

Research Advances in the Treatment of Riehl's Melanosis

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Abstract: Riehl's melanosis (RM) is a contact photodermatitis, with fast progressive gray-brown skin pigmentation as the main manifestation, which can seriously affect the psychology and physiology of patients. Currently, although the etiological factors of Riehl's melanosis is still be unknown, the existing literature proves clearly the cause of it is related to the contacting with suspected allergens. For decades, there has been no standard method for the treatment of RM, but with both conventional drug therapy and laser therapy having been attempted. Topical application of bleaching agents is mainly used as an auxiliary treatment modality. The laser treatment modality remains a hot spot, among which Q-switched Nd:YAG laser is well received for RM. Positive outcomes have been achieved by the combined treatment modalities attempted in recent years also achieve positive outcomes. The purpose of this paper is to review and summarize recent advances in the treatment of the disease.

Keywords: Riehl's melanosis, pigmented contact dermatitis, therapy

Introduction

Riehl's melanosis, commonly considered as pigmented contact dermatitis (PCD) or pigmented cosmetic dermatitis, is regarded as a contact dermatitis to cosmetic products and perfume, which affects the appearance of patients.¹ The disease was reported by Riehl during the First World War, and he attributed its cause to wartime food substitutes, mainly poor-quality flour.² Later, some experts considered Riehl's melanosis almost equivalent to PCD of the face or neck,³ and Nakayama⁴ considered it was mainly caused by allergies after exposure to cosmetic products. It develops over the face and neck with progressive hyperpigmentation as its clinical manifestation.¹ The affected skin is texture rough, with grayish-black, grayish-brown, or purple-brown patches with finely powdered scales on the surface.⁵ Under the dermoscopy,^{6,7} brown or grey pseudonetwork, dots, globules and telangiectasias appeared in all patients. However, various stages mean different dermoscopic features through serial dermoscopy. In the initial stage, only pigment dots are observed, while it is featured by vacuolization of the stratum basale and slight pigment incontinence in histopathology. With the progress of the disease and severe pigment incontinence, the false network structure and grey dot-like pigment structure are finally formed (melanin bacteria diffusely destroys the dermis and eliminates the normal pigment network). Besides, follicular keratotic plugs and perifollicular whitish halo are also commonly found, with basal pigmentation, melanin cell proliferation, skin pigment incontinence, dilated vessels and inflammatory cell infiltration as the main histopathological manifestations.⁸ With the increasing prevalence of RM, the negative psychosocial impact of the disease has become wider. Up to now, there is no standard therapy for the pigmented cosmetic dermatitis and the treatment is still challenging. In this paper, therapies of Riehl's melanosis are mainly reviewed and summarized.

Routine Therapy Allergen Avoidance

Pigmented contact dermatitis, as the name implies, is mainly caused by contacting with suspected allergens, thus, avoiding contacting with allergens or staying away from occupational exposure environment is the key to the treatment.

Table 1 Possible Allergens Causing Pigmented Contact Dermatitis

Fragrance components	Benzyl-salicylate, ylang-ylang oil, jasmine absolute, hydroxycitronellal, benzyl alcohol, cinnamic alcohol, lavender oil, geraniol oil, lemon oil, musk ambrette	[1,42]
Textile allergens	Tinopal CH3566, naphthol AS, mercury compounds, azo dyes, rubber components	[1]
Cosmetic products	Aniline dyes, red and yellow pigments, chromium hydroxide, carbanilides, ricinoleic acid, hair dyes, henna, kumkum, nickel oxide, ethylhexylglycerin	[1,43,44]
Occupational environment	Coal tar, pitch, asphalt, mineral oil, chromates (the material for leather and soap), mask component (formaldehyde, dibromodicyanobutane)	[1,45]
Preservatives	Formaldehyde, cetrimonium bromide, thimerosal (a raw material of disinfectant)	[1,9]
Others	Plathymenia foliosa (a sort of wood dust, airborne allergen), 5% minoxidil, nickel sulfate (metal product), hydroperoxides of limonene (widely used in household cleaning agents, cosmetics products, personal care products and perfume), cobalt	[46,47]

