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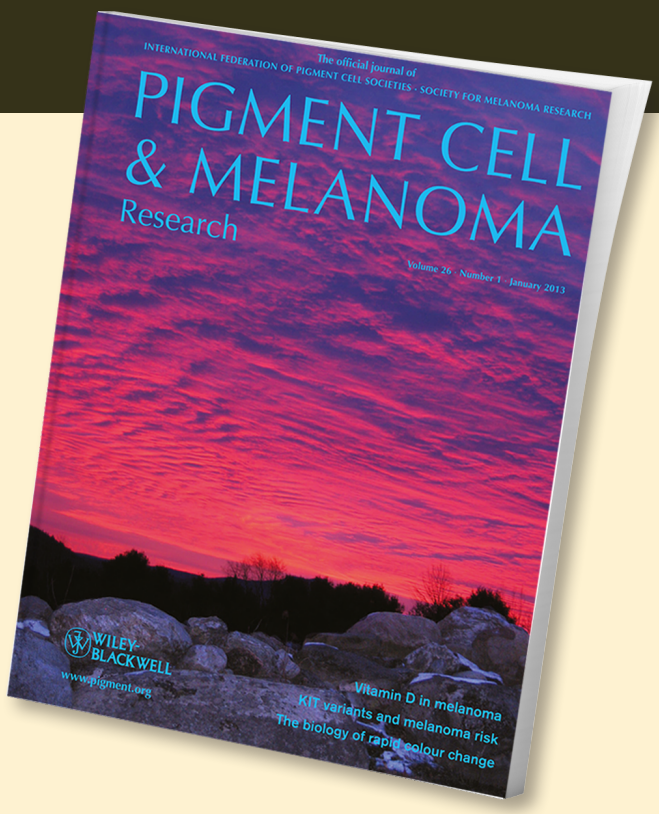

Unveiling the mystery of Riehl's melanosis: An update from pathogenesis, diagnosis to treatment

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REVIEW

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Unveiling the mystery of Riehl's melanosis: An update from pathogenesis, diagnosis to treatment

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Abstract

Riehl's melanosis is a hyperpigmentation disorder that has a significant psychological and social impact on individuals. In the past 10 years, new categories have been developed, raising questions about how to classify Riehl's melanosis. The mechanism of this disease remains unclear, although the type IV hypersensitivity response caused by allergic sensitization, as well as genetic, ultraviolet radiation, and autoimmune factors, is to blame. Clinical manifestation, dermoscopy, reflectance confocal microscopy, patch/photopatch testing, histopathology, and a novel multimodality skin imaging system have been used for the diagnosis. A variety of therapies including topical skin-lightening agents, oral tranexamic acid, glycyrrhizin compound, chemical peels, and lasers and light therapies (intense pulsed light, 1064-nm Q-Switched Nd: YAG laser, 755-nm PicoWay laser, non-ablative 1927-nm fractional thulium fiber laser, new pulsed-type microneedling radiofrequency), with improved effectiveness. The latest findings on possible biomarkers and their relationship to other autoimmune diseases were also summarized.

KEYWORDS
diagnosis, etiology, hyperpigmentation, melanosis, therapy

1 | INTRODUCTION

Riehl's melanosis is an acquired pigmentation disorder that typically affects the face, neck, and upper chest, with a focus on the forehead and zygomatic and/or temporal region (Kumarasinghe et al., 2019). It was initially found and described by Riehl(Pérez-Bernal et al., 2000), in 1917, when several patients noticed a dramatic black pigmentation of the face. For decades, the description of Riehl's melanosis has varied with different names, while scientists have been making progress toward a precise classification of this disease.

1.1 | Definition

Riehl's melanosis was once called "war dermatosis" (Rorsman, 1982) as it vanished after the end of the war, and later "melanosis faciei feminae" (Minami & Noma, 1950). The global consensus published in 2018 summarized Riehl's melanosis as a disease that is "characterized by numerous fine or reticulate, acquired macules of pigmentation of uncertain etiology" (Kumarasinghe et al., 2019).

1.2 | Controversy: Riehl's melanosis and pigmented contact dermatitis

In 1970, Osmundsen brought up the conception of pigmented contact dermatitis (PCD) (Rorsman, 1982) as a result of a widespread acceptance that Riehl's melanosis is secondary to contact dermatitis caused by diverse cosmetics, sensitizers, and allergens, which is a noneczematous presentation of contact dermatitis featuring increased pigmentation with minimal or no inflammation (Subburaj et al., 2022). To this day, the conventional view regards

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Riehl's melanosis and PCD of the face (Daadaa & Tanfous, 2022; Kumarasinghe et al., 2019) as almost identical entities with no discernible distinctions (Sarkar et al., 2022; Sitohang et al., 2020).

Nevertheless, the global consensus statement issued in 2018 stated that only if a definite relevant contact allergy is confirmed in patients with finely reticulated pigmented lesions on the face and neck region can the illness be classified as PCD, highlighting its overlap rather than inclusive relationships with Riehl's melanosis.

1.3 | New classification of Riehl's melanosis: Acquired dermal macular hyperpigmentation (ADMH)

Prior to the consensus, a new term, acquired dermal macular pigmentation (ADMH) (Chandran & Kumarasinghe, 2016; Subburaj et al., 2022; Vinay et al., 2017, 2021), was coined to include Riehl's melanosis, lichen planus pigmentosus (LPP), ashy dermatoses, and idiopathic macular eruptive pigmentation (IMEP), all of which share significant histopathological and clinical similarities (Bishnoi, Vinay, Arshdeep, et al., 2019; Bishnoi, Vinay, Kumaran, & Parsad, 2019; Vinay et al., 2017).

A Delphi consensus on the nomenclature and diagnosis of lichen planus pigmentosus and related entities (Sarkar et al., 2022) across India and Australia has drawn a conclusion that ADMH is an appropriate conglomerate terminology for acquired dermatoses characterized by idiopathic or multifactorial noninflammatory macular dermal hyperpigmentation, with over 80% agreement. Furthermore, participants concurred that it would be appropriate to categorize acquired dermal macular hyperpigmentation under the broad parameters of "with and without contact sensitization" (Bishnoi, Vinay, Arshdeep, et al., 2019; Bishnoi, Vinay, Kumaran, & Parsad, 2019; Sarkar et al., 2022; Sharma et al., 2017) for better patient management.

