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Contents

Editorial

In this new issue of the *International Journal of Pediatric Dermatology*, the remarkable breadth and complexity of some skin disorders affecting children and adolescents worldwide clearly emerges. These conditions range from preventable environmental exposures to rare genetic diseases that remain challenging to treat. The articles presented here highlight the progress achieved in the management of several pediatric dermatologic conditions and the persistent gaps in sun protection strategies.

Kessaris and colleagues provide a timely and much-needed systematic review of sun protection guidelines for children and young people, revealing a striking inconsistency among existing recommendations, despite the well-established role of ultraviolet radiation as the leading cause of melanoma and non-melanoma skin cancer. Particularly compelling is the attention devoted to children with skin of colour, who, although often perceived as lower risk, frequently experience delayed diagnoses and poorer outcomes. This work underscores the urgent need for shared, evidence-based guidelines that account for ethnic and phototype-related differences.

Wright and Rein offer a precise description of the management of chronic bullous disease of childhood in a resource-limited setting, where the absence of immunofluorescence testing required reliance on clinical acumen and pragmatic therapeutic decisions. Their case serves as a powerful reminder that diagnostic investigations must never overshadow the value of careful observation and thorough clinical assessment.

Casati and Lucchini present a case of Staphylococcal Scalded Skin Syndrome (SSSS) in which early recognition was complicated by the initial suspicion of sunburn. The authors emphasize the importance of considering SSSS in any acute bullous eruption in children, particularly when a recent staphylococcal infection is reported. Prompt identification remains essential to ensuring rapid and effective treatment.

The theme of diagnostic complexity also emerges in the case of Symmetrical Acrokeratoderma reported by Bhat and Pujar, which had been misinterpreted for nearly a decade due to its resemblance to other acral hyperkeratotic conditions. The authors remind us that aquagenic maceration and seasonal variation are two highly valuable clinical clues that can support the diagnosis of Symmetrical Acrokeratoderma and help prevent unnecessary diagnostic delays.

Finally, Wahab and colleagues provide a comprehensive narrative review of Porokeratotic Eccrine Ostial and Dermal Duct Nevus, reframing this rare condition as a potential marker of genetic mosaicism and, in some cases, malignancy. By integrating emerging clinical, histopathologic, and genetic insights, particularly the role of connexin 26 dysfunction, the authors highlight both the advances made and the substantial gaps that remain. Their call for standardized monitoring protocols and deeper exploration of genotype–phenotype correlations is both timely and essential.

Taken together, the contributions in this issue reflect the dynamic and continually evolving landscape of pediatric dermatology. Whether addressing global disparities in diagnostic resources or elucidating the molecular underpinnings of rare diseases, our mission remains unchanged: to improve the health and well-being of children worldwide.

We hope that this issue will engage our readers, stimulate critical reflection, and encourage further research on the topics presented.

Editor-in-Chief

Professor Fabio Arcangeli

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Systematic review

Recommendations for Sun Protection in Children and Young People: A Systematic Review of Guidelines and Consensus Statements

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KEYWORDS

Photoprotection, pediatrics, sun protection, ultraviolet radiation, melanoma, SPF, skin cancer prevention, UVA, UVB, UV Index,

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ABSTRACT

Ultraviolet radiation (UVR) is the leading preventable cause of skin cancer, and early-life exposure increases long-term risk. Despite this, guidelines on sun protection for children and young people (CYP) are inconsistent. While those with skin of colour (SOC) are often considered lower risk for skin cancer, they experience delays in diagnosis and poorer prognosis highlighting the importance of tailored guidelines. This systematic review examined recommendations on sun protection for CYP from January 2000 to October 2024. Of 7228 manuscripts, 15 were included: three were paediatric-specific, ten included paediatric recommendations, one was SOC-specific, and two included SOC-specific recommendations. Common themes included UVR avoidance, sunscreen use, and physical protection (hats, clothing, sunglasses). However, specific details varied, with few tailored recommendations for SOC. Expert consensus on sun protection recommendations for CYP is needed, with specific consideration of the needs of CYP with SOC.

1. Intoduction and background

Ultraviolet radiation (UVR) refers to UVA and UVB radiation emitted from the sun, both of which impact skin health. UVA is the most abundant type that reaches earth (1, 2) penetrating the skin to the level of the dermis, with UVB penetrating to the epidermis (1-3). UVR is the major cause of skin cancer (4, 5) with other negative impacts on the skin, including sunburn, photoaging, exacerbation of pigmentary disorders, and photodermatoses (9, 10). Benefits of UVR also exist, including synthesis of vitamin D (needed for healthy bodily functions such as bone health), positive impacts on mood, and a sense of well-being (2, 7).

In 2020, the global incidence of melanoma was 324,635 and accounted for 57,043 deaths (8). The number of new cases of all non-melanoma skin cancers (NMSC) without the inclusion of basal cell carcinoma (BCC) was 1, 198, 073, however the deaths globally of NMSC accounted for 63, 731 (inclusive of BCC) (8). Australia and New Zealand have the highest rates of both melanoma and NMSCs, followed by North America for NMSCs and Western European countries for melanoma (8).

Skin of colour (SOC) refers to skin with increased melanin and darker pigmentation, compared to traditionally viewed White (lightly pigmented) skin. SOC is a spectrum, examples include African, Asian, Latinx, Middle Eastern, and Indigenous Oceanic ancestry (11, 12). Skin cancer incidence in SOC is comparatively lower than that seen in White skin; however, has higher associated mortality, attributed to a delay in detection and treatment (13, 14). People with SOC are more likely to have melanomas in sun-protected sites (especially acral sites) and there are limited studies on their UVR exposure and melanoma risk (15). People with SOC have poorer survival rates for melanoma compared to White skin, with a 2022 study in the US showing the largest disparity in survival rates between Black and White patients with an absolute difference of 25% with no elaboration on which sites were most affected (14). Contributing factors include misconceptions regarding SOC being fully protective against melanoma, socioeconomic barriers to health care, atypical presentations of skin cancer in SOC, a lack of skin cancer preventative behaviours, and a lack of physician awareness of skin cancer risk and recommendations for screening (13, 15, 16).

In Australia, data regarding NMSC in First Nations people are limited, as NMSC are not reportable to cancer registries unlike melanoma (17). Available data from a case series of presentations in Sydney demonstrated First Nations people had late-presentation of skin cancers (including melanoma and NMSC) with high morbidity and mortality, especially in those patients with Fitzpatrick Skin Types (FST) II and III. (18) It is important to note that there is significant phenotypic variation among First Nations people in Australia, and so Indigenous status does not always correlate with higher FST (18). Moreover, it is recognised that population group and ethnicity do not always correlate with a specific FST or skin colour and so should not be used as surrogates (19).

UVR exposure and sunburn in childhood increases the risk of melanoma later in life (10, 20, 21). Younger melanocytes are more susceptible to UVR and exposure during peak melanocytic activity early in life increases the risk of melanoma initiation (10). Children with multiple episodes of sunburn and lighter skin are more at risk (10). Sun exposure also increases the risk of development of naevi, with increased risk of melanoma seen when there is increased number and clinical atypia or histological dysplasia (22, 23).

In view of the significant role that UVR plays early in life, sun protection is fundamental in preventing skin cancers later in life. This systematic review aims to summarise sun protection recommendations for children and young people (CYP).

2. Methods

The protocol has been registered with PROSPERO at the National Institute for Health Research and Centre for Reviews and Dissemination (CRD) and has been reported according to the PRISMA 2020 statement and checklist (Appendix A) (24).

Eligibility criteria

Study design

Review articles, evidence-based guidelines, consensus-based guidelines, expert statements, and position statements published in English with recommendations for sun protection in CYP were eligible for inclusion.

Study population

Studies with recommendations for sun protection in CYP aged up to and including 25 years were eligible for inclusion. Where no age-group was specified, the article was included. There were no restrictions on setting, ethnicity or FST.

Outcomes

The primary outcome was sun protection recommendations to prevent skin cancer and other UVR-related skin disease.

Information sources and search strategy

Literature searches were conducted in MEDLINE (Ovid), EMBASE (Ovid), EMCARE (Ovid) and Web of Science, for English language studies published between 1 January 2000 and 23 October 2024, using the pre-defined search strategies (Appendix A). The reference lists of all included full-text articles and relevant review articles were scanned for additional manuscripts for inclusion. Citation searching of all included full-text articles was performed. A grey literature search of government websites, public health organisations, large clinical organisations (including professional societies or large hospitals) and cancer advocacy organisations was performed using Google Advanced, and the deep web searched using BASE and MedNar. Key words used in the search strategies pertained to 'recommendations' and 'sun protection,' with results limited to the English language and published since 01 January 2000. In total, three separate search strategies were employed: Medline/Embase/Emcare, Web of Science and the grey literature search, the full details of each have been provided in Appendix B.

Selection process

Covidence Systematic Review Software (Veritas Health innovation, Melbourne Australia) was used to aid the selection process, including removal of duplicate records prior to article screening. Two reviewers (HK and DS) independently screened and reviewed the database articles to assess specified inclusion criteria. Discrepancies were resolved through consensus with a third investigator (BR).

Data collection process

One reviewer (HK) extracted the data and a second reviewer (DS) checked all data for accuracy and completeness.

Data items

Summary tables were created to synthesise the recommendations of each included article.

Risk of bias assessment

Two reviewers (HK and DS) critically appraised all included articles using the AGREE-II tool (Appendix C) (25). Disagreements about critical appraisal were resolved by consensus without requiring consultation with a third reviewer (BR).

3. Results

Of 7228 studies identified, 6064 titles and abstracts were screened, accounting for duplicates. 26 full text studies were identified for eligibility, and 3 additional papers through other sources (Fig. 1). 15 articles were eligible and included (Table I). Nine countries are represented, notably all at least middle-upper income countries (26).