A study by Sharma et al⁹ has shown that the common allergens in Indian population may be preservatives (cetrimonium bromide, thimerosal and gallate mix), followed by hair dye components, fragrance components, nickel(II) sulfate hexahydrate, potassium dichromate and emulsifiers. Other reports showed that PCD is caused by henna,^{10–12} a kind of hair dye components. Recently, Hassan et al¹³ also reported a case of Riehl's melanosis caused by ethylhexylglycerin, a synthetic compound used in many cosmetic products, like cleansers and sunscreens. Therefore, it is necessary to remove or stay away from pathogenic factors to prevent further progress and recurrence of Riehl's melanosis. To date, some possible allergens that can cause RM have been tabulated in Table 1.

Sun Protection

Although no experimental report has shown the clear correlation between Riehl's melanosis and ultraviolet exposure, the skin lesions usually occur on the face and neck, because they are easily exposed to ultraviolet light. Besides, Woo et al,¹⁴ by skin biopsy, showed that patients with Riehl's melanosis have higher tissue expression of paracrine melanogenic molecules like SCF/c-kit. Human keratinocytes, fibroblasts, and endothelial cells can promote the production of SCF or c-kit after exposure to UV light. Therefore, the disease can be associated with ultraviolet radiation. Khanna¹⁵ suggests that people should try to avoid exercising during the peak hours of sunlight and use physical sunscreen (parasols and broad rimmed hats) or sunscreensing cream timely. Meanwhile, it is necessary to avoid contacting sunscreens with allergens contained.

Drug Therapy

So far, it has been challenging to conduct treatment of intractable hyperpigmentation disease with drug therapies. For facial melanoses (FM), Riehl's melanosis is one of the defined causes.¹⁵ Application of topical depigmenting agents alone shows varying degrees of efficacy in the treatment of FM. Hydroquinone (HQ) may be the gold standard for FM, azelaic acid, kojic acid, retinoids, glycolic acid, tretinoin and topical corticosteroids are also used for RM, but lack dependable and controlled clinical trials.^{15,16} In the future, meaningful statistical analysis is allowed to appear in the literatures' study design. A case report by Iwayama¹² found the patient's pigmentation still persisted after various treatment drugs tried such as HQ ointments, ointments containing vitamin C, tranexamic acid (TA) tablets and other antihistamine tablets. Recommended drug therapy includes hydroquinone creams plus tretinoin or glycolic acid.¹⁶ In a prospective pilot study, Xu¹⁷ reported that oral tranexamic acid combined with glycyrrhizic acid could increase the curative effect of treatment of recalcitrant Riehl's melanosis. They found that tranexamic acid directly inhibited melanin synthesis in melanocytes and inhibited neovascularization at the same time and glycyrrhizic acid, aiming to prevent or reduce the inflammatory response, could relieve the facial itchiness, erythema and edema of patients. The final result showed that mean Melanin Index (MI) and Erythema Index (EI) scores of ten RM patients were significantly decreased after six-month treatment. Yumei¹⁸ suggested that oral viaminat capsules combined with topical hydrocortisone butyrate

cream had a good effect on the treatment of occupational melanosis with relatively few side effects. Thus, compared to the application of the decolorization agents alone, drug combinations are one of the significant therapy for RM patients. What is noteworthy is that in an open-label pilot study, oral mycophenolate mofetil was initially applied in acquired dermal macular hyperpigmentation (ADMH), an umbrella term including RM.^{19,20} Mycophenolate mofetil is one of immunomodulators, which can reduce immunosuppressive effect. It can reduce the hyperpigmentation through targeting the lymphocytes' de-novo purine production pathway and probably inhibiting fibroblasts, which are also recognized with melanin contained. Thirty-five of 46 patients showed >10% reduction in dermal pigmentation area and severity index. Nevertheless, mycophenolate mofetil may have a more profound impact on stable period of the disease and cause observable reduction in the degree of hyperpigmentation. In addition, using the therapy for a long time is also necessary.

