanocytes including healthy melanocytes with normal melanogenic activity and melanocytes with few or no immature melanosomes without cellular alterations. Depigmentation seemed to be found in two stages; loss of melanogenic activity in certain melanocytes and elimination of inactive melanocytes. These defects of melanocytes might imply that they occur as result of the aging process.

4.2 Chronic Ultraviolet Exposure

Because IGH lesions usually develop on sun-exposed areas, UV radiation is one of the implicated factors. In 2005, Kaya et al. [3] reported a strong relationship between UV exposure and IGH lesions by widespread IGH development on the trunk following 4-month narrowband-UVB phototherapy in a mycosis fungoides (MF) patient. Later, this evidence was confirmed by Friedland et al. [11]. They reported that 8 % of early-stage MF patients who underwent phototherapy (narrowband-UVB or Psoralen and Ultraviolet A monotherapy) developed IGH-like lesions on the areas exposed to UV light. Additionally, the IGH-like lesions were not restricted to the pre-treated MF lesions. Consequently, this suggests a possible pathogenic role of UV radiation in IGH. In addition, IGH lesions were demonstrated on a distribution similar to that of squamous

cell carcinoma, which has been shown to be associated with sunlight exposure [1].

Histopathologic findings of IGH lesions on the face showed that nearly 70 % of them had concurrently solar elastosis, a histologic marker of chronic UV exposure. Moreover, perivascular infiltration by monocytes was also observed in the lesions, which contradicts a previous belief that IGH was a non-inflammatory disease [1]. For ultrastructural study, focal elastotic changes have also been demonstrated by an electron microscopy study [12]. Therefore, there is evidence that supports the role of UV radiation in IGH pathogenesis.

4.3 Genetic Factors

Two studies have found that genetics play a role in the development of IGH. First, a family aggregation survey by Falabella et al. [2] revealed that the prevalence of IGH was significantly higher among a family of IGH patients than those of a control group. This finding clearly indicates that IGH patients might have a genetic predisposition. In the second study, a comparative case–control study was conducted with a group of renal transplant patients with IGH. It demonstrated that there was a significant association between human leukocyte antigen-DQ3 and the presence of IGH; whereas, there was no correlation between human leukocyte antigen-DR8 and IGH [13].

The analysis of the different pedigrees indicated that a recessive or a sex-linked hereditary mechanism could be ruled out; nonetheless, the definitive mode of transmission is still unknown. Because this condition usually develops later in life, it is difficult to collect data of several generations in the same family for a long-term follow-up study [2].

4.4 Trauma

Initially, it was believed that local trauma was not involved in the pathogenesis of IGH. According to a histopathological study by Wilson et al. [9], no scarring features such as loss of surface markings, flattening of the epidermis, and collinear arrangement of fine collagen bundles in the subepidermal region was observed. Furthermore, IGH lesions were usually seen more often on the anterior tibial surfaces or sometimes on the lower central region of the back. It may be owing to the fact that both areas have less subcutaneous tissue and are vulnerable to trauma. As a result, the higher prevalence of IGH in these areas supports traumatic factor association [1].

4.5 Autoimmune Process

Wilson et al. [9] tested circulating autoantibodies among IGH patients. One-third of the subjects had circulating antibodies to gastric parietal cells. Therefore, this condition may be associated with autoimmunity. However, there was no correlation of increased prevalence of autoimmune diseases in IGH patients or their relatives. Anti-thyroglobulin and antinuclear antibodies were also negative in all cases and the thyroid microsomal titer was normal. Positive antibodies to gastric parietal cells may be only an age-related change. Nevertheless, further investigations are needed to confirm this evidence.

4.6 Local Inhibition of Melanogenesis

Some authors hypothesized that IGH was the result of an active process of depigmentation by inhibiting melanogenesis. Falabella et al. [2] grafted normal skin into IGH lesions. At the 18-month follow-up, the normally pigmented graft caused depigmentation and there was no spreading of the pigmentation. The IGH graft not only remained white but depigmentation also extended to the periphery. The grafted implantation did not modify the achromic defects. This could suggest that there might be some local dermoepidermal factors rather than a simple residual pigmentary defect.