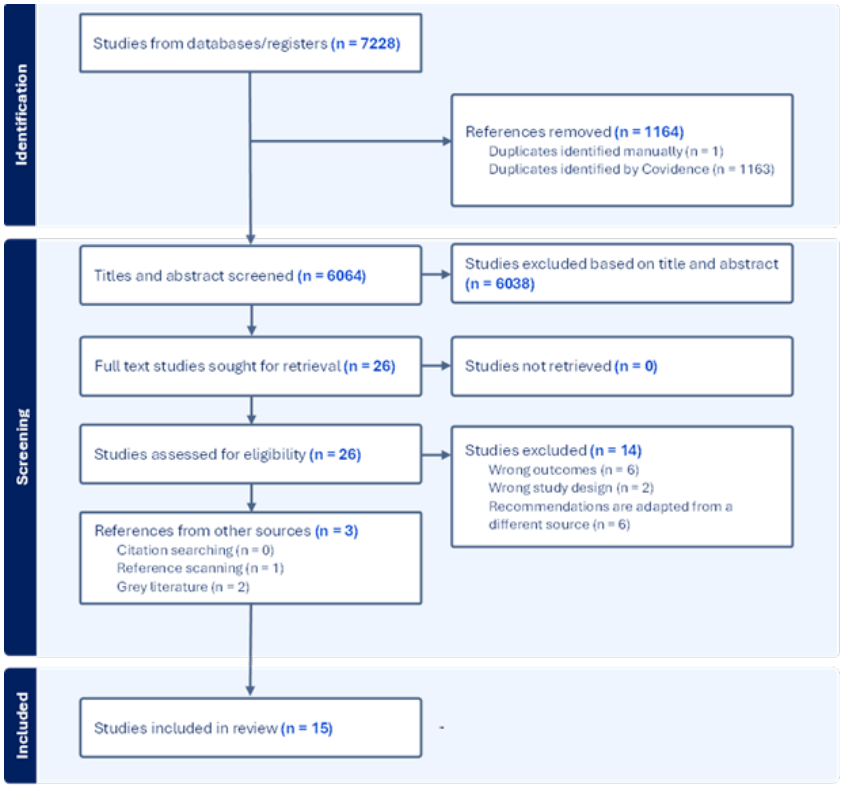

Fig. 1. *Flowchart of systematic review according to the PRISMA 2020 statement.*

Table I. *Summary of included articles.*

Article reference	Country of publication	Year of publication	Population described
Cancer council (27)	Australia	2022	General population
Schalka et al. (28)	Brazil	2014	Brazilian population
Marrett et al. (29)	Canada	2016	General population
Berneberg & Surber (30)	Germany	2009	Children
Elsner et al. (31)	Germany	2007	General population
Garbe et al. (32)	Germany	2024	Fair-skinned populations
Greinert et al. (33)	Germany	2015	General population
Narbutt et al. (34)	Poland	2018	General population
Tod et al. (19)	South Africa	2024	South African population
Lautenschlager et al. (35)	Switzerland	2007	General population
NICE (36)	UK	2016	General population
AAFP (37)	USA	2000	Not defined
Agbai et al. (38)	USA	2014	Skin of colour
Balk et al. (39)	USA	2011	Children and adolescents
Julian et al. (40)	USA	2015	Children

Five major themes were identified: avoiding UVR, sunscreen use, protective clothing, hat and sunglasses (Table II). The most frequent specific recommendations for each of these five themes are summarised, along with paediatric- and SOC-specific recommendations (Table III). A full breakdown of the recommendations are available in Table V (Appendix D). A synthesis of recommendations for CYP, including CYP with SOC has been complied (Table IV).

Table II. *Broad sun protection recommendations in the included articles.*

Recommendations	Article reference														
	(27)	(28)	(29)	(30)	(31)	(32)	(33)	(34)	(19)	(35)	(36)	(37)	(38)	(39)	(40)
Avoidance of UVR															
Artificial UV-source avoidance															
Sunscreen															
Protective clothing															
Hat															
Sunglasses															

Green = Yes
Red = No

Table III. *Most frequent specific sun protection recommendations in the included articles (See appendix for full breakdown of recommendations).*

Specific recommendations	Article reference
Specific time of day to avoid UVR	
Seek shade	(38)*, (39)^, (30)^, (32), (33), (35), (29), (34), (28), (19), (36), (27)
When the UVI is ≥ 3	(32),(29), (27)
Between 10am and 4pm	(39)^, (19), (37)
Type of sunscreen	
Broad-spectrum	(38)*, (39)^, (30)^, (31), (32), (33), (40)^, (35), (29), (4), (28), (19), (36), (27)
Water-resistant if outside for a prolonged time, or where sweating or water-contact likely	(31), (34), (28), (36)
Frequency of sunscreen use	
Daily	(38)*, (30)^, (31), (33), (34), (19), (37)
When the UV index is ≥ 3	(32), (29), (28), (27)
SPF	
SPF ≥ 15	(39)^, (31), (35), (37)
SPF ≥ 30	(38)*, (33), (40)^, (29), (36)
Timing of sunscreen application	
15-30 mins before sun exposure	(38)*, (39)^, (33), (35), (19)
Reapplication 2-hourly	(38)*, (39)^, (33), (40)^, (34), (28), (19), (27)
Reapplication when outdoors, after swimming, towel drying, sweating or if rubbed off.	(38)*, (39)^, (30)^, (33), (40)^, (34), (28), (19), (36), (37)
Method of sunscreen application	
Apply liberally	(38)*, (39)^, (35), (29), (28),(19), (36), (37), (27)
Cover all sun-exposed areas	(38)*, (39)^, (30)^, (31)4, (32), (40)^, (35), (29), (34), (28), (19), (36), (37)
Apply 2 mg/cm2 of sunscreen on the body surface to protect the skin	(39)^, (30)^, (33), (29), (34), (28), (19), (27)
Type of clothing	
Tightly-woven fabric	(39)^, (33), (40)^, (29), (34), (28), (19), (36), (37), (27)
Long clothing	(39)^, (30)^, (32), (33), (40)^, (35), (29), (34), (28), (19), (36), (37), (27)
Type of hat	
Wide-brimmed	(38)*, (39)^, (30)^, (31), (32), (33), (40)^, (29), (34), (28), (19), (36), (37), (27)
Hat or cap	(34), (28)
Type of sunglasses	
UV-absorbing/protective lenses	(38)*, (39)^, (30)^, (31), (33), (29), (28), (19), (37), (27)
Skin of colour	
No recommendations	(39)^, (30)^, (31), (32), (33), (40)^, (35), (29), (34), (36), (37), (27)
Organic sunscreens are more cosmetically acceptable for skin of colour	(38)*, (19)
Photoprotective measures recommended for individuals of any skin colour	(38)*, (28), (19)
Tinted sunscreens are beneficial for patients with pigmentary disorders	(19)
Paediatric	
Infants younger than 6 months should be kept out of direct sunlight	(39)^, (32), (34), (28), (19), (36)
Sun exposure up to 2-4 years of age should be limited	(27), (40)^
Avoidance of sunscreen on infants <6 months	(40)^, (27)
Avoidance of organic sunscreens in young infants/children/2 years of age	(35), (19), (40)^, (34), (28)

Table IV. *Synthesis of recommendations for CYP, including CYP with skin of colour.*

Broad category	Recommendation
UVR avoidance	Avoid sun exposure when the UVI is ≥ 3, seek shade always when outdoors
Type of sunscreen	Broad-spectrum, water-resistant sunscreen. For CYP (over the age of 2) with SOC, organic sunscreens may be more cosmetically acceptable
SPF	SPF ≥ 50+
Frequency of sunscreen use	Daily year-round
Timing of sunscreen application	15-30 mins before sun exposure in two layers, then 2-hourly re-application thereafter, or after swimming, sweating or if it is rubbed off
Method of sunscreen application	2 mg/cm^2, which can be simplified to use the equivalent amount required to fill the child's cupped hand
Type of clothing	Long and tightly woven clothing that covers the arms and legs, including footwear that covers the entire foot
Type of hat	Wide-brimmed or legionnaire-style hats
Type of sunglasses	UV-absorbing/protective lenses (spectrum of absorption to up to 400nm) that cover the eye and periorbital skin area as much as possible
Infants	Infants under 6 months of age should be kept out of the sun and avoid the use of sunscreens in this age group
Young children	Use inorganic sunscreens from the age of 6 months to 2 years and limit sun exposure as much as possible

UVR avoidance

All papers recommended UVR avoidance, 12 advised seeking shade and 11 advised avoiding artificial UVR sources. Specific times to avoid UVR varied: four based on UV index (UVI >3 or "when at the highest"), (27-30), with nine giving specific times for UV avoidance within the range of 10am to 4pm (19, 30-32, 34-37). Three papers advised avoidance of UVR exposure, ranging from 1-2 hours before and after the solar apex. (27, 38-39).

Sunscreen Use

All studies recommended the use of sunscreen with 14 specifying broad spectrum. (19, 27-36, 38-40). Two advised water-resistant products (28, 29), particularly during prolonged outdoor activity/sweating or water contact (33-35, 38). Concerns about oxybenzone's weak oestrogenic effect were considered (36) and traditional clay based 'sunscreens' were suggested if sunscreen was unavailable (19).

Frequency of use

Sunscreen recommendation varied: daily use (19, 30, 33, 37-40), applications when UVI ≥ 3 (27-29, 34), when sunburn was possible (39) and in areas of high isolation (31).

SPF recommendations

Guidance differed: four recommended SPF ≥ 15 (31, 36-38), other SPF ≥ 30 (28, 30, 32, 35, 40) with variations for season (33), duration outdoors and risk group with lower risk expected in for Afro -descendent patients (34). The highest recommendation was SPF 50+, (29) with others using qualitative terms like "high protection" (39).