2 | EPIDEMIOLOGY

Riehl's melanosis is more common in darker-skinned population and particular ethnic groups such as Hispanic and East Asian people (Costescu et al., 2017; Vinay et al., 2021; Wang & Xu, 2014; Yoo, 2022). Young to middle-aged women are more worried than males, mainly around the reproductive period (Costescu et al., 2017), although Riehl's melanosis is uncommon in youngsters. The bulk of cases have been documented in Japan (Daadaa & Tanfous, 2022), but there have also been cases reported from South Africa (Choi et al., 2022; Kim & Lee, 2021;Woo, Jung, et al., 2020; Woo, Park, et al., 2020), Europe, South America, and India.

Studies by Choi et al (Choi et al., 2022) and (Woo et al., 2018) came to similar conclusions, noting that older or female patients were more associated with hair coloring, of which henna is a rising culprit. In recent research, individuals suspected of having PCD were found to be much older and to have used hair color for a longer period of time.

3 | PATHOGENESIS

The pathogenesis of Riehl's melanosis is still largely unknown. Potential causes of Riehl's melanosis are listed and summarized in Figure 1.

3.1 | Genetics and transcriptomic studies

Up to now, little evidence has demonstrated the genetic or transcriptomic influence on Riehl's melanosis. Jung et al. (2020) used Next-Generation Sequencing (NGS) to show that guanine deaminase (GDA) gene expression was significantly elevated in Riehl's melanosis lesions. Some specialists speculated that keratinocyte damage and basement membrane deterioration may be caused by a hereditary predisposition (Woo, Jung, et al., 2020; Woo, Park, et al., 2020). Correlative research, for instance, the inherent susceptibility of an ethnic population, should be carried out (Bishnoi, Vinay, Arshdeep, et al., 2019; Bishnoi, Vinay, Kumaran, & Parsad, 2019).

3.2 | Ultraviolet light irradiation

Ultraviolet light exposure is suggested as a significant contributing factor due to the clinical features of photo-exposed pigmentation sites and the property of photosensitization by few allergens, especially considering that the manifestations are dependent on the severity of the immune response and the disposition of involved sites (Seike et al., 2003). The effect of photopatch testing to produce identical pigmentation at test sites lends credence to the notion that ultraviolet radiation plays a role in disease development (Vinay et al., 2021).

3.3 | Type IV hypersensitivity reaction

Type IV hypersensitivity reaction is thought to be the most generally accepted pathogenesis. Since Riehl's melanosis prefers locations where contactants such as fragrance and other cosmetic product components have been applied, allergic sensitization caused by repeated exposure to low concentrations of endogenous and exogenous allergens might be the primary cause (Choi et al., 2022). Chronic inflammation of the local skin under long-term low concentration stimulation leads to a type IV cytolytic reaction characterized by basal cell liquefaction and degeneration, resulting in anomalies in the production, transport, distribution, and degradation of melanin granules in the epidermal keratin-forming cells. Once the basement membrane is damaged, the melanin granules are disrupted, and melanins from the destroyed cells drop into the superficial dermis

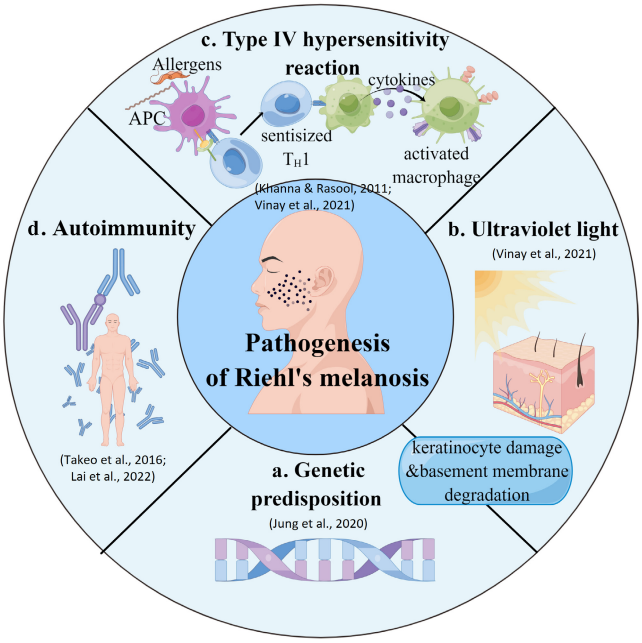

FIGURE 1 Possible pathogenesis of Riehl's melanosis. The pathological mechanism including genetic predisposition (a) that remains to be investigated, ultraviolet light (b) stimulation, type IV hypersensitivity reaction (c), and autoimmunity disorders (d). *By Figdraw.*

(Khanna & Rasool, 2011; Vinay et al., 2021). They are phagocytosed and deposited by specific macrophages, giving rise to the formation of melanophages and pigment incontinence. To clearly determine the etiology of hyperpigmentation, suspected allergen challenge tests or repeated treatments with the incriminated substance might be used (Costescu et al., 2017).

3.4 | Autoimmunity-related presumption

Riehl's melanosis/Riehl's melanosis-like pigmentation has been constantly reported coexisting with other diseases, for instance, lichen planus (Seike et al., 2003), Idiopathic choroidal neovascularization (CNV) (Wu & Li, 2007), acquired immune deficiency syndrome (AIDS) (Hanada et al., 1994), Sjogren's syndrome (SS) (Miyoshi & Kodama, 1997; Takeo et al., 2016), lupus erythematosus, and thyroiditis (Lai et al., 2022). Despite the lack of explanation for these cases, experts hypothesized that Riehl's melanosis was a cutaneous manifestation of autoimmunity. Riehl's melanosis has been thought to be an uncommon cutaneous manifestation of systemic lupus erythematosus (SLE) (Algarra et al., 2020) or SS (Miyoshi & Kodama, 1997).

Anti-SSA (Ro) positive expression on the keratinocytes is likely to cause the development of melanosis, and ultraviolet irradiation is thought to play a role in anti-SSA (Ro) antibody positive patients since the pigmentation disappeared with ultraviolet protection. One hypothesis is that anti-SSA acts on extracellular matrix (ECM) and that excessive or inadequate ECM degradation contributes to autoimmune pathologic disorders (Lisi et al., 2009).

4 | DIAGNOSIS

It remains challenging to distinguish Riehl's melanosis from other hyperpigmentation using one single approach. Here we summarize a couple of feasible methods for diagnosis.