5 Clinical Findings

IGH manifests with discrete, sharply demarcated, round or oval, smooth porcelain-white macules of approximately 0.5–6 mm in diameter. Occasionally, the lesions may be up to 2.5 cm in diameter; nonetheless, they generally do not change in size or coalesce. However, 16 % of IGH subjects complained of the progression in the size of their lesions [1].

The number of lesions per subject ranged from 1 to 134, and the average number was around 13 lesions [1]. When IGH was found in young patients belonging to the first or second decade of life, the total number of lesions was fewer than five and their size was not larger than 2 mm. In contrast, numerous (usually more than 30 or 50) and larger lesions (3–5 mm) were commonly found at age 50 years and above [2].

IGH is usually located on sun-exposed areas of the skin such as the extensor surfaces of arms and shins and sometimes it can become widespread. However, it rarely occurs on the face. According to the study in 2010 [8], the arm was the most common site, followed by the distal part of the lower extremity. Only 6 % of subjects had lesions on their face. In subjects whom IGH occurred on the face, the lesions demonstrated a predilection for the marginal rather than the central area of the face. Furthermore, almost three quarters of patients had IGH lesions on both sun-exposed and sun-protected areas [1]. They were usually asymptomatic. Hairs within the lesions were usually spared.

According to the study by Kumarasinghe [14], there were three morphological variants of IGH lesions.

1. Solitary or multiple hypopigmented macules on a background of sun-damaged skin in sun-exposed areas;
2. Solitary ivory white, stellate, well-circumscribed, sclerotic macules related to sun exposure, which can be seen on both sun-exposed and non-sun-exposed areas;
3. Small well-circumscribed hypopigmented macules with keratotic flat crust and a scalloped border.

Nevertheless, insufficient evidence has been reported to describe whether these three morphologic variants could share the same pathogenesis.

6 Differential Diagnosis

Clinically, IGH lesions must be distinguished from several hypopigmented conditions such as macular hypomelanosis, vitiligo, pityriasis versicolor, tuberous sclerosis, lichen sclerosus et atrophicus, guttate morphea, and post-inflammatory hypopigmentation.

Macular hypomelanosis is quite similar to IGH. It can be differentiated from IGH by its reduced depigmentation and less sharply demarcated border. Moreover, glyphic markings were observed less frequently in macular hypomelanosis [15]. The appearance of an IGH lesion might be confused with early stages of vitiligo. However, vitiligo can be distinguished by its age of inception, size, and distribution of lesions [1]. Pityriasis versicolor might look like IGH. Nevertheless, it usually has a fine scale and it is frequently found on the upper trunk and shoulder. An examination for fungus would readily rule out this condition. Post-inflammatory hypopigmentation can be excluded because of its lack of previous history to dermatitis.

7 Dermoscopic Findings

Occasionally, IGH cannot be distinguished from other depigmented to hypopigmented lesions. Dermoscopic examination appears to be a non-invasive method to improve diagnostic precision.

A recent study in 2015 [16] demonstrated four dermoscopic patterns of IGH lesions. Amoeboid, feathery, petaloid, and nebuloid patterns were the most frequently observed in 46.66, 40, 23.33, and 3.33 %, respectively. However, the combination of the dermoscopic patterns could be seen in 13.3 % of the subjects. Dermoscopic findings could be related to some clinical characteristics. Feather-like striations were commonly found in the patients who had IGH for a longer period of time. The nebuloid pattern, an indistinct-border feature, was observed in the new lesions and also among older patients.