Timing and reapplication

11 papers recommended application timing ranging from 15 to 30 mins before sun exposure (19, 29-31, 33-34, 36-38, 40). Four papers recommended double application with varying protocols. Eight recommended reapplication every 2 hours (19, 29-30, 32-34, 36, 40) and 10 recommended reapplications after swimming, sweating, towel drying or being rubbed off (19, 30, 32-37, 39, 40). One paper suggested water-resistant products to reduce reapplication needs (32).

Application methods

Key themes included liberal application, (19, 28-29, 31, 34-37, 40) covering all uncovered skin, (19, 27-28, 31-40) and aiming for 2mg/cm2 to the body (19, 28-30, 33-34, 36, 39). Simplified methods included the teaspoon method (28-29, 34-35) or using the child's cupped hand as a guide (32).

Clothing

Thirteen papers advised long clothes (19, 27-37, 39), 10 recommended tightly woven clothes (19, 28-30, 32-37), with a preference for dark colours (19, 29, 32, 34, 36), ultraviolet protection factor (UPF)-rated (19, 27-29, 36, 37) or chemically treated fabrics (27, 31, 33-34, 36). Some recommended materials including wool, synthetic materials, and denim (27, 31, 34, 36). Some recommended general "sun protective clothing", or full

coverage, including feet (38 -40).

Hats

Wide brimmed hats were strongly recommended by 14 papers (19, 27-30, 32-40), with some noting specific brim widths (≥ 6-15cm) or widths depending on hat style (19, 29, 38). Caps were mentioned but recognised as offering less protection (33-34).

Eye Protection

UV- protective/absorbing sunglasses were widely advised (19, 28-30, 34, 36-40) with specifics on fit (close, wrap around, wide frames) (19, 28-29, 33-35) and protection (95-100% UV block, up to 400nm, regional standards) (28-29, 33-36).

SOC

Three papers included SOC recommendations (19, 34, 40). All advised sun protection regardless of skin type, though noted cosmetic limitations of inorganic sunscreens containing zinc and titanium dioxide leaving white residue (19, 40). They also highlighted the role of sun protection in managing pigmentary disorders such as melasma and hyperpigmentation, which are more common in SOC (19, 34, 40).

Paediatric recommendations

Six papers advised infants under six months be kept out of direct sunlight (19, 27, 33-36), with two papers extending age cut-off for limiting exposure (2-4 years) (29, 32). Sun avoidance and clothing were preferred over sunscreen for infants (especially under six months) (33, 36), with sunscreen used only if other measures weren't feasible. Organic sunscreens were generally discouraged (19, 33-34). SPF recommendations varied by age and skin type, from ≥ 15 for infants over 6 months (33) to SPF 50+ for fair or atopic children (34).

The AGREE-II tool was used to assess the quality of the guidelines and risk of bias. The ratings of each component of every domain and overall assessment are in Appendix B. One article was deemed poor quality with a score of 1/7, and thus not recommended for use, failing in the areas of stakeholder involvement, rigour of development, and editorial independence. The remaining articles were recommended for use, either with or without recommendations and with overall quality scores ranging from 3/7 to 6/7.

4. Discussion

This is the first systematic review of sun protection recommendations for CYP. Across guidelines, core strategies were consistent including UVR avoidance, sunscreen, and protective clothing. For infants and young children, emphasis was placed on minimising sun exposure and using protective garments, with sunscreen use recommended only when these alternate interventions are not achievable. From around two years of age, recommendations aligned with those for the general population.

Variation in recommendations reflected regional context, audience, and publication date. SPF thresholds rose over time, from ≥15 in older guidelines to ≥50 in more recent ones, in line with product availability. Some papers advised double application to improve coverage, supported by the literature (42-44). Traditional alternatives, such as clay-based sunscreens, were noted but offered minimal protection (SPF 3.6–4) (46). Concerns about oxybenzone's oestrogenic effects were raised, though not supported by human evidence (47).

The variability in recommendations across guidelines reflects differences in regional priorities, target populations, and available evidence, yet highlights a critical public health gap: the absence of nuanced, population-specific sun protection advice. Most guidelines fail to account for age, geographic UV burden, or FST, leaving CYP — especially those with SOC — without tailored recommendations. This is concerning, given that SOC populations often experience delays in the diagnosis of skin cancer and poorer outcomes (15), as well as being at greater risk for pigmentary disorders (such as post-inflammatory hyperpigmentation and melasma) where photoprotection is essential. Despite the variability we attempt to synthesise the recommendations found in this review in Table IV.

The results of this systematic review suggest that for individuals with SOC, general sun protection recommendations apply, with the exception of inorganic sunscreens being discouraged due to poor cosmesis. Research gaps remain regarding sunscreen efficacy in SOC and SPF performance on darker skin types, and no guidelines specifically address CYP with SOC (15).

Findings from this review, alongside the conclusions of a recent international expert panel, (48) reinforce the central role of early-life sun protection as a skin cancer prevention strategy. Universal measures — avoidance of direct UVR in infancy, use of protective clothing including tightly-woven fabrics, hats and sunglasses, and

water-resistant sunscreens on exposed areas — remain foundational. However, for SOC, recommendations must also consider cosmetic acceptability of formulations, cultural practices, burden of specific dermatoses, and barriers to access to ensure adherence and equity.

Limitations

Exploring the benefits (i.e. vitamin D exposure) and balancing this with harms of sun exposure was beyond the scope of this article; however, this is a critical consideration for sun protection recommendations in CYP, especially CYP with SOC. Hence this review highlights the importance of ongoing efforts to establish tailored sun protection guidance for CYP, aiming to balance the risks and benefits of sun exposure, similar to adult guidelines recently published in Australia (49). Grouping similar recommendations into broad themes (Table III) may have introduced bias from misinterpretation. Grey literature searching found many resources from government and prominent health organisations, however they did not meet the inclusion criteria. The results were also limited by the author's location, search engine algorithm, coverage and results displayed. This may have limited the volume of information from various countries. Finally, whilst we did not limit our search by geography, our study inclusion was limited to the English language, likely excluding articles from many countries, including those with SOC populations. This can create bias due to the collated evidence and guidelines not comprehensively representing the available research globally.

5. Conclusion

The findings of this systematic review highlight the need for harmonised, evidence-based sun protection guidelines that explicitly address the needs of CYP across diverse skin types and populations, including CYP with SOC. Developing such nuanced recommendations represents not only a dermatological priority but also a public health imperative to ensure equitable prevention strategies to reduce disparities in skin cancer outcomes.

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Case report

Blisters Beyond Borders: Managing Chronic Bullous Disease of Childhood without Diagnostics

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KEYWORDS

Chronic Bullous Disease of Childhood (CHDC), linear IgA bullous dermatosis, autoimmune blistering disorder, pediatric dermatology

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ABSTRACT

Chronic bullous disease of childhood (CBDC) is a rare autoimmune blistering disorder typically diagnosed using direct immunofluorescence, which reveals linear IgA deposition along the basement membrane zone (1). However, in low-resource settings, such diagnostic tools are often unavailable, necessitating clinical diagnosis and empiric treatment. We describe a 3-year-old boy in rural Central Africa who presented with widespread tense bullae and erosions. Despite the lack of diagnostic testing, clinical features were highly consistent with CBDC. The patient showed significant improvement with corticosteroids and dapsone, highlighting the value of pattern recognition and pragmatic management in resource-limited environments.

1. Background

Chronic bullous disease of childhood (CBDC), the pediatric variant of linear IgA bullous dermatosis, is a rare autoimmune blistering condition. It usually manifests before age five with abrupt onset of tense vesicles and bullae arranged in characteristic linear or annular configurations—the "string of pearls" sign (2). Lesions typically affect the trunk and extremities, with occasional mucosal involvement, particularly oral and anogenital areas.

Diagnosis traditionally relies on direct immunofluorescence (DIF), which demonstrates linear IgA deposition at the basement membrane zone (1). However, in many under-resourced settings, including much of sub-Saharan Africa, DIF and skin biopsy are unavailable, making clinical diagnosis essential. The literature on CBDC from Africa is sparse, likely due to underdiagnosis, limited access to dermatologic care, and lack of awareness (3).

First-line treatment includes systemic corticosteroids and dapsone, the latter serving as a steroid-sparing agent (4). Dapsone's efficacy is well-documented, but it carries the risk of hemolysis in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency. In regions where G6PD testing is unavailable, cautious inpatient initiation and monitoring become critical (5).

2. Case Description

In January, a 3-year-old boy from a remote region in the Central African Republic presented with a two-month history of progressive blistering. He had received multiple courses of broad-spectrum antibiotics—including nafcillin, gentamicin, ceftriaxone, and clindamycin—with no improvement. On admission, he was hemodynamically stable but appeared tired. Dermatologic examination revealed over 70% body surface area involvement with tense bullae, shallow erosions, and hypopigmented patches in various stages of healing. Lesions followed a linear distribution and spared the palms, soles, and most mucous membranes except the prepuce (Fig. 1, 2). Nikolsky's sign was negative. Basic infectious workup, including testing for HIV, syphilis, malaria, and tuberculosis, was negative. No biopsy, DIF, or serologic testing was available. A clinical diagnosis of CBDC was made based on morphology and exclusion of other causes (Wojnarowska et al.). The patient was started on oral prednisone at 1 mg/kg/day, with moderate improvement. Due to new lesions, the dose was increased to 2 mg/kg/day. Although the disease came under control, attempts to taper prednisone resulted in flares. Signs of steroid-induced myopathy, including proximal muscle weakness, developed. Dapsone was available at the facility due to its historical use for leprosy. Although G6PD testing was not accessible, the medication was initiated cautiously under close inpatient monitoring. The absence of screening raised clinical concern, as dapsone can precipitate acute hemolytic anemia in individuals with G6PD deficiency—a risk that necessitates vigilant observation for signs such as jaundice, dark urine, fatigue, or rapid hemoglobin decline. Fortunately, the patient tolerated dapsone at 1 mg/kg/day without adverse effects, allowing for successful tapering of prednisone. At his most recent follow-up, he remained lesion-free, with progressive repigmentation and no complications or infections (4).