Laser Therapy

In recent years, with the development and maturity of cosmetic laser technology, it has begun to be applied to the treatment of Riehl's melanosis. While researches focus on the application of intense pulsed light (IPL) and Q-switched Nd: YAG (QSNY) laser, picosecond alexandrite laser or fractional thulium fiber laser (TFL) is attempted to be a promising and feasible option for RM.

Intense Pulsed Light

So far, IPL has been used extensively to treat a variety of pigmentation diseases.²¹ It converts light energy into heat energy, directly targeting melanin in the epidermis and making melanosomes in epidermis move to the upper layer of skin quickly, showing the characteristics of decolorization.²² There are few literature reports confirming the effectiveness of IPL for treating Riehl's melanosis. Oiso et al²³ used IPL to treat an elderly woman diagnosed with RM. 12 J/cm² was set to the initial fluence of IPL and the wavelength of 500 nm. After applying nine sessions at monthly intervals, the therapy showed excellent improvements without significant negative events noticed. The author speculated that IPL not only eliminated melanin granules in the epidermis, but also realized improvement in the photoaged skin. But only one patient was treated and patch test showed a negative reaction to her commonly used cosmetics. Later, Li et al²⁴ implemented a pilot study to evaluate the efficacy of IPL for the treatment of RM. They used the randomized, split-face pattern, with half of their face exposing to IPL treatment. After treating eight to ten sessions with using cut-off filters of 590, 640, and 695 nm in serial treatment and a fluence ranging from 11 to 17 J/cm², they came to satisfactory outcomes. The average MI and EI values of the experimental group showed a remarkable decrease trend compared to the control group. On the other hand, the results of histology of skin biopsies confirmed that IPL eliminated the melanosomes both in epidermis and dermis. In both the subjective clinical improvement and standardized photographs, all patients exhibited good to exceptional improvement throughout the 6-month follow-up. The slight and transient cutaneous erythema and edema were noticed at the end of the treatment, but no serious adverse reactions were permitted while patients were receiving treatment. The above researches indicate that IPL is effective in clinical treatment of RM patients, and there are certain adverse reactions. However, due to limited clinical applications and incomplete clinical data, further expansion of sample size and improvement of controlled trials are needed to obtain effective conclusions.

Q-Switched Nd:YAG Laser

1064 nm Q-switched Nd: YAG laser is widely utilized in clinical dermatosis, which can induce non-ablation of target pigments and selective photopyrolysis. It is reported that the using the laser to treat chronic hyperpigmentation diseases like chloasma and post-inflammatory hyperpigmentation (PIH) shows significant benefits.²⁵ 1064 nm QSNY can precisely target melanin phages of lesion and destroy the melanin particles within lesional melanin phages.²⁶ Compared to short wavelength laser (523 nm), the selected long wavelength laser (1064 nm) can be easier to pass through the epidermis to the dermis. Therefore, long wavelength laser can target the deeper pigmentation and obtain better effects compared with the short wavelength.²⁶⁻²⁸ Recently, a variety of studies have been attempted to show the effectiveness of low fluence 1064 nm Q-switched Nd:YAG laser for RM, although the general sessions of treatment may be relatively long.²⁹⁻³¹ In a case report conducted by On,²⁹ two patients caused by hair dye were treated with a low-pulsed 1064 nm QSNY laser at the settings of 1.8 J/cm² and 8 mm spot size. Compared to initial biopsy specimen, there