4.1 | Clinical manifestation

The clinical manifestations of Riehl's melanosis are diverse in pigmentation patterns and colors. Lesions usually begin from the forehead and temples, spreading to the rest of the face, as well as the chest, neck, scalp, hands, and forearms, while those caused by textiles often affect the anterior portion of the thighs and axillae (Khanna & Rasool, 2011). The most characteristic rash is diffuse-to-reticulated pigmentation (Yoo, 2022), which is usually brown or blue-gray in color. In most cases, pigmentation is the only symptom of the disease (Costescu et al., 2017). It is sometimes preceded by sudden onsets of erythema and pruritis. Satellite perifollicular pigmented macules and scaly follicular hyperkeratosis are also seen. According to the global consensus in 2018, the most typical manifestations can be defined as "numerous fine (few millimeters in size) or reticulate, acquired macules of pigmentation of uncertain etiology occurring on the face, neck, and upper chest" (Kumarasinghe et al., 2019).

4.2 | Dermoscopy

Dermoscopy has proved to be a noninvasive method for diagnosing Riehl's melanosis. The most common findings are pseudonetwork patterns with brown/gray dots/globules grouped in an arcuate, semiarcuate, or hexagonal way (Honigman & Rodrigues, 2022; Yim et al., 2019). Telangiectatic vessels, tiny scales, perifollicular hypopigmented halos, and follicular keratotic plugs can also be seen (Krueger et al., 2022; Subburaj et al., 2022).

Vinay et al. established a severity score criterion. In addition to diagnosis, dermoscopy may be used to evaluate disease severity (Vinay et al., 2017). Based on dots, globules, and blotches density and pattern, four dermatoscopic disease severity classifications were established. Grade 1 has mostly random dots which are sparsely distributed and light brown maculo-patches. Grade 2 is mostly dots with occasional globules structured as broken lines and semiarcuate formations resembling Chinese lettering. Grade 3 has reticulate dots and globules with occasional blotches. Grade 4 includes thick spots, globules, and blotches that destroy the pigment network. Most grade 4 patients have widespread brownish black coloring.

4.3 | Reflectance confocal microscopy

Reflectance confocal microscopy (RCM), also known as confocal laser scanning microscopy (CLSM) or skin computer tomography (CT) (Lu et al., 2019), has been used to evaluate various skin conditions

through the construction of three-dimensional structures from sets of images obtained at different depths, demonstrating good correlation with histopathological results while preserving the normal functions of cells and tissues.

The most distinguishing features of Riehl's melanosis (Lu & Jiang, 2021) under RCM are as follows: (a) Round-to-polygonal bright structures indicative of epidermal inflammatory cell infiltration, (b) basal layer vacuolization and degeneration presented as obscured papillary rims and obliteration of the high refractive ring-like structure around the dermal papillae (Wang & Xu, 2014), (c) the existence of pigment incontinence, which is characterized by a considerable amount of melanophages that are visible as brightly refractile, plump, oval to stellate-shaped cells, and monocytes infiltrated in the layer of superficial dermis, (d) dilated vessels appearing as prominent round or linear dark canalicular structures, (e) mildly-refractive and round-to-polygonal cells surrounding the dermal vessels signifying perivascular inflammatory cell infiltration, (f) dilated infundibulum appearing as black round or oval lumina, (g) highly refractive material within the infundibula indicated hyperkeratotic adnexal infundibula.

4.4 | Patch testing and photopatch testing

Patch testing and photopatch testing are routine diagnostic tests (Costescu et al., 2017) for contact and photocontact allergies (Sachdeep et al., 2022). Patch testing is performed using standard series, cosmetic series, and fragrance series comprised of indigenous allergens to which the local population is particularly more susceptible, and the International Contact Dermatitis Research Group (ICDRG) scoring system is often used to evaluate the results. Photopatch testing may result in similar pigmentation at patch test locations, indicating that UV plays a role in disease pathogenesis (Vinay et al., 2021). The interpretation of photopatch testing should be performed in accordance with standard photopatch criteria.

If patch or photopatch testing is negative or equivocal, due to the low concentration of the allergen in cosmetic and fragrance series, repeated open application test (ROAT) can be considered. In case of an equivocal result in ROAT done on the forearm, the test may be repeated with the patient's cosmetic over the affected face or regions (Shenoi & Rao, 2007).

Patch testing and photopatch testing can be helpful in diagnosing Riehl's melanosis and identifying the causative agents. The percentage of positive patch test results varied across studies, but generally most of them reporting high rates of positive results in Riehl's melanosis patients. For instance, Choi et al. (2022) reported positive patch test results in 76.5% of patients. Teinthavorn (2013) compared provisional diagnosis and actual cases with a positive patch test result by diagnosis. Those that were diagnosed with PCD had positive patch tests in 80% of cases, higher than LPP and AD. Bishnoi el al. reported that out of 108 patients diagnosed as ADMH, 39 (36.1%) had positive patch/photopatch tests (Bishnoi, Vinay, Arshdeep, et al., 2019; Bishnoi, Vinay, Kumaran, & Parsad, 2019).

Nickel, cobalt, and benzyl salicylate are the most common sensitizing agents, while hair dye is another potential agent. According to Bishnoi et al., 35 of 39 patients had a positive reaction to their own hair coloring products, while 16 of 39 patients showed a positive reaction to allergens from commercial ones, with the most common being paraphenylenediamine. Positive patch test results to hair coloring agents, in the absence of telltale signs of contact dermatitis, are considered important findings in diagnosing Riehl's melanosis. In cases where henna is suspected as a cause of Riehl's melanosis, patch testing with commercially available natural henna powders in 10% aqueous solutions can be done. Woo el al. observed a 100% (5/5) positive reaction to henna extract in patients with PCD (Woo et al., 2018).

The role of sun exposure is crucial as a causative and aggravating factor, and some allergens become activated only by exposure to sunlight. Photopatch testing can help identify the joint impact of allergen and sunlight (Sachdeep et al., 2022). Photopatch testing yielded positive results in seven out of 39 patients of ADMH, which is less sensitive that patch test. Delayed pigmentation was noted later with positive photopatch tests (Bishnoi et al., 2019, 2019b).