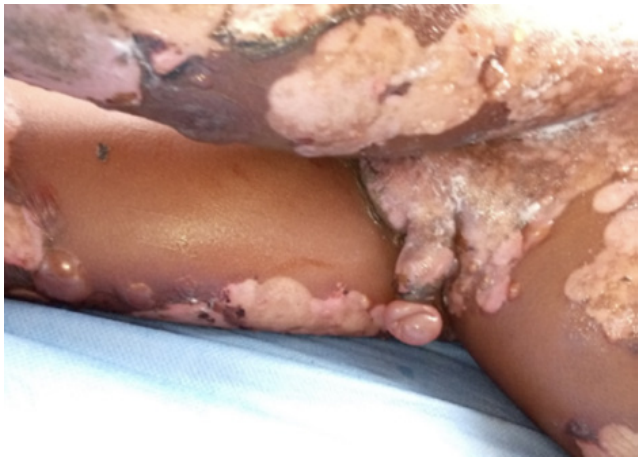

Fig. 1. *Widespread tense bullae on the trunk and extremities, many in linear arrangements—classic "string of pearls" sign indicative of CBDC.*

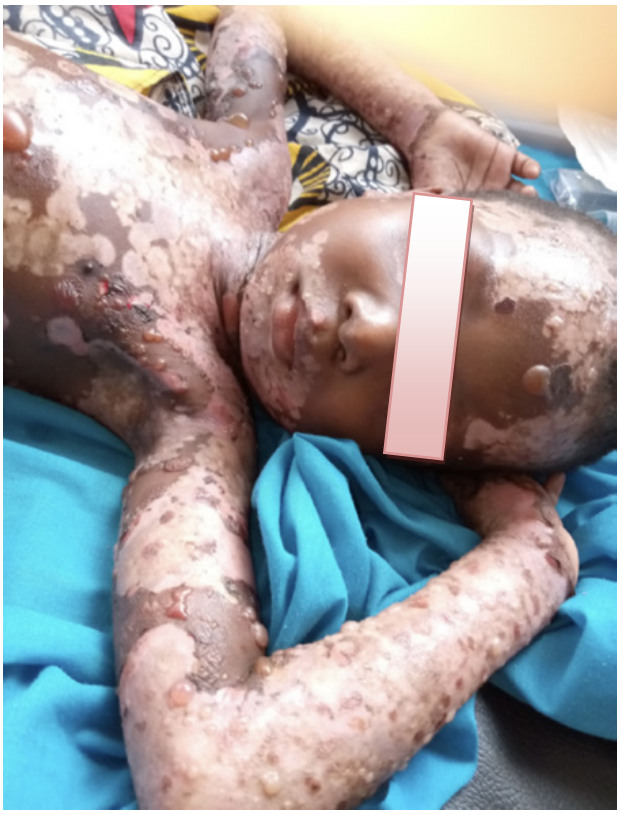

Fig. 2. *Widespread tense bullae on the trunk and extremities, many in linear arrangements—classic "string of pearls" sign indicative of CBDC.*

3. Treatment Timeline

Time Point	Intervention	Rationale / Response
Pre-admission	Empiric antibiotics (nafcillin, gentamicin, ceftriaxone, clindamycin)	No improvement; presumed bacterial infection ruled out
Day 1 (Admission)	Prednisone 1 mg/kg/day	Partial improvement noted
Day 7	Prednisone increased to 2 mg/kg/day	Ongoing new lesions; more effective disease control

Week 3	Attempted steroid taper	Disease flared; signs of steroid-induced myopathy (proximal muscle weakness) emerged
Week 4	Dapsone 1 mg/kg/day initiated (G6PD testing unavailable)	Started under close inpatient monitoring; no adverse effects
Week 6	Prednisone tapered successfully	Patient remained lesion-free; signs of repigmentation; no relapse noted

4. Discussion

This case underscores the importance of clinical acumen in diagnosing and treating dermatologic conditions when diagnostic tools are unavailable. The child's lesion distribution, disease course, and failure to respond to antibiotics strongly supported a diagnosis of CBDC (2). Despite the absence of DIF, the pattern was highly characteristic.

High-dose corticosteroids led to disease control but induced steroid myopathy. The addition of dapsone, a known steroid-sparing agent, allowed safe tapering. In many regions, G6PD testing is unavailable, making dapsone initiation a calculated risk. Given the historical use of dapsone for leprosy at the treatment center, staff were familiar with its adverse effects. The patient was admitted for close inpatient monitoring, including:

- Daily physical exams and symptom review;
- Serial hemoglobin and reticulocyte counts;
- Vigilant observation for signs of hemolysis (e.g., jaundice, dark urine, fatigue).

He tolerated treatment well without signs of hemolysis. This approach—close inpatient monitoring with readiness to discontinue dapsone at the first sign of hemolysis—provides a potential model for safe use in low-resource settings.

Literature on CBDC from Africa remains scarce. Fagbule and Ogunbiyi report a similar case in Nigeria, where diagnosis and treatment were likewise guided by clinical features (3). Broader recognition of CBDC in endemic regions may be hindered by its rarity, overlap with infectious diseases, and lack of dermatologic training in rural health systems. This case contributes to a growing recognition that CBDC occurs globally and can be effectively managed even in the absence of immunopathologic confirmation.

5. Conclusion

This case highlights the value of clinical judgment and adaptive therapeutic strategies in diagnosing and managing chronic bullous disease of childhood in low-resource settings. Despite the absence of confirmatory testing, pattern recognition enabled timely treatment with corticosteroids and dapsone, leading to disease control and recovery. Broader training in clinical dermatology and development of pragmatic treatment protocols could improve care for children with autoimmune skin disease in underserved areas.

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Case report

SSSS in Pediatric Patients: Is Early Recognition Always Straightforward?

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KEYWORDS

Staphylococcal scalded skin syndrome, exfoliative toxins, Staphylococcus aureus

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ABSTRACT

Staphylococcal Scalded Skin Syndrome (SSSS) is a rare bullous dermatosis caused by staphylococcal exfoliative toxins, predominantly affecting children under six years of age. A six-year-old boy developed intense erythema and facial edema while camping, following recent impetigo. The initial presentation included peri-orificial erythema, hyperemic lips, and conjunctivitis without fever. Within 48 hours, desquamation, bullae, and a positive Nikolsky sign developed. Treatment with clindamycin resulted in rapid clinical improvement. The camping setting initially suggested sunburn; however, the characteristic peri-orificial distribution and positive Nikolsky sign confirmed the diagnosis of SSSS. This case highlights the importance of considering SSSS in pediatric bullous eruptions following staphylococcal infections. Although rare, SSSS requires prompt recognition and appropriate antibiotic therapy. Clinicians should maintain high suspicion for SSSS in pediatric patients with acute bullous lesions, even when clinical settings suggest alternative diagnoses.

1. Introduction

Staphylococcal Scalded Skin Syndrome (SSSS) represents a serious skin disorder triggered by specific *Staphylococcus aureus* strains that release exfoliative toxins into the bloodstream (1). The overall incidence of SSSS in the general population is estimated to range between 0.09 and 0.56 cases per one million people (2). In the United States, the annual incidence is 7.67 (range 1.83–11.88) per one million children, with 45.1 cases per one million infants under two years of age (3). However, the highest incidence is observed in infants aged two to three years (4).

The disease predominantly affects pediatric populations and individuals with compromised immune systems. It is characterized by extensive superficial skin peeling and erythema that can resemble other critical dermatological emergencies such as Stevens–Johnson syndrome or toxic epidermal necrolysis (5). We present this case because recent epidemiological data suggest an increasing prevalence of SSSS, highlighting the need for greater clinical awareness to facilitate prompt recognition and management.

2. Case report

A six-year-old boy on vacation at a campsite with his parents came to our attention due to the onset of burning and pruritic erythema. For several days, he had been treated with topical antibiotic therapy for impetigo. He had no fever, had not taken any medications, and had no known allergies.

The child appeared distressed and complained of burning pain and intense itching while maintaining good general condition. The erythema was markedly intense, involving the face, neck, and trunk. The lips were hyperemic, the face appeared edematous, and purulent conjunctivitis was present. The remaining physical examination was normal. A rapid strep test was negative.

After the administration of an antihistamine with minimal benefit, and suspecting a bacterial etiology, oral amoxicillin–clavulanic acid (50 mg/kg/day) was started. However, it was discontinued after one day when the clinical picture became consistent with SSSS. Blood chemistry tests showed mild neutrophilic leukocytosis and negative inflammatory markers (CRP). The nasopharyngeal swab for viruses and common bacteria was negative.

Within the following 48 hours, the erythema began to desquamate (Fig. 1), and bullae and vesicles started to appear, which rapidly ruptured (Fig. 2). Peri-oral fissures worsened. Nikolsky's sign was positive. With a strong suspicion of bullous dermatitis caused by epidermolytic exotoxins (Staphylococcal Scalded Skin Syndrome - SSSS), intravenous clindamycin therapy was started at a dose of 40 mg/kg/day, divided into three doses, resulting in rapid improvement of the clinical picture. After four days, the therapy was switched to the oral route as the patient was returning to his home country. The skin swab for MRSA was negative.