was a significant decrease trend in melanocytes and lymphocytes in the dermis, and both clinical evaluation and histological evaluation came to significant changes. However, lacking of samples and long course treatment, treating deeper and larger pigmentation of RM with a low fluence 1064 nm QSNY laser may be obviously insufficient. Therefore, after five years, Cho et al³² performed a retrospective review. A total of 21 patients' lesions were treating with middle fluence of 1064 nm QSNY laser, setting of 3.5–5 J/cm² and 5-mm spot size. To assess the effectiveness, standardized photographs, the Melasma Area and Severity Index (MASI) scores and skin biopsy were used. The final outcomes showed that 76.1% of patients obtained moderate to much improvement, with side effects of only itching and erythema. Both the average MASI score and mean number of melanophages decreased obviously. Compared to other pigmentary disorders, the deeper pigmentation that occurs during RM needs higher fluence modality, while medium energy can destroy melanin phages in the dermis and be slowly absorbed. Accordingly, the treatment with a mid-fluence 1064 nm QSNY laser is a safe and available method for RM.

Picosecond Alexandrite Laser

The 755 nm picosecond alexandrite laser can provide more fine-tuning energy to cause simultaneous photothermal and photoacoustic effects, selectively damage melanin without causing excessive thermal damage to surrounding tissues. In this way, it can significantly clean out pigments, promote the growth of new collagen cells and improve skin color.^{33,34} This laser has good curative effect on wrinkle, tattoo removal, scar, acne, Nevus of Ota and facial photopigmentation.³⁵ In a study by Iwayama,¹² a Japanese woman (type IV) who was diagnosed with henna-induced Riehl's melanosis, was treated with the 755 nm picosecond alexandrite laser in total seven sessions at monthly intervals, substantial improvement observed in clinical appearance and histopathology findings. Meanwhile, the adverse events like edema, erythema or hyperpigmentation were not noticed at the follow-up visit. It illustrates that 755 nm picosecond alexandrite laser possibly is an reliable and effective method to alleviate the pigmentation of RM, which can destroy melanosomes by generating selective photodisruptive and photothermal effects. However, this study only included one patient and contingency cannot be excluded. Therefore, a great quantity of clinical studies, especially randomized control trials, are needed to verify the availability of the laser in the future.

Non-Ablative Fractional Thulium Fiber Laser

Most studies on 1927 nm non-ablative fractional thulium fiber laser focus on the phototherapies of postinflammatory hyperpigmentation and melasma, suggesting that the application of this laser to treat pigmented disorders is a secure and efficient choice. The laser can probably target epidermal cells, reverse the disruption of the dermoepidermal junction (basement membrane), and induce neocollagenosis and elastinogenesis in the upper dermis.³⁶ Kim et al³⁷ considered that TFL could be a viable and promising therapy option for Riehl's melanosis and has recently been attempted in their study, given that histopathologically RM and postinflammatory hyperpigmentation are similar. All nine patients were treated with more than three to seven sessions of TFL at the energy between 10 and 20 mJ. To observe the effectiveness of TFL, the quartile grading scale of clinical improvement, dermal pigmentation area and severity index (DPASI) and biopsy specimens in one patient were used. The final results showed that the average grade of clinical improvement was 2.89, while the mean DPASI score decreased from 9.55 to 5.25. Besides, after the comparison before and after 7 sessions treatment in one patient, there was a remarkable decreasing trend of melanosomes in the epidermis and superficial dermis. Regarding side effects, slight and transient erythema were observed and resolved in three days. As the shallow penetration of TFL, it can be recommended for RM patients with pigmentation in the epidermis and upper dermis. Some clinical trials of single therapy have been summarized in Table 2.

Combined Treatment

At the present time, for recalcitrant forms, combination of therapies should be considered. The combined use of several therapies not only can increase the efficacy, but also reduce adverse events.