8 Histologic Findings

According to the study in 2010 [8] comparing histologic findings between IGH lesions and perilesional normal skin, hyperkeratosis of the stratum corneum (38.3 %), flattened rete ridges (14.9 %), epidermal atrophy (10.6 %), and acanthotic epidermis (10.6 %) were the features of IGH that were more frequently seen than in normal skin. However, only epidermal atrophy was more often observed in non sun-exposed areas than sun-exposed areas, which was statistically significant.

Regarding pigmentary changes, the amount of melanin pigment and number of melanocytes in IGH lesions dramatically decreased [7–9, 17, 18]. Ploysangam et al. [17], Ortonne et al. [10], and Hamada and Saito [7] had found that the number of dopa-positive melanocytes in IGH was considerably lower than that in normal skin. In addition, the melanocytes were unevenly distributed throughout the lesion [17]. Around 80 % of IGH lesions showed small areas of retained melanin in the basal layer alternating with large areas of melanin loss [19]. As a result, this may be a characteristic histopathological feature of IGH. Later investigation by Kim et al. [8] also found that the amount of melanin was significantly reduced in the epidermal layers with Fontana–Masson staining. Moreover, a reduction in the amount of melanin pigment was also represented by a weakened expression of immunohistochemical marker, NKI/beteb, and MART-1.

A thicker grenz zone and increased glycosaminoglycans compared with adjacent skin were demonstrated by hale staining. A massive increase in thick, curled, branched elastic fibers called elastosis was also observed by luna stain [15].

9 Ultrastructural Changes of Idiopathic Guttate Hypomelanosis

An ultrastructural study demonstrated melanocyte degeneration with a decreased number of melanosomes [4, 8–10, 17]. Findings from electron microscopy visualized melanocyte degeneration, decreased numbers of melanosomes, attenuation or absence of melanocyte dendrites, dilatation of the endoplasmic reticulum, and swelling of the mitochondria [8, 10]. Furthermore, the number of melanosomes in the neighboring keratinocytes was also diminished [9, 17].

On the contrary, Kakepis et al. [12] presented that keratinocytes could not take up as many melanosomes, as less uptake in some areas occurred despite the fact that the

number and structure of melanocytes were normal. According to this remark, it was proposed that dysfunction of keratinocytes was associated with IGH rather than abnormality of melanocytes.

Moreover, the structural features of scars, a flattened dermo-epidermal junction and dense, thin, parallel collagen bundles, were not observed [9].

10 Treatments

IGH may not be a significant problem in fair skin; however, it leads to cosmetic concerns and psychological impacts in patients with darker-skin types. Consequently, many patients seek medical care despite the benign course of disease progression.

Currently, no standard treatment for IGH has been established, although many medical and surgical options have been studied. This part will review both medical and surgical options for the treatment of IGH (Table 1).

10.1 Medical Treatment

10.1.1 Intralesional Corticosteroids

The benefit of corticosteroids in the treatment of IGH was first described in a study by Falabella et al. in 1987 [2]. Fifteen patients with IGH were included. Three lesions