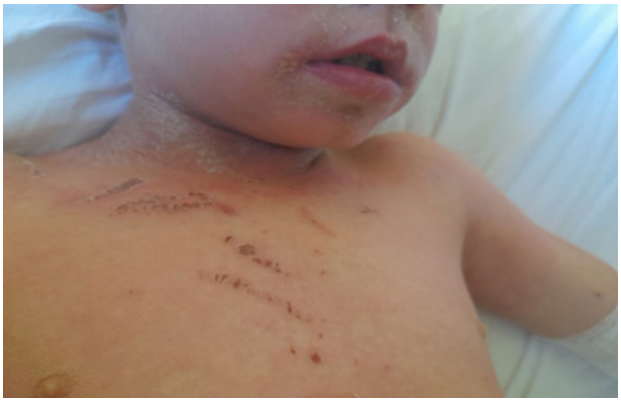

Fig. 1. *Generalized erythroderma with superficial desquamation of the neck and peri-labial area where honey-crusted lesions are visible. Ruptured bullae leave superficial erosions with brown crusts.*

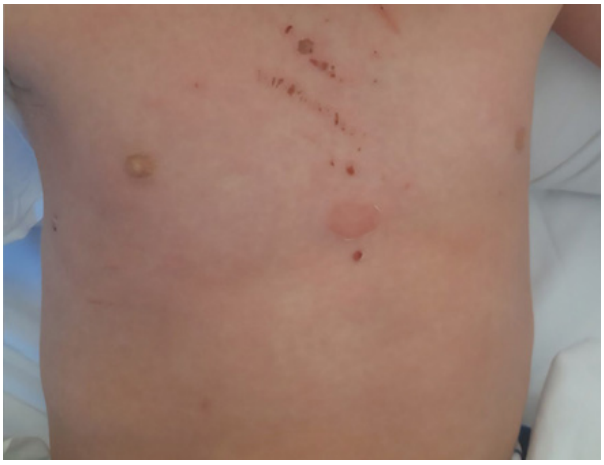

Fig. 2. *Ruptured bullous lesion over the sternum with exposed denuded skin.*

3. Discussion

SSSS is a bullous dermatosis caused by exfoliative exotoxins (ETA and ETB) produced by certain strains of *Staphylococcus aureus* (5). It predominantly affects neonates and children under six years of age (4–5), often occurring after impetigo, pharyngotonsillitis, or conjunctivitis. The onset is typically acute, with cutaneous pain as a characteristic feature.

Erythema, intensely hyperemic, initially develops in skin folds and the peri-orificial region. Subsequently, flaccid bullae and widespread desquamation appear, accompanied by a positive Nikolsky sign (gentle pressure causes detachment of the upper epidermal layers). Facial edema is frequent, and radial peri-oral fissures are typical. Fever, lethargy, irritability, and reduced oral intake may also occur.

The diagnosis is essentially clinical, as laboratory tests are not definitive. Culture swabs from the suspected source of infection may help confirm the presence of *S. aureus* and guide targeted antibiotic therapy based on antibiogram results. Differential diagnoses include Stevens–Johnson syndrome (usually with mucosal involvement), toxic epidermal necrolysis (often following drug exposure), and scarlatiniform rash (typically with pharyngitis and a positive strep test). Treatment is primarily antibiotic (anti-staphylococcal) and supportive when necessary (6).

This case exemplifies a classic presentation of SSSS in a pediatric patient. The six-year-old patient presented with the characteristic triad of burning erythema, facial edema, and peri-oral involvement, following a preceding impetigo infection—a well-recognized trigger for SSSS development. The early phase demonstrated pathognomonic signs: intense erythema with peri-orificial distribution, hyperemic lips, and facial edema consistent with exotoxin-mediated epidermal damage. The absence of fever and maintenance of good general condition align with the typical presentation of SSSS, distinguishing it from more systemic conditions.

The diagnostic approach illustrates both the challenges and typical laboratory patterns associated with SSSS. The negative rapid strep test appropriately ruled out Group A Streptococcal (GAS) involvement, while mild neutrophilic leukocytosis with negative inflammatory markers (CRP) reflects the localized nature of toxin production rather than systemic bacterial invasion. The evolution to desquamation, bullae formation, and positive Nikolsky sign within 48 hours provided definitive clinical confirmation. This temporal evolution is characteristic of SSSS, where exfoliative toxins (ETA and ETB) cause loss of cell-to-cell adhesion in the granular layer of the epidermis, resulting in superficial blistering and subsequent desquamation (7).

The clinical presentation required careful consideration of several conditions within the differential diagnosis. Initially, given the camping setting and intense erythema, sunburn or solar erythema could have been considered; however, the characteristic peri-orificial distribution, facial edema, and associated pain pattern were inconsistent with typical sun exposure injury. Stevens–Johnson syndrome was appropriately excluded given the absence of mucosal involvement. Toxic epidermal necrolysis was less likely given the patient's age and absence of drug exposure history. Negative strep testing helped differentiate from scarlatiniform eruptions, which typically present with pharyngitis and positive GAS results.

The initial empirical therapy with amoxicillin–clavulanate represented a reasonable broad-spectrum approach for a suspected bacterial etiology. However, the subsequent switch to clindamycin demonstrated appropriate clinical reasoning, as clindamycin provides superior anti-staphylococcal coverage and has the additional benefit of inhibiting bacterial protein synthesis, thereby reducing toxin production (6, 8, 9). The rapid clinical improvement following clindamycin initiation supports the diagnosis and highlights the importance of prompt, appropriate antibiotic therapy in SSSS management. The negative MRSA culture confirmed that this case involved methicillin-sensitive *Staphylococcus aureus*, making clindamycin an optimal therapeutic choice (6-10). In Italy, the MRSA rate stood at 26.6% in 2023, with clindamycin resistance accounting for 34.7% (11).

This case underscores several important clinical principles in SSSS management. Early recognition based on characteristic clinical features—particularly the positive Nikolsky sign and typical distribution pattern—enables prompt therapeutic intervention (12). The excellent response to targeted antibiotic therapy demonstrates the generally favorable prognosis of SSSS when appropriately managed, particularly in immunocompetent pediatric patients. The case also highlights the importance of considering SSSS in children presenting with bullous eruptions following superficial staphylococcal infections, emphasizing close monitoring of even minor skin infections in the pediatric population.

4. Conclusion

Although Staphylococcal Scalded Skin Syndrome remains a relatively uncommon condition, this case highlights the critical importance of including SSSS in the differential diagnosis of pediatric patients presenting with acute erythematous and bullous skin lesions. Early recognition of characteristic clinical features, particularly following antecedent staphylococcal infections, enables prompt initiation of appropriate therapy and prevents potential complications associated with delayed diagnosis. Clinicians should maintain a high index of suspicion for SSSS in the appropriate clinical context, as timely intervention significantly impacts patient outcomes and prevents progression to more severe manifestations of this toxin-mediated dermatologic emergency

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Case report

A Case of Symmetrical Acrokeratoderma in an Indian Patient: A Decade-Long Misdiagnosis

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KEYWORDS

Symmetrical acrokeratoderma, pigmented aqua-exacerbated symmetrical acral hyperkeratosis, aquagenic maceration

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ABSTRACT

Symmetrical acrokeratoderma (SA) is a rare dermatosis characterized by symmetric, hyperkeratotic plaques on the dorsum of the hands, wrists, feet, and ankles, often misdiagnosed due to its resemblance to other acral hyperkeratotic conditions. We report a case of a 20-year-old Indian male with a decade-long history of asymptomatic, bilaterally symmetrical plaques on the wrists and ankles, exhibiting aquagenic maceration and seasonal variation. Clinical findings, supported by histopathology showing hyperkeratosis, acanthosis, and mild perivascular inflammation, confirmed the diagnosis. Treatment with oral acitretin (25 mg) resulted in marked improvement, which was maintained at the third month of follow-up. This case highlights the importance of recognizing SA's distinct clinical features, such as the aquagenic response and seasonal aggravation, to avoid misdiagnosis. We emphasize the need for increased awareness and further research into its pathogenesis and effective therapies, particularly in Indian populations where reports are scarce.

1. Introduction

Symmetrical acrokeratoderma (SA), also known as pigmented aqua-exacerbated symmetrical acral hyperkeratosis, is a rare dermatosis first described in Han-Chinese populations in 2010 (1). It is characterized by symmetric, non-pruritic, brownish-black hyperkeratotic plaques on the dorsum of the hands, wrists, feet, and ankles, sparing the palms and soles. Lesions exhibit transient maceration in warm weather and improve in cooler weather (2).

Although the exact prevalence of SA remains unknown, most documented cases involve young males of Asian descent, particularly from China and India (3, 4). Its rarity, along with overlapping features with other dermatoses such as aquagenic acrokeratoderma, palmoplantar keratodermas, and acanthosis nigricans, contributes to underdiagnosis and misclassification. This case report describes a classic presentation of SA in a young Indian male and integrates histopathologic and immunologic findings with current literature to raise awareness and highlight potential diagnostic pitfalls.

2. Case Report

A 20-year-old male presented to our outpatient dermatology clinic with bilateral, symmetrical, asymptomatic brownish plaques over the dorsum of both wrists (Fig. 1, 2) and lateral ankles (Fig. 3). The lesions first appeared at 10 years of age and had gradually increased in size and pigmentation.