Table 2 Mechanism of Different Single Treatment Modalities

First Author, Year	Treatment and Follow-Up	Number of Subjects	Major Outcomes	Adverse Events	Comments
Anuradha Bishnoi, 2021 ¹⁹	Mycophenolate mofetil 500 mg twice daily for 2 weeks, 1000 mg twice daily for following 22 weeks, 12-week follow-up	46	Clinically and dermatoscopically appreciable improvement in hyperpigmentation	Mild leucopenia, minor nausea, diarrhoea, transient transaminitis occurred and resolved after discontinuation.	Mycophenolate mofetil treatment may be available for stable period of hyperpigmentation
Oiso, 2010 ²³	Wavelength and fluence: 500 nm with 12 J/cm ² , nine sessions at monthly intervals	1	The therapy achieved remarkable improvements	No obvious adverse events	Small simple size
Yuan-Hong Li, 2011 ²⁴	Eight to ten sessions with using cut-off filters of 590, 640, and 695 nm in serial treatment and a fluence ranging from 11 to 17 J/cm ² , 6-month follow-up	6	Average MI and EI values, clinical improvement and standardized photographs exhibited good to exceptional improvement, both epidermis and dermis were eliminated	Mild to moderate but tolerable pain, slight and transient cutaneous erythema and edema, PIH occurred in one patient and treated within 1 month	No specific time interval for laser use
Hye Rang On, 2015 ²⁹	Wavelength and fluence: low-plused 1064 nm with 1.8 J/cm ² , spot size: 8 mm, 8 and 13 sessions individually at three-week intervals, 3-month follow-up	2	Clinical evaluation and histological evaluation came to significant changes	Mild erythema	Small simple size.
Mi Yeon Cho, 2019 ³²	Wavelength and fluence: mid-plused 1064 nm with 3.5–5 J/cm ² , spot size: 5 mm, 3 to 12 sessions at initially four-week intervals	21	76.1% of patients obtained moderate to much improvement through standardized photographs, the melasma area and severity index scores and skin biopsy	Tolerable itching in one case and disappeared within few days, prolonged erythema and resolved within 2 weeks	Lack of control group
Takanori Iwayama, 2020 ¹²	Wavelength and fluence: 755 nm with 0.25–0.71 J/cm ² , pulse-width: 750 ps, seven sessions at monthly intervals	1	Substantial improvement observed in clinical appearance and histopathology findings	None	Small simple size.
Su Min Kim, 2021 ³⁷	TFL at the energy between 10 and 20 mj, three to seven sessions at monthly intervals	9	Dermal pigmentation area and severity index score decreased from 9.55 to 5.25, the skin histology in one patient revealed a marked decrease in melanosomes in the epidermis and superficial dermis	Transient erythema and swelling	The shallow penetration of TFL cannot reach the deeper skin layer

Salicylic Acid Plus Others

Salicylic acid (SA), as a peeling agent, is a member of a class of substances known as hydroxy acids that inhibits melanin production by inhibiting prostaglandin and tyrosinase production.³⁸ It contains whitening and anti-inflammatory properties by affecting the rapid differentiation of keratinocytes, making the necrotic melanocytes of keratinocytes migrate upward and enhancing the transport of melanophages.^{38,39} The above effects make salicylic acid become a reasonable and effective way of treatment of RM. At present, the application of salicylic acid individually for Riehl's melanosis has not been introduced. In the study by Wang et al,⁴⁰ VISIA (Canfield Imaging Systems) showed that both brownish and red area of patients all alleviated in different sessions after being given a triple combination therapy including 30% salicylic acid, glycyrrhizin compound (150 mg

daily) and Vitamin C (100 mg daily) given for about 16 weeks. Besides, it also demonstrated that salicylic acid combined with bleaching agents is a feasible and safe treatment modality for Riehl's melanosis, with mild side effect.

Q-Switched Nd:YAG Laser Plus Others

In a study conducted by Kwon et al,⁴¹ eight patients (type III–V) were treated with 1064 nm QSNY for 10 to 18 sessions at a three-week interval. After assessing the skin type of patients, the appropriate mode was chosen (1.1–1.3 J/cm² and 10-mm spot size). For improving the efficacy of light, during the laser treatment period, 4% HQ cream, one common bleaching agent, was applied to patients, with tranexamic acid tablets 250 mg taken daily also. Improvements were found through clinical assessment. Besides, comparing to the baseline, average MI and EI values and histopathological score showed a great decrease trend with statistical significance. At the same time, in the dosage range, no significant adverse events are observed. For the treatment of intractable Riehl's melanosis, combination effects with light-based therapies are more stable without notable side effects. In another retrospective study,³¹ after using 1064 nm QSNY with topical 4% HQ for RM, it was also shown that the combined treatment modality is effective. Notably, according to the researchers, the patients with dark brown hyperpigmentation, in contrast to those with mild brown hyperpigmentation, showed more significant development. They reasoned that it is probably related to the quantity and location of the pigment melanin in the skin. There have been listed certain clinical trials of combination therapy in Table 3.