4.5 | Histopathology

The gold standard for diagnosis remains a skin biopsy. The predominant histological hallmark is basal layer vacuolar degeneration, which results in pigment incontinence, along with the involvement of pilosebaceous units, accompanied by increased melanophages into the dermis (Park et al., 2012; Serrano et al., 1989). Furthermore, lymphocytes, mononuclear cells, and eosinophil infiltration cause perivascular inflammatory cell infiltration, epidermal and dermal inflammatory cell infiltration, and interface changes. The majority of perilesional normal-appearing skin in Riehl melanosis has typical histological abnormalities, although reduced to a minor extent (Kim et al., 2020). However, the histopathology results are all nonspecific. Interface dermatitis is not necessarily a feature required to diagnose Riehl's melanosis.

4.6 | Multimodality skin imaging system

Patients are often hesitant to have face biopsies due to the discomfort, suffering, and possible hazards. As a result, it is critical to developing an innovative way to prevent invasive surgery while obtaining a clear diagnosis. Shen et al. used the multimodality skin imaging analysis systems, containing a cellular resolution optical coherence tomography (OCT) and new skin diagnosis system, to investigate whether it could improve diagnostic accuracy and enable the noninvasive, real-time evaluation of Riehl's melanosis, or other pigmentary diseases (Shen et al., 2022).

Promising results showed that cellular resolution OCT accurately depicted the details of the skin, which corresponded to histological features such as increased melanocyte capping, disrupted

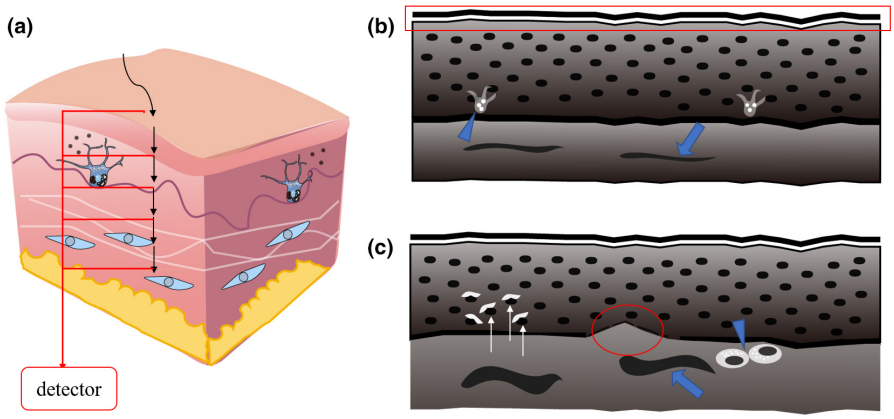

FIGURE 2 The theory of OCT, features of normal skin and hyperpigmented lesional skin of Riehl's melanosis on cellular resolution OCT. (a) OCT technology uses light to illuminate the skin and analyze the returning light to produce cross-sectional pictures of the skin. (b) Normal skin on OCT. The areas shown in the red box are stratum corneum (with an upper hyper-reflective layer and a gray-black zone) and the stratum granulosum with a thin layer of hyper-reflective cells. A grayish-thick area below is stratum spinosum layer with rounded, tiny, hypo-reflective keratinocytes. The basal cell layer occasionally displays the hyper-reflective melanin (shown in blue triangle). Separated by dermal-epidermal junction, the cutaneous region has an irregular pattern with embedded black linear blood veins (shown in blue arrow). (c) Riehl's melanosis lesion on OCT. Hyper-reflective supranuclear capping can be seen (shown in white arrow). The dermis also exhibits hyper-reflective melanophages (shown in blue triangle) and spots with a doughnut shape. Degeneration of basal keratinocytes is shown by a blurred DEJ (shown in red circle). Dermal inflammation is indicated by irregular acanthosis and vessels dilating (shown in blue arrow).

basement membrane, telangiectatic blood vessels, and melanophages in the dermis. Intriguingly, the advanced skin diagnosis system can also detect subclinical erythema of the skin, highlighting the inflammatory nature of the disease, thus intuitively reflecting the pathohistological changes in Riehl's melanosis (Figure 2). As compared to other approaches, this strategy may lower the visual detection threshold and highlight the areas of concern more than other methods.

4.7 | DPASI: Scoring system to assess severity

For a long time, there was no quantitative technique to quantify disease severity in ADMH, which made reliable evaluation of medication response and patient counseling on disease severity extremely difficult. Acquired dermal macular hyperpigmentation area and severity index (DPASI) (Bhor & Pande, 2006; Vinay et al., 2021) is an objective scoring system that attempts to grade the disease severity of ADMH involving the face and neck through dividing the above areas into six different segments in which the disease severity is assessed by dermatoscopy and multiplied by a multiplication factor. To determine the reliability and validity of DPASI, Kumaran evaluated 55 patients and revealed it could serve as a relatively validated instrument for quantitatively assessing disease severity in ADMH, including Riehl's melanosis.

5 | TREATMENT AND MANAGEMENT

The treatment of Riehl's melanosis remains inconclusive. Patients must strictly adhere to general instructions (Pérez-Bernal et al., 2000). For example, if an allergen has been identified, avoidance of the suspected causal agents is essential in preventing disease progression (Vinay et al., 2021). In the following sections, we will discuss the latest therapies and advanced treatment options in the past decade (Table 1).

5.1 | Topical skin-lightening agents

Topical whitening treatments comprising hydroquinone, tretinoin, glycolic acid, or azelaic acid have been used to treat Riehl's melanosis. Hydroquinone inhibits the tyrosinase enzyme, which prevents the conversion of dopa to melanin. Inhibition of DNA and RNA production, degradation of melanosomes, and death of melanocytes are additional hypothesized mechanisms of action. According to clinical research, 2% (Chan & Ma, 2019) or 4% hydroquinone cream (Choi et al., 2019; Pérez-Bernal et al., 2000) has a therapeutic effect on Riehl's melanosis.

Recently, Chan and Ma (2019) described a case of PCD induced by hair dyes and moisturizers containing hydrocarbon oils in a patient who was treated with topical Lignin Peroxidase (LiP) cream. LiP is a naturally occurring ligninolytic enzyme found in the extracellular medium of *Phanerochaete chrysosporium*. LiP may oxidize and denature aberrant melanin in the skin that resembles lignin biologically. Clinical evidence revealed that crude LiP decolorizes synthetic melanin. This was further shown by the findings of another research demonstrating that LiP acts as a melanolytic enzyme capable of breaking down melanin in human skin. The LiP cream had a much more rapid impact on skin whitening than the tyrosinase inhibitor (Draelos, 2015). In the case study, LiP cream used twice a day for 6 months was well tolerated and effective without adverse effects.