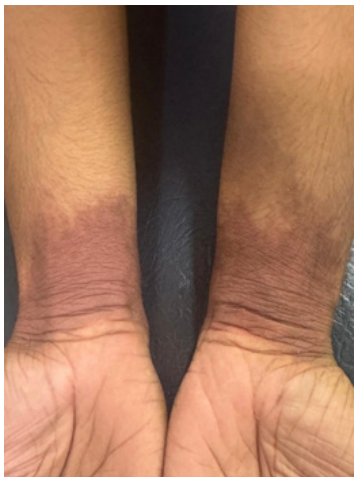

Fig. 1. *Hyperpigmented plaques noted over the flexors of both wrists before water immersion test.*

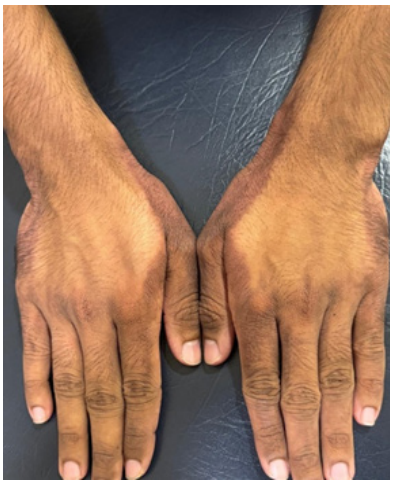

Fig. 2. *Hyperpigmented plaques noted over the lateral aspects of both hands.*

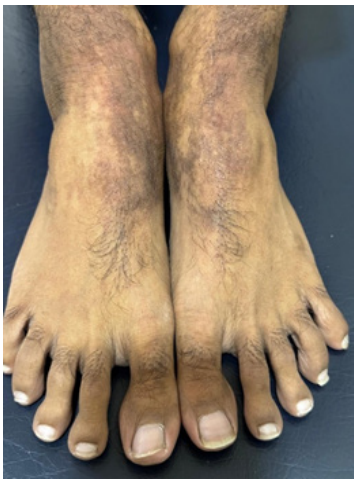

Fig. 3. *Hyperpigmented plaques noted over the dorsum of both feet.*

There was no family history of similar skin disorders. The patient denied pruritus, pain, or burning. He had no history of systemic comorbidities or history of prior drug intake. Notably, he reported that the lesions became whitish and macerated after bathing, returning to their original appearance once dry. He also noted worsening of the lesions during summer and spontaneous improvement during winter.

He had been previously prescribed moderate-potency topical corticosteroids, with no significant improvement.

Cutaneous examination revealed well-demarcated, bilaterally symmetrical, brownish hyperkeratotic plaques localized to the lateral aspect of wrists and ankles. Palms and soles were spared. All mucosae and nails were normal.

A water immersion test resulted in the lesions turning pale white and wrinkled within 2–3 minutes (Fig. 4). The changes reversed within 30 minutes of drying, confirming the aquagenic response.

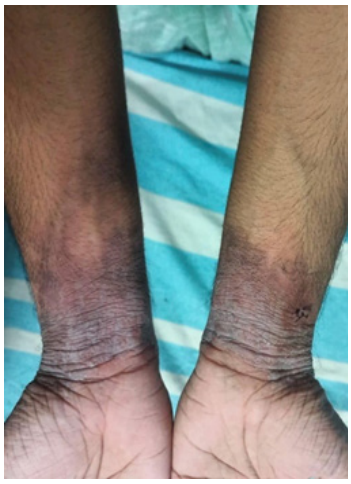

Fig. 4. *Macerated plaques noted over the flexors of both wrists after water immersion test.*

Systemic examination was unremarkable.

A Skin biopsy was done from the affected area and revealed hyperkeratosis, focal parakeratosis, acanthosis and normal granular layer. Dermis showed few dilated capillaries with mild perivascular and periadnexal chronic inflammatory infiltrate (Fig. 5).

No fungal elements were seen in the section.

These findings aligned with previous reports describing epidermal hyperplasia with chronic inflammatory changes (1, 2).

The patient was initiated on Oral Acitretin and showed significant improvement on 2nd month of follow up with complete resolution of lesions over the feet (Fig. 6, 7).

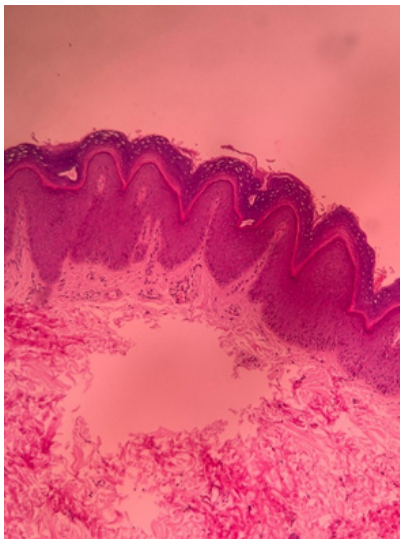

Fig. 5. *Histopathology of the section showing Hyperkeratosis, focal parakeratosis and mild perivascular inflammatory infiltrate.*

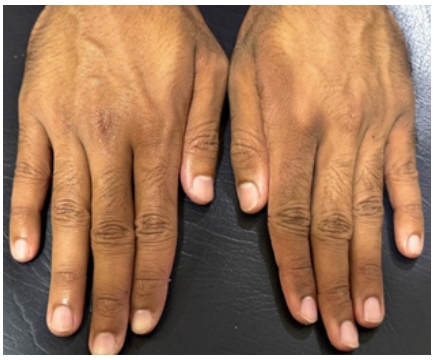

Fig. 6. *Follow up 2 months later shows marked improvement of lesions*

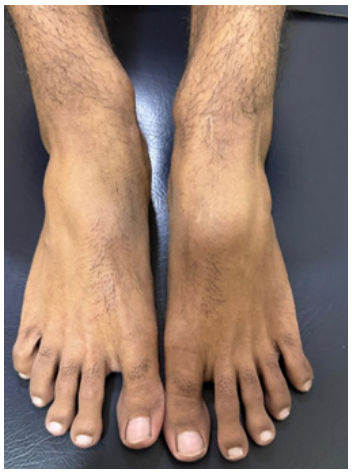

Fig. 7. *Complete resolution of lesions over feet after 2 months of Oral Acitretin.*

4. Discussion

Symmetrical acrokeratoderma has been predominantly reported in East Asian populations, particularly China. Indian case reports remain few, but suggest a similar presentation and course (2, 3).

The condition usually manifests in late childhood or adolescence, with a chronic, non-progressive course. Seasonal aggravation is commonly reported, with flare-ups during humid, warm months and resolution in colder climates. SAK presents as asymptomatic brownish plaques distributed symmetrically over the acral sites like wrists and ankles.

Our patient's clinical course—onset at 10 years, bilaterally symmetric acral involvement, aquagenic maceration, and seasonal variation (Fig. 1-4), is consistent with classical presentations.

The pathogenesis remains incompletely understood. Proposed mechanisms include:

- **Genetic predisposition:** Mutations in the Transcription Factor 4 (TCF4) gene may lead to overexpression of epidermal differentiation markers such as KRT1 and KRT14, loricrin, involucrin which results in epidermal hyperkeratosis (4).
- **Aquaporin-3 dysregulation:** Downregulation in lesional and perilesional skin causes increased trans-epidermal water loss which increases dryness and structural fragility (4).

Table I summarizes the differential diagnoses of symmetrical acrokeratoderma based on clinical features and distinguishing factors (5).

Table I. *Comparison of differential diagnoses for SA.*

Differential Diagnosis	Typical Sites Affected	Common Age/ Sex Profile	Key Clinical Features	Symptoms During Water Immersion	Other Associated Features
Symmetrical Acrokeratoderma	Dorsum of hands and feet; spares palms and soles	Young males, especially Asians	Brownish-black symmetric hyperkeratotic plaques; exacerbates in summer	Whitish maceration after water, reverting on drying	Seasonal variation; asymptomatic
Aquagenic Syringeal Acrokeratoderma	Palms and soles	More common in adolescent females	Burning, tingling sensation, translucent whitish papules after water exposure	Prominent symptoms; "hand-in-the-bucket sign"	Often associated with cystic fibrosis

Differential Diagnosis	Typical Sites Affected	Common Age/ Sex Profile	Key Clinical Features	Symptoms During Water Immersion	Other Associated Features
Acral Acanthosis Nigricans	Acral areas, commonly around joints	Middle-aged to elderly adults	Velvety, hyperpigmented plaques, usually non-palpable thickening	No effect on water immersion	Associated with obesity, insulin resistance
Palmoplantar Keratoderma	Palms and soles	Common in adolescents	Diffuse or focal hyperkeratosis; itching, burning, or pain	No change or effect with water immersion	May have genetic background; sometimes painful

Histopathologically epidermal hyperkeratosis, irregular acanthosis, orthokeratosis of stratum corneum and perivascular lymphocytic infiltrate in papillary dermis is noted, consistent with the findings observed in our case (Fig. 6).

Currently, there is no definitive treatment. Topical corticosteroids, are typically ineffective. Oral Acitretin 25mg was used in our case following which patient showed marked symptomatic improvement. Other topicals like Retinoids, Salicylic acid and Urea provide symptomatic relief. Botulinum toxin has been used recently which showed improvement in skin texture, thickness, pigmentation and extent of lesions (6, 7). A study done by Keshavamurthy et al. (2016) on Indian case reports on symmetrical acrokeratoderma described the most common sites of presentations of Symmetrical acrokeratoderma in Indian patients and their response to treatment (8) (Table II).

Table II. *Clinical presentation and treatment response in indian patients with SA.*

Patient No	Age at Onset (Years)	Duration of Disease (Years)	Sites Involved	Treatment Received	Response
1	11/M	4	Knuckles, interphalangeal joint, wrist, elbow	Topical retinoic acid + 10% urea, Acitretin 10 mg/day 16 weeks	Complete clearance
2	21/M	2	Knuckles, wrist, ankle	Acitretin 25 mg/day 12 weeks, topical 10% urea	Complete clearance; seasonal recurrence
3	24/M	6	Dorsum of hand and feet, wrist, flexural forearm, ankle, shins, knee	Topical retinoic acid 0.1% gel, 10% urea	Mild improvement; relapse in summer
4	28/M	5	Dorsum of hand and feet, forearm	Acitretin 25 mg 4 weeks, topical 10% urea	Complete clearance; seasonal recurrence
5	31/M	4	Dorsum of hand and feet, forearm, shin	Acitretin 25 mg 8 weeks then 10 mg 16 weeks, topical 10% urea	Complete clearance; seasonal recurrence

Patient education remains vital, particularly regarding avoidance of prolonged water exposure and managing expectations about the chronic course.