Table 3 Clinical Trials of Combination Therapy for RM

First Author, Year	Treatment	Number of Subjects	Outcome(s) [Subjective]: Physician and Participant Assessed	Outcome(s) [Objective]: Objective Measurements	Adverse Events
Xu Z, 2019 ¹⁷	For 3 months, taking tranexamic acid 250 mg twice a day together with glycyrrhizin 50 mg three times daily, following by 500 mg TA per day orally alone for an additional three months	10	70%: marked improvement 20%: moderate improvement 10%: minimal improvement	Dermatoscopy and RCM demonstrated that erythema and pigmentation were greatly improved, as seen by the reduction of telangiectatic vessels and pigment granules	No serious adverse events
Yumei Z, 2011 ¹⁸	For 4 weeks, taking 50 mg of viaminate capsules three times a day along with hydrocortisone butyrate cream	42	72.73%: pigmented lesions completely subsided or subsided≥90%	None	Mild dry lips, dry skin, constipation
Wang L, 2020 ⁴⁰	For 16–24 weeks, taking 150 mg of glycyrrhizin compound daily, 100 mg of vitamin C daily, and salicylic acid 30% peels once every 2 weeks	3	Lesions of all patients achieved remarkable improvements after different sessions	Canfield Imaging Systems revealed a markedly reduced amount of brownish and red area	Mild burning
Choi CW, 2019 ³¹	4% hydroquinone cream and 1064 nm Q-switched Nd:YAG laser setting of 2.0 J/cm ² every three weeks	10	70%: near total improvement(51–75% improvement)	None	Guttate hypopigmentation, transient aggravation of pigmentation
Kwon HH, 2017 ⁴¹	All subjects applied tranexamic acid 250 mg daily, 4% hydroquinone cream and 1064 nm Q-switched Nd:YAG laser settings of 1.1–1.3 J/cm ²	8	37%: almost clear 63%: marked improvement	Melanin content, basal vacuolation, and superficial perivascular lymphocytic infiltration were appropriately reduced for histopathologic tests	No serious adverse events

Conclusion

There is no single medication that can ensure guaranteed efficacy for Riehl's melanosis, despite the variety of treatment options that are now available, lacking of randomized controlled trials. For pigmented contact dermatitis, routine therapy including keeping away from suspected allergens and sun protection is significantly necessary. In general, the existing literature show that laser treatment modalities are more effective than topically application of bleaching agents. Intense pulsed light and Q-switched Nd: YAG laser, picosecond alexandrite laser and fractional thulium fiber laser were clinically responsive to proper settings, with the risk of irritation and subsequent pigmentation increasing. QSNY laser, whether low fluence or medium fluence, is still the most principal and reliable treatment. For deeper pigmentary disorders, mid-fluence is probably more available and effective. The combination of QSNY laser and HQ cream successfully comes to positive clinical improvement, with fewer adverse reactions than that in other experiments. Intense pulsed light, picosecond alexandrite laser and fractional thulium fiber laser still need to expand the sample size and extend the follow-up time in the treatment of RM to further explore its indications, effectiveness, safety, incidence of adverse reactions, and recurrence rate. In summary, in real clinical environment, determining the specific relevant allergens and avoiding possible causative factor are both difficult in the majority of patients. Therefore, getting a more comprehensive and profound understanding of the pathogeny and pathogenesis of Riehl's melanosis will help to develop more effective and targeted and treatment methods.

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