Table 1 Medical and surgical therapies for idiopathic guttate hypomelanosis

First author	Treatment	Dosage or method	Results	Adverse effects
Medical treatment				
Falabella [2]	Intralesional corticosteroids	Intralesional triamcinolone monthly for 3 months	46.67 % (7/15) of the patients achieved a good response	
Pagnoni [15]	Topical retinoids	0.025 % tretinoin once nightly for 1 week, then 0.05 % tretinoin for 1 week, and 0.1 % tretinoin until completing the 4-month period	100 % (40/40) of the lesions clinically disappeared after 4 months	
Asawanonda [20]	1 % pimecrolimus cream	1 % pimecrolimus cream twice daily for 8 weeks	75 % (3/4) of the subjects demonstrated 25–75 % clinical improvement	
Rerknimitr [21]	0.1 % tacrolimus ointment	0.1 % tacrolimus ointment twice daily for 6 months	11 % (3/26) of the patients demonstrated some degree of repigmentation	Transient skin burning
Ravikiran [24]	88 % phenol peeling	Cotton-tipped application of 88 % phenol monthly for 2 sessions	64 % (89/139) of the lesions showed repigmentation, which in almost half of the lesions showed more than 75 % improvement	Persistent crust, PIH, ulceration, secondary infection, and scarring
Surgical treatment				
Ploysangam [17]	10 s cryotherapy	Single application of a 10-s cryoprobe	90.8 % (79/87) of the treated lesions reached complete repigmentation in 6–8 weeks	Blisters (of all lesions)
Kumarasinghe [14]	3–5 s cryotherapy	Single application of a 3- to 5-s cryogen	All treated lesions showed good repigmentation	Blisters, slight hyperpigmentation
Hexsel [25]	Superficial dermabrasion	Single session of dermabrader	80 % (16/20) of the patients showed repigmentation	Erythema for up to 90 days
Shin [26]	Fractional CO_2 laser	Single session of fractional CO_2 laser	42.7 % (17/40) of the patients showed more than 75 % clinical improvement	Burning sensation, erythema, PIH.
Goldust [27]	Fractional CO_2 laser	Single session of fractional CO_2 laser	47.9 % (115/240) of the patients showed more than 75 % clinical improvement	Pain, burning sensation, erythema, PIH
Rerknimitr [28]	Non-ablative fractional photothermolysis	Four sessions of fractional 1550-nm ytterbium/erbium laser monthly	60 % (72/120) of the lesions showed more than 50 % clinical improvement	Mild erythema, edema, and bronzing
Falabella [2]	Skin grafting	Normal autologous skin graft on depigmented lesions	6.66 % (1/15) of the patients showed repigmentation	

CO_2 carbon dioxide, *PIH* postinflammatory hyperpigmentation

were selected in each one of the patients; two of them were grafted, and the remaining one was injected with triamcinolone alone. The implanted lesions were divided into two groups; with and without additional intralesional triamcinolone injection. Among the 15 patients, 11 patients with grafts and triamcinolone infiltrations achieved good repigmentation, which accounted for 73.33 % of the lesions, whereas nearly half (46.67 %) of the lesions with triamcinolone injection alone developed a good pigmentary response. However, there was no significant difference between the results of these two groups. To sum up, the pigmentary response was noticed from both a graft with triamcinolone or triamcinolone alone. Induction of pigmentation may be the result of the immunosuppressive effect of corticosteroids on the local environment.

As a result, both intralesional triamcinolone with and without grafting provided good repigmentation in IGH lesions. However, this observation did not extend beyond 6 months and there was no evidence to establish true stimulation of melanocytes and melanin production. Therefore, the use of intralesional corticosteroids should be carefully applied to the IGH lesions.

10.1.2 Topical Retinoids

A cohort study [15] performed on 40 Caucasian women showed significant improvement of IGH lesions after applying topical tretinoin once nightly for 4 months. All subjects applied tretinoin on one side of the arm, while a placebo cream was applied on the other side. The dosage of topical tretinoin began with 0.025 % for 1 week, then increased to 0.05 % for 1 week, and finally to 0.1 % for the rest of the period. This study was conducted during the autumn and winter when all subjects were wearing long-sleeved clothing. The tretinoin-treated IGH had clinically repigmentation from the second month of treatment and IGH lesions completely disappeared after 4 months of topical application. Parallel-polarized photos and silicon replicas showed a reorganization of the glyphics pattern, while UVA and epiluminescence photos demonstrated partial repigmentation. There was a statistically significant increase of distensibility and gross elasticity in IGH lesions compared with the placebo side. For the histologic study, topical tretinoin-treated lesions demonstrated epidermal acanthosis with atypia correction. Furthermore, the rete ridges were moderately redeveloped and the density of melanin pigment was increased. Meanwhile, there was no change in the placebo-treated lesions. The mechanism of tretinoin-induced repigmentation was discussed. It was proposed that increased melanin pigmentation after tretinoin could indicate improvement in melanin transfer to keratinocytes or stimulation of synthesis.