5. Conclusion

Symmetrical acrokeratoderma is an underrecognized, benign dermatological entity. Characterized by symmetric acral plaques with water-induced maceration and seasonal variability, it is often misdiagnosed or given ineffective treatment due to lack of existing literature.

Recognition of its unique clinical features, particularly the aquagenic maceration, seasonal pattern and its association with atopy is crucial for dermatologists. Histopathology supports the diagnosis, though is not pathognomonic.

This case adds to the growing evidence of symmetrical acrokeratoderma in Indian populations and underscores the need for awareness and further study into its pathogenesis and treatment.

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Narrative review

Beyond the Surface: Porokeratotic Eccrine Nevus as a Marker of Genetic Mosaicism and Potential Malignancy

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KEYWORDS

Porokeratotic eccrine ostial and dermal duct nevus, PEODDN, mosaicism, GJB2, connexin 26, eccrine duct, gap junction dysfunction, skin cancer, adnexal hamartoma, narrative review, malignancy surveillance

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ABSTRACT

Porokeratotic eccrine ostial and dermal duct nevus (PEODDN) is a rare skin condition that usually appears as clusters of thickened, wart-like bumps tracing the body's natural skin lines. While it's generally considered harmless, there's growing evidence that it may sometimes evolve into skin cancer, particularly squamous cell carcinoma. Recent research suggests that the condition may stem from mosaic mutations in the GJB2 gene specifically affecting a protein called connexin 26, which plays a key role in how skin cells and sweat glands communicate. This narrative review aims to be the first comprehensive synthesis that brings together what we currently know about PEODDN, from how it looks and behaves to the genetic factors behind it and the risk of it turning cancerous. A central focus is the role of connexin 26 dysfunction in breaking down the normal interactions between skin layers and sweat gland ducts. We also highlight a major gap in the research: there's still no clear model linking the underlying genetic changes to the skin changes we see under the microscope, how the condition progresses over time, or the likelihood of cancer. We conducted a comprehensive review of studies published from 2015 to 2025, using databases like PubMed, Scopus, and Web of Science. We focused on articles that explored the genetics, clinical features, risk of malignancy, or treatments for PEODDN. Only English-language studies with full-text access were included. Our aim was to identify patterns, highlight knowledge gaps, and suggest directions for future research.Across the literature, mosaic mutations in GJB2 and the resulting issues with connexin 26 emerge as a recurring theme in how this condition starts and possibly leads to cancer. Yet, despite numerous case studies, there's still no unified explanation that connects these genetic findings to the clinical course or cancer risk. There are no formal guidelines for monitoring patients, and current treatments mainly surgical removal or laser therapy offer mixed results. This review offers a new way of looking at PEODDN by tying together its clinical, genetic, and cancer-related aspects. We propose a working model that connects connexin dysfunction to both the development of lesions and the possibility of malignancy. There's a clear need for standardized diagnostic tools, long-term monitoring protocols, and genetic counseling for patients with widespread or unusual presentations.

1. Intoduction

Porokeratotic Eccrine Ostial and Dermal Duct Nevus (PEODDN) is a rare cutaneous hamartomatous disorder distinguished by abnormal keratinization involving the eccrine sweat glands (particularly the acrosyringium) and by characteristic histologic features, including cornoid lamellae. Clinically, patients typically present with multiple punctate or keratotic papules that are often localized to the palms or soles. These lesions frequently follow linear or blaschkoid patterns, reflecting mosaic epidermal cell migration established during embryogenesis.

Epidemiologically, PEODDN remains exceedingly uncommon. Until recently, estimates often cited "fewer than 100 documented cases" in the literature. A review in 2021 reported at least 81 cases identified; more recent case reports and series continue to add new instances, including atypical adult-onset and solitary lesion presentations. There is no clear gender predilection, and though most cases are congenital or manifest in infancy or early childhood, there is a nontrivial proportion of late-onset cases. At the molecular level, recent advances have strengthened the hypothesis that PEODDN is a mosaic skin disorder caused by somatic mutations, particularly in GJB2 (the gene encoding connexin-26). Studies have identified somatic GJB2 mutations in affected tissue that are absent in unaffected skin, supporting post-zygotic mutation and clonal expansion of altered epidermal cells. The mosaicism model aligns with the linear (Blaschkoid) distribution of lesions and with the observed variability in clinical presentation—even among patients with similar genetic findings.

In terms of clinical behavior, while PEODDN lesions are generally benign and asymptomatic, there have been reports of malignant transformation, most notably squamous cell carcinoma arising within long-standing lesions. Also, associations with other conditions—such as sensory polyneuropathy, hyperthyroidism, deafness, breast hypoplasia, and even systemic manifestations—have been documented, suggesting that even though the disease is primarily skin-limited, its impact can be broader in certain cases.

Given the rarity of PEODDN, the variability of its onset, presentation, and associated risks, there remains a need for comprehensive reviews integrating the most recent epidemiologic, genetic, and clinical data. This review aims to synthesize these findings in order to aid recognition, diagnosis, risk stratification, and management of PEODDN, and to highlight gaps for future research.

2. Clinical and Histologic Features of PEODDN

Typical lesion morphology of porokeratotic eccrine ostial and dermal duct nevus (PEODDN) comprises linear arrays of pinpoint to filiform, spiny keratotic papules that may coalesce into verrucous plaques; lesions can occasionally form cutaneous horn–like projections and often involve acral skin, including palms/soles, with ostial keratotic plugs visible clinically (1). Many cases are congenital or arise in early childhood (2). The disease may be widespread or remain localized and can be asymptomatic or pruritic (3). The coronoid lamella, a thin column of tightly packed parakeratotic cells overlying an area of epidermal dyskeratosis, is typically centered over eccrine ducts, which distinguishes PEODDN from other porokeratoses and epidermal nevi.

The distribution of PEODDN characteristically follows the lines of Blaschko in linear or whorled patterns, reflecting mosaicism (4). The involvement may be unilateral or, less commonly, extensive and bilateral and widespread (4). Blaschkoid distribution across extremities and trunk has been repeatedly documented, with frequent distal extremity predominance and palmoplantar extension (4). Rarely, atypical presentations have been documented, including localized, non-Blaschkoid or segmental lesions, and rare cases with systematized or widespread involvement (5). While the Blaschkoid distribution is most common, the diagnosis of PEODDN should not be excluded solely based on atypical or non-Blaschkoid presentation.

Histopathology typically reveals hallmark porokeratotic columns (cornoid lamellae) originating from adnexal ostia (6). This is most commonly found in the eccrine acrosyringia and, in some cases, hair follicles that are overlying areas of acanthosis and hyperkeratosis (6). Serial sections may demonstrate direct continuity with the eccrine ductal openings. Common misdiagnoses include inflammatory linear verrucous epidermal nevus (ILVEN), linear porokeratosis, linear epidermal nevus, viral warts, linear psoriasis, and other keratinization disorders. Key clinical features and differential diagnoses are summarized in Table I.

Table I. *Summary of clinical features and differential diagnosis.*

Category	Summary
Typical age at onset	Congenital or early childhood (rarely later)
Morphology	Linear arrays of small, spiny or filiform hyperkeratotic papules; may coalesce into verrucous plaques; ostial keratotic plugs often visible; occasional cutaneous horn–like projections
Distribution	Acral predilection (palms, soles, distal extremities); localized or widespread/systematized involvement; commonly follows lines of Blaschko in linear, whorled, or blaschkoid patterns; unilateral or extensive bilateral in systematized cases
Symptoms	Often asymptomatic; pruritus possible
Histopathology	Hyperkeratosis and acanthosis with hallmark porokeratotic columns (cornoid lamellae) arising from adnexal ostia—classically eccrine acrosyringia—with parakeratotic plugs and diminished/absent granular layer; serial sections may show continuity with eccrine ducts; occasional follicular involvement
Genetics	Somatic GJB2 mutations in mosaic pattern identified in subset of cases
Differential diagnosis	Inflammatory linear verrucous epidermal nevus (ILVEN); linear porokeratosis; linear epidermal nevus; verruca vulgaris; linear psoriasis; other keratinization disorders
Distinguishing clues	Adnexal-based cornoid lamellae favor PEODDN/PAON over classic porokeratosis variants
Associated findings	Rare extracutaneous anomalies; very rare malignant transformation in widespread disease—surveillance recommended in extensive cases
Treatment Options	Topical keratolytics, retinoids, cryotherapy, CO_2 laser, surgical excision; variable efficacy

Out of these, ILVEN and linear porokeratosis are particularly challenging to differentiate from PEODDN since both can present with linear, verrucous, or psoriasiform lesions. Linear psoriasis can also mimic PEODDN, especially if distributed along Blaschko's lines. Clinical annularity alone is insufficient for diagnosis; the presence of adnexal-based cornoid lamellae favors PEODDN over classic porokeratosis variants (6).

3. Genetic Mosaicism and the Role of *GJB2*

Postzygotic mosaicism provides a compelling explanation for the emergence of PEODDN, evidenced by molecular studies showing pathogenic GJB2 mutations present exclusively in lesional skin. For example, whole-exome sequencing revealed a somatic p.Gly45Glu (G45E) mutation in GJB2, observed in affected tissue but absent in blood, confirming that a somatic mutation alone suffices to produce PEODDN lesions (7). Another case identified both a germline heterozygous and a postzygotic somatic GJB2 mutation in PEODDN tissue, indicating that compound mosaicism may broaden the mutational spectrum and contribute to disease phenotype (8). Broader reviews affirm that PEODDN results from GJB2 (Cx26) mutations confined to affected keratinocytes, consistent with mosaic forms of keratitis-ichthyosis-deafness (KID) syndrome, and emphasize the necessity of genetic counseling because of potential germline or gonadal involvement (9, 6). These findings reinforce a clear model wherein connexin 26 disruption via postzygotic mosaicism underlies the localized skin pathology of PEODDN and carries reproductive implications.