TABLE 1 Summary of advanced treatments of Riehl's melanosis.

Author	Article	Year	Patients	Treatment	Follow-up	Results	Complications
Chan et al	Case report	2019	1 (Chineses, Fitzpatrick skin type III, hair dye-induced)	Topical Lignin Peroxidase (LiP) cream twice a day	6 months	The patients had a gradual improvement of the hyperpigmentation, skin texture and roughness	None
Kwon et al	Pilot study	2017	8 (Koreans, Fitzpatrick skin type III to V, recalcitrant)	Low-fluence Q-switched 1064-nm Nd:YAG laser at 3-week intervals, 4% hydroquinone cream every night and oral tranexamic acid 250 mg/d	54 weeks	3/8 "almost clear" grade 5/8 "marked improvement" grade	None
Xu et al	Pilot study	2018	10 (Chinese, Fitzpatrick skin type III to V, recalcitrant)	Oral tranexamic acid (250 mg/d twice a day) with Glycyrrhizin compound (50 mg/d three times a day) for 3 months Oral tranexamic acid 200 mg/d twice a day alone for 3 months	6 months	7/10 "marked improvement" 2/10 "moderate improvement" 1/10 "minimal improvement"	None
Wang et al	Case report	2019	3 (Chinese, Fitzpatrick skin type III to IV)	Glycyrrhizin compound (150 mg/d), vitamin C (100 mg/d), and salicylic acid 30% peels once every 2 weeks	6 months	All patients received obvious improvement	None
Li et al	Pilot study	2011	6 (Chinese, Fitzpatrick skin type V)	Intense Pulsed Light(filters of 590, 640, and 694 nm, with fluences ranging from 11 to 17 J/cm2)	6 months	5/6 "good improvement" 1/6 "excellent improvement"	Postinflammatory hyperpigmentation occurred in one case but resolved in 1 month
Smucker et al	Case report	2014	1 (American, failure of IPL therapy)	532-nm Q-Switch FD Nd:YAG Laser(with the fluence of 400 mJ/cm2(1st)-800 mJ/cm2(2nd-3rd)) at monthly intervals	5 months	The patient significantly improved	Five days of erythema
On et al	Case report	2015	2 (Koreans, hair dye-induced)	Low-pulse energy 1064-nm Q-switched Nd:YAG laser(with the fluence of 1.8 J/cm2, a 8-mm spot size) at three-week intervals	51 weeks	Both patients demonstrated marked clinical improvement	None
Chung et al	Pilot study	2014	6 (Koreans, Fitzpatrick skin type III to IV)	Dual-pulsed 1064-nm Q-switched Nd:YAG laser(a dual pulse mode with the fluences from 2.0 to 4.0 J/cm2, a spot size of 7 mm and frequency of 10 Hz) every 2 weeks for 4 months	20 weeks	4/6 "marked improvement" 2/6 "moderate improvement"	None
Cho et al	Retrospective Study	2020	21 (Koreans, Fitzpatrick skin type III to IV)	Mid-Fluence Q-Switched Nd:YAG 1064-nm Laser(3.5-5 J/cm2 with a spot size of 5 mm and a pulse rate of 10 Hz)at a 4-week interval	8 months on average	6/21 "moderate improvement" 8/21 "much improvement" 2/21 "very much improvement"	No severe side effect

TABLE 1 (Continued)

Author	Article	Year	Patients	Treatment	Follow-up	Results	Complications
Choi et al	Retrospective Study	2019	10 (Korean, Fitzpatrick skin type III to IV)	1064-nm Nd:YAG Laser(with the fluence from 0.9 J/cm2 to 2.0 J/cm2, a 7-mm-sized spot and frequency of 10 Hz) at 3-week intervals with 4% topical hydroquinone	81 weeks	7/10 "near total improvement" 2/10 "marked improvemt" 1/10 "minimal improvement"	Three patients complained of guttate hypopigmentation
Iwayama et al	Case report	2020	1 (Japanese, Fitzpatrick skin type IV, henna-induced)	755-nm picosecond alexandrite laser(fluence gradually increased by 0.25 (1st)–0.71 (7th) J/cm2, and pulse width was 750 ps) at 4-week intervals	28 weeks	The patient had substantial improvement	None
Kim et al	Retrospective Study	2020	9 (Koreans, Fitzpatrick skin type III to IV)	Non-Ablative 1927 nm Fractional Thulium Fiber Laser (with settings of 5 W for the output power and 10–20 mJ for the pulse energy) at monthly intervals	7 months	6/9 "marked improvement" 1/9 "significant improvement" 2/9 "moderate improvement"	Mild erythema which faded away within 3 days

5.2 | Oral tranexamic acid

Tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine (Kim & Lim, 2022) that blocks the contacts between melanocytes and keratinocytes by suppressing the activity of epidermal melanocyte tyrosinase. This is accomplished by inhibiting the plasminogen/plasmin system. TXA is widely used in several pigmentation diseases, especially melasma, with an effective dosage range from 250 mg/d to 500 mg/d for a treatment period of 8 to 12 weeks.

Kwon et al. (2017) performed a prospective pilot study in which they gave eight patients suffering from recalcitrant Riehl's melanosis 250 mg of TXA every day, in addition to using 4% hydroquinone cream every night and undergoing Q-Switched Nd: YAG laser treatments at a 3-week interval. Three and five patients, respectively, obtained the result of "almost clear" and "marked improvement". Their conclusions indicated that consistent administration of these three modalities over extended durations would dramatically ameliorate frustrating Riehl's melanosis conditions without obvious adverse effects.

5.3 | Glycyrrhizin compound

Over many years, glycyrrhizin, which is comparable to corticosteroids in terms of pharmacological efficacy but with fewer and less severe adverse effects, has been used to treat a number of dermatological disorders efficiently. According to previous research, glycyrrhizin has a variety of effects, including anti-inflammatory, antiviral (Shimshak et al., 2022), anti-allergy, anti-carcinogenesis, and antithrombin properties. The inhibition of monocyte migration and induction of apoptosis is a plausible explanation for the mechanism of glycyrrhizin therapy in Riehl's melanosis.