To conclude, topical tretinoin appeared to be a safe, effective, and inexpensive option to treat IGH.

10.1.3 Topical Calcineurin Inhibitors

Both pimecrolimus and tacrolimus have been studied and show benefits for IGH repigmentation. Asawanonda et al. [20] showed the efficacy of 1 % pimecrolimus cream as a treatment of IGH lesions in four subjects. Three patients demonstrated 25–75 % improvement measured by both subjective and objective assessments within 8 weeks. The lesions revealed a reduction in depigmentation and fewer well-circumscribed macules, indicating better responses.

Later, a larger double-blinded, randomized, placebo-controlled trial from Rerknimitr et al. [21] exhibited that there was a significant improvement after daily application of 0.1 % topical tacrolimus ointment two times per day for 6 months. The outcome showed gradual decline in the mean luminosity scale on the tacrolimus-treated side and reached a statistically significant difference compared with the placebo group at 6 months of therapy. In regard to subjective assessments, around 10 % of the patients showed improvement of IGH lesions on the treated side with no statistical difference between the treatment and placebo group. Consequently, it was assumed that the measurement by colorimeter for the luminosity scale might be more sensitive than a physicians' ability to detect the difference. The patients that assessed themselves showed more repigmentation on the treated side (81 %) than on the placebo side (58 %). There was only mild and transient burning sensation at the application site in approximately 20 % of the patients.

It is believed that there are three mechanisms involved in repigmentation following topical calcineurin inhibitor treatment. First, calcineurin inhibitors may have an ability to stimulate tyrosinase activity, resulting in an increase in the melanin content. Second, there may be an increase in the proliferation and migration rate of melanocytes and melanoblasts [22, 23]. Last, immunosuppression from calcineurin inhibitors may be involved in the repigmentation. Topical calcineurin inhibitors may suppress many factors in chronic inflammation caused by senile degeneration in IGH.

In conclusion, topical calcineurin inhibitors appear to be an effective and safe treatment of choice for IGH.

10.1.4 Chemical Peelings

Spot peeling with 88 % phenol has been determined to be an effective treatment for IGH. Ravikiran et al. [24] included 20 patients with a total of 139 IGH lesions. All lesions were treated with 88 % phenol by a cotton-tipped applicator. Uniform white frost appeared in 30 s and

disappeared in 30 min. The procedure was repeated once after a 1-month interval.

At the end of 3 months, 64 % of the lesions showed repigmentation and almost half of these showed more than 75 % improvement. The most common side effect was persistent crust for more than 15 days in 17.2 % of the lesions. The second most common adverse effect was post-inflammatory hyperpigmentation (11.5 %), followed by ulceration, secondary infection, and scarring at 7.9, 8.6, and 5.6 %, respectively.

Therapeutic wounding may inactivate an inhibitory enzyme or chemokine that allows repigmentation of IGH. Another proposed possibility is that chemical peeling could destroy the overlying keratinocytes, thereby stimulating the negative effects of melanogenesis or melanosome transfer to the keratinocytes.

To sum up, topical 88 % phenol is an inexpensive, simple, and effective choice in the treatment of IGH. However, it must be used cautiously because of its cardiac toxicity.

10.2 Surgical Treatment

10.2.1 Cryotherapy

Treating IGH with liquid nitrogen was first introduced by Ploysangam et al. in 1990 [17]. Ten patients were enrolled in the study. Five to fifteen lesions on the upper extremity of each patient were chosen. The total number of treated lesions was 87. Each lesion was treated with a cryoprobe for 10 s.

All treated lesions developed blisters during the first week after cryotherapy. Perifollicular repigmentation was first observed in the third week and nearly all of the treated lesions (90.8 %) reached complete repigmentation within 6–8 weeks. Hypopigmented lesions had better responses than achromic spots. Afterwards, the repigmentation persisted after a 10-month follow-up period.

Subsequently, Kumarasinghe et al. [14] demonstrated that a 3- to 5-s liquid nitrogen freeze was sufficient to induce repigmentation. More than 15 lesions were treated.

At the sixth week after cryotherapy, all lesions showed good repigmentation according to the physician's as well as the patients' assessment. Only one lesion developed a blister and a few lesions showed slight hyperpigmentation. Kumarasinghe et al. discussed that this procedure might need an expert to perform the procedure to avoid deeper cryo-injury leading to scarring.

After cryotherapy, the amount of melanin and number of dopa-positive melanocytes were dramatically increased although their numbers were still fewer than that in normal controls [17]. This could be a result of the mitosis and migration of melanocytes from adjacent normal skin or hair follicles. Because melanocytes are sensitive to cold (−3 to −13 °C), the regrowth of local melanocytes is unlikely.

The exact mechanism of IGH repigmentation through freezing has not been clearly determined. However, freezing could probably inactivate inhibitory enzymes or chemokines that make the lesion resistant to melanogenesis [14, 17]. Another possibility is that liquid nitrogen may destroy the overlying keratinocytes, causing some destructive effects on melanocytes at IGH lesions or have a negative effect on melanogenesis or melanosome transfer [14]. The third possibility is that this repigmentation is occurring post-inflammation [14].

In conclusion, cryotherapy is a low-cost, minimally invasive procedure to treat IGH effectively. A 3- to 5-s short freeze appears to be sufficient for repigmentation and vesication is not necessary to achieve repigmentation.

10.2.2 Superficial Dermabrasion

Hexsel et al. reported the successful treatment of IGH by localized dermabrasion [25]. In the study, 20 IGH patients were treated with a standard dermabrader with small diamond fraises. The speed used for abrasion varied between 10,000 and 15,000 rpm. The objective depth was around the papillary dermis level without bleeding.

The treated area formed crusts, which fell off within 10 days. Then, there was redness in the area for up to 3 months, followed by normal or slightly decreased pigmentation. A recommended size of IGH for this method was less than 5 mm in diameter. Preferred sites of dermabrasion were exposed and hairy areas because melanocytes from the hair follicles would migrate to the new epidermis. In the study, 80 % of patients had satisfactory repigmentation.

Finally, superficial dermabrasion appears to be one of the effective surgical options for the treatment of IGH; nevertheless, it should be performed under expert supervision.

10.2.3 Fractional CO_2 laser

Fractional carbon dioxide laser (CO_2FL) has been reported as an effective and safe treatment option for IGH patients. The advantage beyond superficial dermabrasion is that it does not ablate the entire epidermis. Normal skin can be spared to be the reservoir for faster wound healing.

The first pilot study was performed on 40 Korean patients [26]. The IGH lesions were treated with only one session of CO_2FL. The treatment settings consisted of 100 mJ pulse energy, a spot density of 150 spots/cm^2 in static mode, and then two passes were delivered with a

300-spot-density tip. The patients were assessed 2 months after the treatment.

Approximately 42.7 % of the patients showed more than 75 % clinical improvement. Almost half of the patients showed 51–75 % improvement. In addition, 40 % of the patients were very satisfied with their outcomes. All patients experienced pain during the procedure as well as a burning sensation and erythema. However, those adverse reactions subsided within a day. There was longstanding erythema in two patients and it disappeared after about 2 months. Four patients reported post-inflammatory hyperpigmentation, which progressively regressed over 3 months. No serious adverse effects such as infection, scarring, or aggravation were observed. After a 1-year follow up, there was no recurrence of depigmentation.