The effectiveness of glycyrrhizin compound for recalcitrant Riehl's melanosis in conjunction with oral TXA was tested in a prospective pilot study conducted by Xu et al. (2019) in China. During the first 3 months of their therapy, 10 patients got a combination of 500 mg TXA and 150 mg glycyrrhizin, followed by 500 mg TXA alone for the last 3 months. All patients improved with no adverse responses seen at 3 and 6 months, and 70% of them demonstrated a significant decrease in their melanin index. On the basis of this result, it appears that recalcitrant Riehl's melanosis may benefit from an effective and safe treatment that combines the oral administration of TXA and a compound containing glycoryrhizic acid.

5.4 | Chemical peels

A chemical peel is chemexfoliation, a process of application of a chemical substance to the skin that causes controlled chemical destruction of the epidermis with or without part of the dermis leading to skin regeneration and remodeling (Rani & Ahuja, 2022).

Alpha hydroxy acid and salicylic acid, which are the most common treatments in treating Riehl's melanosis, have anti-inflammatory and whitening effects by inhibiting the production of prostaglandin and tyrosinase, inducing a rapid differentiation of keratinocytes, an upward transfer of melanosomes with necrotic keratinocytes and enhanced transport by melanophages.

Wang et al. (2020) investigated the effectiveness of a triple combination therapy in treating Riehl's melanosis in Chinese patients. The therapy included 30% salicylic acid chemical peels once every 2 weeks, oral glycyrrhizin compound 150 mg/d, and vitamin C 100 mg/d. All three patients showed significant improvement after 4 to 6 months of follow-up, and none of them reported any negative side effects.

Rani et al. (Rani & Ahuja, 2022) utilized 33% glycolic acid and 7% kojic acid in six PCD patients along with a continuation of topical treatment because the patients had previously shown very limited improvement. Visible clinical improvement was found in all patients after a total of 15 or 16 treatment sessions, and there were no adverse effects seen. In addition to topical demelanizing medications and stringent sun protection while avoiding allergy triggers, a chemical peel can be administered as an adjuvant therapy.

5.5 | Lasers and light therapies

Laser therapy is unsatisfactory for the treatment of Riehl's melanosis and should be tried only after other therapeutic alternatives have failed. Possible alternatives include intense pulsed light, 1064-nm Q-Switched Nd: YAG Laser, 755-nm PicoWay, and non-Ablative 1927-nm fractional thulium fiber laser.

5.6 | Intense pulsed light

Because of its broad wavelength range of 500–1200 nm, intense pulsed light (IPL) has been used to treat pigmentary dyschromia in the epidermis and dermis, such as melasma and Riehl's melanosis, by producing microcrusts and eliminating melanin granules through photothermal effects (Oiso et al., 2010). Furthermore, heat damage to the papillary and upper reticular dermis promotes fibroblast activation and stimulates the formation of new collagen and extracellular matrix, which ultimately leads to an improvement in the appearance of photoaged skin.

Li et al. (2011) applied intense pulsed light in a split-face way to treat six cases of Riehl's melanosis with a satisfactory consequence after a 6-month follow-up, yet one patient reported postinflammatory hyperpigmentation (PIH). They hypothesized that accelerated keratinocyte differentiation, an upward transfer of melanosomes with necrotic keratinocytes, the breakdown of pigment deposits in the dermis, and faster transport by melanophages were responsible for this effect of IPL (Gold, 2011). According to Cai et al. (2022), IPL may be utilized as a preliminary or supplemental therapy for Riehl's melanosis.

5.7 | 1064-nm Q-Switched Nd: YAG Laser

The low-fluence Q-Switched Nd: YAG laser has been a canonical treatment modality for melasma. The theory of mechanism is proposed to induce nonablative and selective photothermolysis, which is an ultrashort, nanosecond bursts of energy that can precisely target lesional melanophages and cause subcellular damage to the melanin particles within the melanophages.

Smucker and Kirby (2014) first reported an American patient with Riehl's melanosis who failed IPL therapy and turned to monthly 532-nm Q-Switch frequency-doubled (FD) Nd: YAG laser 400 mJ/cm2 the first time and 800 mJ/cm2 the second and third times. The patient was treated for 3 months and reported remarkable improvement after the last treatment. On et al. (2015) reached a similar conclusion in two cases of Riehl's melanosis treated with a low-pulse energy 1064-nm Q-Switched Nd: YAG laser that had less effect in inducing inflammation compared to 532-nm Q-Switched Nd: YAG laser.

However, standard low-fluence Q-Switch FD Nd: YAG laser treatment for Riehl's melanosis, especially during the erythematous stage, may increase the risk of PIH. Based on this issue, Chung et al. (2014) presented a case series of Riehl's melanosis that was effectively treated with a novel Q-switched Nd: YAG laser operated as a dual-pulse at half-fluence and 140 s intervals, with four and two patients exhibiting marked and moderate improvement without any side effects. According to the team's basic research, the conventional mode considerably enhanced proinflammatory transcription factors and cytokines compared to the dual pulse mode.

Other possible adverse effects include hypopigmentation or rebound aggravation (Kim et al., 2013). Choi et al. (2019) found guttate hypopigmentation in three of 10 patients treated with low-fluence 1064-nm Nd: YAG laser and 4% topical hydroquinone, which may be caused by melanogenesis impairment rather than melanocyte apoptosis. However, the laser treatment terminated early at the hypopigmentation spot, preventing additional pigmentary alteration and leading to self-improvement.

Another concern is that the low-fluence laser has only a marginal effect on Riehl's melanosis pigmentation because it is deeper and larger. Cho and Roh (2020) made an attempt to validate the hypothesis that a mid-fluence Q-Switched Nd: YAG 1064-nm laser may reach a more beneficial effect. As a result, 76.1% of patients improved moderately or significantly, with no severe side effects. The team hypothesized that Riehl's melanosis would respond well to a mid-fluence laser because of the presence of dermal melanophages in the upper dermis.

5.8 | 755-nm PicoWay laser

Picosecond lasers are effective in treating hyperpigmentation conditions like melasma and PIH. As melanosomes' thermal relaxation time is longer than a 755-nm picosecond alexandrite laser's pulse duration, a picosecond alexandrite laser may strongly and selectively photothermal and photodisrupt melanosomes by irradiating melanin.

Iwayama et al. (2020) treated a Japanese woman with henna-induced Riehl's melanosis safely and successfully using a 755-nm picosecond alexandrite laser, with no adverse events during follow-up, implying 755-nm PicoWay laser might be a safe and effective option for treating Riehl's melanosis.

5.9 | Nonablative 1927-nm fractional thulium fiber laser

The nonablative 1927 nm fractional thulium fiber laser (TFL) targets superficial skin layers like the epidermis and papillary dermis because of its high water absorption. By targeting epidermal cells, the thulium laser restores dermo-epidermal junction disruption, produces upper dermis neocollagenosis and elastinogenesis, and lowers inflammation.

TFL has been successfully applied in treating PIH, which has a pathophysiology and histology comparable to Riehl's melanosis. Thus, Kim et al. (2021) investigated whether TFL may alleviate hyperpigmentation in Riehl's melanosis. Surprisingly, all patients showed a medium or higher response. TFL targets the epidermis and upper dermis with few side effects, although its shallow penetration may limit its treatment of Riehl's melanosis if it has pigmentation in both layers.

5.10 | Novel therapy techniques: New Pulsed-Type microneedling radiofrequency

Recently, a novel radiofrequency (RF) device with a brief pulse length was unveiled. Park et al. (2022) evaluated the efficacy and safety of a pulsed-type microneedling RF device for the treatment of Riehl's melanosis, and the majority of patients showed clinical improvement after treatment with decreased expression of CD44 and b-FGF. No serious adverse events were observed, suggesting that pulsed-type microneedling RF could be a promising treatment option for Riehl's melanosis.

6 | RESEARCH ADVANCES

Recent research on Riehl's melanosis generally focuses on the pathomechanisms of this disease such as promising pathways, biomarkers, and comorbidities, mostly autoimmune-related disorders (Figure 3).

6.1 | Potential biomarkers for Riehl's melanosis

Jung et al. (2020) have studied the role of GDA in Riehl's melanosis, of which the expression is increased in the lesions. The authors revealed that GDA could promote melanogenesis by upregulating stem cell factor (SCF) and endothelin-1 (ET-1), suggesting that GDA expression on keratinocytes can be novel biomarkers for the disease. Their finding also implicates the underlying function of epidermal keratinocytes in the development of Riehl's melanosis.

Woo, Jung, et al. (2020); Woo, Park, et al. (2020) further discussed the impact of these paracrine melanogenic molecules above secreted by keratinocytes, fibroblasts, and endothelial cells in Riehl's melanosis. They found the expression of SCF/c-kit and ET-1 was elevated in Riehl's melanosis, speculating that UV exposure and inflammation could upregulate the production of SCF and interact with ET-1. Moreover, the increased number and proliferation of mast cells are considered to be related to the activation of SCF itself and melanocytes via the SCF/c-kit pathway. Targeting cutaneous SCF/c-kit and ET-1 may represent promising management options for Riehl's melanosis.

Another recent study by Woo et al. (2021) validated the increased expression of estrogen receptor (ER) β and progesterone receptor (PR) in both the epidermal and dermal layer of Riehl's melanosis, strengthening the paracrine effect on the microenvironmental change in the vasculature and fibroblasts in the dermis. Keratinocytes expressing ERβ might have the potential to stimulate the epidermal melanin unit in Riehl's melanosis. Estrogen can induce the increased expression of KGF from keratinocytes while progesterone can increase the number of infiltrating dermal dendritic cells and regulate the proliferation of endothelial cells, thus increasing pigment production and deposition.

In addition to keratinocytes, dermal fibroblasts play an important role in pigmentation. Xu et al. demonstrated that the fibroblast-derived protein CCN1, which is overexpressed in the dermis of solar lentigines and Riehl's melanosis and may be activated by UV radiation, might be a viable target for the treatment of hyperpigmentation disorders (Xu et al., 2018). They discovered that CCN1 released by UVB-irradiated human cutaneous fibroblasts induces normal human epidermal melanocyte (NHEM) melanogenesis on both transcriptional and translational levels. Moreover, their results uncovered that CCN1 promotes melanogenesis via binding to the integrin a6b1 receptor on NHEMs, which activates the p38 mitogen-activated protein kinase (MAPK) and ERK1/2 signaling pathways, resulting in the activation of microphthalmia-associated transcription factor (MITF), tyrosinase related protein-1(TRP-1), and tyrosinase.

6.2 | Comorbidity with autoimmune disorders

As mentioned in the pathogenesis of Riehl's melanosis, other autoimmune disorders accompanied by Riehl's melanosis may indicate the potential "coworker" relation between these diseases.

Besides the possible role of anti-SSA (Ro) in the Riehl's melanosis-like eruptions associated with primary Sjögren's syndrome, Takeo et al. (2016) reported an association with specific types of human leukocyte antigen (HLA) and infiltrating lymphocytes in three similar cases, carrying the presumption that specific HLA loci HLA-A2, DPA1 (02:02), and DPB1 (05:01) represent the specific HLA subset of pigmented cosmetic dermatitis-like eruptions, while subsets of T cells infiltrated in the dermis are mainly CD8 and CD45RO. Moreover, the coexistence of Riehl's melanosis with autoimmune thyroid disease was reported by Lai et al. (2022) and Song et al. (2018). They