A larger study by Goldust et al. in 2013 [27] used 10,600-nm CO_2FL with similar parameter settings and protocol to treat the IGH lesions in 240 patients. Two months after a single treatment session, almost 90 % of patients showed more than 50 % clinical improvement. Additionally, 39.6 % and 42.5 % of patients were very satisfied and satisfied with the results, respectively. Recurrence in the treated areas was not observed within 1 year after treatment. The adverse effects were similar to those of the study from Korea. Fifteen patients (6.2 %) reported a persistent redness, which disappeared after about 2 months. Thirty patients (12.5 %) exhibited post-inflammatory hyperpigmentation, which also spontaneously regressed within 3 months. No severe adverse effect was found.

Regarding the possible mechanisms, CO_2FL might remove dysfunctional melanocytes by ablation of the epidermis. Then, melanocytes from hair follicles and surrounding skin might migrate into the lesions during the re-epithelialization phase. Afterwards, there would be an increased production of many heat-shock proteins, cytokines, and growth factors during the wound-healing process. These results might increase melanogenesis after CO_2FL therapy [26, 27].

To sum up, CO_2FL may be an effective treatment for IGH without serious side effects. Moreover, CO_2FL may be associated with improved patient compliance compared with topical treatment.

10.2.4 Non-ablative Fractional Photothermolysis

CO_2FL may result in post-inflammatory hyperpigmentation in darker-skinned individuals undergoing IGH treatment. Rerknimitr et al. performed a double-blind, randomized controlled trial using a fractional 1550-nm ytterbium/erbium fiber laser to treat IGH [28]. The laser was used in a total of 120 IGH lesions from 30 patients with skin phototypes 3 and 4. The parameter setting energy ranged from 25 to 30 mJ/cm^2; total density was 600 MTZ/cm^2. Each patient received four consecutive treatments at 4-week intervals.

The relative lightness index was gradually decreased and reached a statistically significant difference at week 8. Sixty percent of the patients experienced more than 50 % improvement after being assessed by blinded dermatologists. Furthermore, patients' assessment showed more improvement on the treated site. Side effects included mild erythema and edema, which spontaneously resolved within 1 day. Bronzing was seen in less than 10 % of the patients and it subsided after 4–6 weeks. Interestingly, no post-inflammatory hyperpigmentation was observed.

The mechanism of non-ablative fractional photothermolysis was proposed to be similar to that of ablative fractional laser.

In conclusion, non-ablative fractional laser seems to be a good alternative treatment especially in darker-skinned individuals to avoid post-inflammatory hyperpigmentation.

10.2.5 Skin Grafting

In 1989 [18], split thickness skin grafts from patients with acquired hypomelanosiss were grafted onto nude mice. Interestingly, the study demonstrated repigmentation. Though the dopa reaction of the hypopigmented macules revealed a reduction in the number of melanocytes compared with the surrounding normal skin, the number of melanocytes of repigmented areas increased significantly at 8 weeks after the engraftment.

Falabella et al. [2] investigated the pigmentary changes, comparing normal autologous skin graft alone, normal autologous skin graft combined with intralesional steroids, and intralesional steroids alone on individuals with IGH lesions. Both intralesional triamcinolone injection with or without grafting demonstrated good clinical results and showed statistically significant repigmented responses. Only 1 out of the 15 grafted lesions showed repigmentation. Thus, the graft alone did not reveal a favorable outcome. Nevertheless, Falabella et al. did not propose intralesional steroids as a treatment of choice because of the short follow-up period.

11 Conclusion

IGH is a commonly acquired leukoderma of uncertain etiology. It is most commonly seen among the older population especially those with a history of long-term sun exposure. IGH is generally diagnosed by clinical presentation. However, dermoscopic findings, histopathology, and dopa staining may be helpful to distinguish it from other depigmented conditions. Numerous therapeutic

methods including medical and surgical options have been used with varying outcomes. Therefore, further studies of the pathogenesis and treatment of IGH should be performed.

Compliance with Ethical Standards

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Conflict of interest Premjit Juntongjin and Kulwadee Laosakul have no conflicts of interest.

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