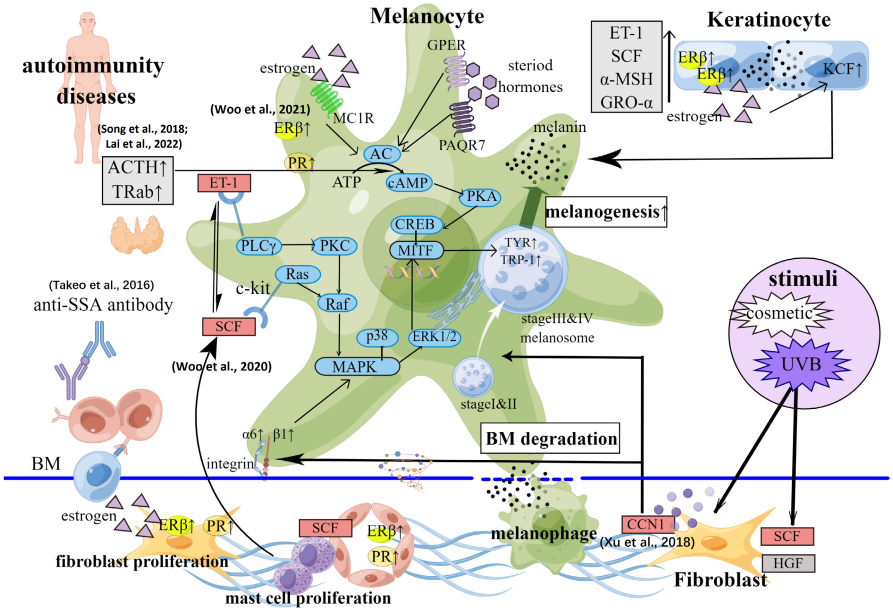

FIGURE 3 The potential mechanism of Riehl's melanosis. UV light and other allergy simulations trigger fibroblasts to produce CCN1, SCF, and HGF. CCN1 then operates on the integrin pathway (especially α6β1) and stimulates melanosome maturation, both of which induce melanogenesis. In Riehl's melanosis, the production of paracrine melanogenic substances such as SCF, ET-1, ERβ, and PR produced by keratinocytes, fibroblasts, and endothelial cells is increased and interacts with one another. Autoimmune illnesses such as autoimmune thyroid disease and Sjögren's syndrome may contribute to the melanogenesis of Riehl's melanosis by increasing ACTH, TRab, and the anti-SSA antibody. *By Figdraw.*

speculated the elevation of adrenocorticotrophic hormone (ACTH) and anti-TSH receptor antibody (TRab) could stimulate the production of cAMP, promoting the proliferation and differentiation of melanocytes, leading to the hyperpigmentation of skin (Lai et al., 2022). ACTH is the activator of melanocortin 1 receptor (MC1R), which can activate adenylate cyclase, and increase intracellular cAMP synthesis. The major biological effects of cAMP are mediated through cAMP-dependent protein kinase A (PKA) which results in the phosphorylation of cAMP response element-binding protein (CREB) and the induction of MITF gene expression. MITF upregulation induces tyrosine expression, resulting in the increase of melanogenesis (D'Mello et al., 2016; Videira et al., 2013). In the meanwhile, TRab acts on thyroid stimulating hormone (TSH) receptors and mimics the action of TSH through activating G protein and stimulating the cAMP/PKA pathway. Addison's Disease and Nelson Syndrome were shown to be associated with hyperpigmentation (Lin & Fisher, 2007; Park et al., 2009; Slominski et al., 2004), suggesting the potential correlation between ACTH and Riehl's melanosis.

7 | DISCUSSION

Riehl's melanosis is an acquired dermal macular hyperpigmentation disorder that commonly manifests as a reticulate gray-brown to black pigmentation on the face and neck. When there is a history of specific contact allergies, the condition is known as pigmented contact dermatitis (PCD). With an increasing understanding of this condition, dermatologists must appropriately identify and define it. To achieve much-needed consistency, global consensus should be regularly developed and updated.

The pathogenesis of Riehl melanosis remains to be elucidated. However, it is thought to be caused mostly by contact sensitivity. Repeated exposure to low concentrations of allergens causes a type IV hypersensitivity response in PCD patients, culminating in basal cell vacuolization and melanin incontinence. Pathological studies point to the role of subclinical damage or inflammation in the development of pigmentation. During the COVID-19 outbreak, mask-covered skin becomes vulnerable to contact dermatitis, due to multiple potential allergens on the masks (Kim & Lee, 2021), which may give rise to elevated incidence of Riehl's melanosis.

The precise diagnostic criteria for Riehl melanosis have not been clearly defined. A patch or photopatch test may be useful in identifying potential causal factors. Meanwhile, dermoscopy, reflectance confocal microscopy, skin diagnostic imaging, and innovative high-resolution OCT analyses may be useful diagnostic techniques. Because histopathology is frequently identical between Riehl's melanosis, LPP and ashy dermatoses, we need to establish a standard diagnostic process as well as a validated scoring system that can demonstrate severity assessment to maintain consistency in reporting results across different research groups, which is instructive for individual managements (Kang, 2012; Park et al., 2012).

Treatment for Riehl's melanosis has always been challenging and disheartening. Aside from a few pilot trials, no systematic treatment regimen has been validated. Legislation restricting the use of allergens in cosmetic goods may ensure long-term treatment

and prevention of PCD. Apart from conventional medication such as topical skin-lightening agents (hydroquinone and tretinoin), oral tranexamic acid, glycyrrhizin compound, and chemical peels (alpha hydroxy acid and salicylic acid), new therapeutic options must be decoded in addition to general instructions such as topical sunscreen application, avoidance of excessive sun exposure, and long-term administration of vitamin C. LiP, a combination of oral tranexamic acid and glycyrrhizin compound, a combination of glycyrrhizin compound, vitamin C, and salicylic acid may open up new avenues for therapy, particularly for refractory patients.

Excessive light stimulation might result in several negative effects if laser procedures are not standardized. Although intense pulse light has been shown to be beneficial, it may trigger postinflammatory hyperpigmentation. Long wavelength lasers, such as the 1064 nm Q-switched Nd: YAG laser, may penetrate deeper into the dermis and are therefore often used to treat dermal pigmentation. Nevertheless, the most appropriate fluence should be explored to prevent hypopigmentation or rebound aggravation. Recent research has also shown that 755-nm PicoWay, nonablative 1927-nm fractional thulium fiber Laser, and novel pulsed-type microneedling radiofrequency may effectively treat Riehl's melanosis. TFL may be useful in the treatment of PIH followed by various conditions, including Riehl's melanosis. Randomized clinical trials are required to testify to the efficacy of these novel therapies.

Pathomechanism studies in the hyperpigmentation of Riehl's melanosis have recently been undertaken on a cellular or molecular level. GDA, SCF/c-kit and ET-1, ER, PR, and CCN1 are among the promising biomarkers in Riehl's melanosis. The role of paracrine melanogenic molecules and immune responses caused by intrinsic or extrinsic factors has been proposed. Further studies may focus on the exploration of other biomarkers and pathways, the interaction between keratinocytes, fibroblasts, endothelial cells, and melanocytes, and the potential relationship between Riehl's melanosis and autoimmunity disorders.

With the deepening of our understanding of Riehl's melanosis, we will eventually be able to wipe this stubborn muck off the face.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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