Connexin 26 (GJB2) encodes a gap-junction protein essential for intercellular communication, forming connexons that permit ions and signaling molecules to pass between adjacent epidermal and eccrine duct cells (10). Mutations affecting the protein's structure can impair docking, gating, or calcium regulation, thereby disrupting keratinocyte differentiation and eccrine duct function. In syndromic disorders such as KID syndrome, dominant GJB2 mutations similarly compromise skin and hearing through altered connexin function, offering a mechanistic parallel to PEODDN (11, 12). Moreover, mosaic manifestations of "lethal" GJB2 mutations in conditions like spiny hyperkeratosis illustrate how the timing and localization of somatic mutations shape phenotype dramatically (6, 13). These parallels underscore that localized connexin-26 dysfunction not only drives the keratotic adnexal lesions seen in PEODDN, but may also confer an elevated risk of malignant transformation through disruption of cell–cell signaling.

4. Malignancy Risk: Case Reports and Molecular Clues

PEODDN has been considered a rare, benign hamartoma of abnormal keratinization with unclear pathogenesis, with fewer than 100 reported cases to date. It shares some overlapping clinical features with porocarcinoma a malignant adnexal neoplasm with nuclear pleomorphism, atypical mitoses, and invasive growth patterns (14). However, the typical histologic presentation of PEODDN lacks these malignant cytologic features, distancing it from malignancy. Despite this, rare associations of PEODDN with squamous cell carcinoma (SCC) have been reported, along with other associated conditions such as hyperthyroidism, sensory polyneuropathy, and developmental delays (15). These associations suggest that PEODDN may represent a disorder with broader systemic conditions rather than being confined to a simple cutaneous process. In addition to two cases of SCC in situ have been described in PEODDN, one involving a lesion on the left sole and another presenting with widespread PEODDN with diffuse ulcers, Fang et al. reported the first case of PEODDN that progressed to metastatic SCC with lymph node (16). Altogether, these three cases indicate that although PEODDN is generally benign, it may carry a low but recognizable risk of malignant transformation and metastasis in certain clinical scenarios (Table II).

Table II. *Malignancy Risk Factors Reported in Porokeratotic Eccrine Ostial and Dermal Duct Nevus (PEODDN).*

Risk Factor	Description
Widespread or systematized involvement	Extensive cutaneous involvement increases the likelihood of secondary mutational events and chronic irritation, and has been observed in cases progressing to squamous cell carcinoma (SCC).
Ulceration or chronic erosion	Ulcerative lesions show increased cellular turnover and inflammation, creating a microenvironment prone to dysplasia and malignant transformation.
Long-standing duration	Long-persistent lesions may accumulate additional somatic mutations over time, facilitating progression from benign hamartoma to SCC in situ or invasive SCC.
Compound or second-hit GJB2 mutations	The presence of both germline and somatic GJB2 mutations (or additional somatic oncogenic mutations) results in greater connexin-26 dysfunction and genomic instability.
Delayed or missed diagnosis	Misclassification as inflammatory or keratotic dermatosis may delay histologic confirmation and surveillance, allowing malignancy to remain unnoticed.
Coexisting chronic inflammation	Overlapping inflammatory conditions may promote keratinocyte atypia and accelerate oncogenic pathways.
Underrepresentation in skin-of-color diagnostic references	Reduced contrast and variability in lesion appearance may lead to diagnostic delay in patients with darker skin tones, prolonging exposure of affected cells to oncogenic triggers.

5. Management Strategies and Therapeutic Outcomes

There are no standardized treatment guidelines for PEODDN, and only limited therapies have been described in the literature. Reported management strategies range from conservative observation to procedural intervention, with treatment decisions typically guided by lesion extent, symptom burden, and concern for malignant transformation. Spontaneous resolution has been reported, and as lesions are often asymptomatic, PEODDN may not always warrant treatment (14, 20-22). In such cases, careful observation with periodic follow-up may be an appropriate strategy. When therapy is pursued, conventional topical treatments such as corticosteroids, keratolytic agents, and topical retinoids have generally shown limited efficacy (23, 24). One group reported the first successful use of topical flufenamic acid (FFA), a hemichannel inhibitor that improved skin lesions in mouse models carrying GJB2 gene variants (24). This targeted approach may hold promise for patients with confirmed connexin 26 mutations. Beyond topicals, systemic retinoids have shown mixed results, with favorable outcomes only in select cases (25). Overall, medical approaches have shown inconsistent results with no clear evidence to guide best practice.

Procedural interventions are another avenue of treatment for PEODDN. For localized disease, surgical excision via shave removal, for instance, offers histopathologic confirmation and the potential for complete removal, making it particularly suitable for small, well-circumscribed lesions (26-28). Ablative laser techniques, most notably CO2 laser and combined erbium/CO2 laser, have shown great promise due to favorable short-term improvement and cosmetic outcomes (14, 28). However, recurrence rates remain poorly characterized due to limited long-term follow up. Significant gaps persist in PEODDN care, including the absence of evidence-based treatment algorithms, lack of long-term outcome data, and minimal patient-reported quality of life assessments. Recurrence rates following excision or laser therapy are unknown, and the durability of medical interventions is uncertain. The possibility of progression to squamous cell carcinoma (29) further complicates management decisions, emphasizing the need for shared decision-making with patients regarding treatment benefits and risks, structured surveillance protocols, and thresholds for prophylactic excision. There is currently no consensus on malignancy risk stratification or the role of genetic counseling. Addressing these unmet needs will require multicenter registries, randomized controlled trials, and prospective longitudinal follow-up.

6. Diagnostic Limitations and Differential Considerations

Porokeratotic eccrine ostial and dermal duct nevus (PEODDN) often presents diagnostic challenges due to its rarity, fewer than 100 reported cases, and variable clinical presentation. Due to its punctate or linear keratotic papules and Blaschkoid distribution, it is often mistaken for common dermatologic entities such as comedo nevus or linear porokeratosis. While PEODDN is traditionally considered a pediatric condition, in some cases, patients with solitary adult-onset lesions have been initially misdiagnosed as inflammatory or common keratotic dermatoses, delaying appropriate treatment. For example, one reported case involved a late-onset, solitary ankle lesion in a 64-year-old, emphasizing that PEODDN can present atypically (14). This puzzled clinicians who were accustomed to pediatric presentations. This case highlights the importance of including PEODDN in the differential diagnosis for solitary lesions in atypical locations, even in older patients. Bandyopadhyay et al. expanded upon this by presenting a detailed case of a 23-year-old man with linear lesions on the palm and forearm, where PEODDN was initially mistaken for inflammatory dermatoses (30).

PEODDN recognition can be more challenging in patients with darker skin tones due to their underrepresentation in dermatologic literature and educational resources. Alvarado et al. (31) expand upon this by examining how dermatology educational materials, such as textbooks, online cases, and atlases, predominantly feature lighter skin tones. This imbalance impairs clinicians' ability to recognize dermatological conditions on darker skin tones. For example, one patient with a rash was diagnosed with toxic epidermal necrolysis but waited in the emergency room for several hours because the natural pigmentation of their skin made the "characteristic" redness that dermatologists look for appear far more subtle (32). Unfamiliarity with darker skin often contributes to the delay in diagnosis and treatment for this patient. This underrepresentation extends to artificial intelligence diagnostic models, which depict decre-

ased performance on images from patients with skin of color, especially for rare conditions such as PEODDN (33). The reduced contrast and pigmentation variations regularly mask important features, contributing to delayed or missed diagnoses. Integrating skin-of-color clinical presentations and image databases into dermatologic education will enhance representation and improve early recognition for PEODDN in all skin types.

Furthermore, another factor for diagnostic delays for PEODDN is the histologic overlap with other common dermatologic disorders. Under the microscope, PEODDN reveals a hallmark coronoid lamella overlying dilated acrosyringia, accompanied by loss of the granular layer and occasional dyskeratosis (34, 35). However, similar coronoid lamellae can be seen in linear porokeratosis or porokeratosis of Mibelli, potentially misleading interpretation (14). Nevus comedonicus can also mimic the clinical appearance, especially in locations lacking pilosebaceous units, such as palms and soles. In addition, inflammatory linear verrucous epidermal nevus (ILVEN), linear psoriasis, and other adnexal hamartomas often overlap histologically, further confusing the diagnostic picture (35). Therefore, close collaborations between dermatologists and pathologists are often needed.

Finally, PEODDN is now understood to arise from somatic mosaic mutations in the GJB2 gene affecting connexin 26. Awareness of its genetic basis can help prompt consideration of PEODDN in atypical or ambiguous presentations (36). Understanding the role of GJB2 mutations not only accounts for the mosaic distribution pattern but also provides a framework for interpreting unusual cases. Chang et al. explained a "two-hit" model, in which a germline heterozygous GJB2 mutation is followed by a postzygotic somatic mutation, as shown in an 18-year-old female with congenital, linear hyperkeratotic papules on the fingers (37). This dual-mutation mechanism may explain the variability in lesion morphology and why clinicopathologic findings can at times be equivocal. Thus, improved clinical recognition combined with genetic insights will reduce misdiagnosis and delays in treatment.

7. Future Research and Surveillance Guidelines

Molecular and Genetic Investigations

Future investigations into PEODDN, a rare adnexal hamartoma, should prioritize elucidating its molecular underpinnings, particularly its association with postzygotic mosaic mutations in GJB2, which encodes connexin-26. These mutations have been identified in both isolated lesions and syndromic presentations, supporting a broader spectrum of connexin-related mosaic disorders (38-40). Further research should aim to uncover additional genetic drivers through whole-exome or targeted sequencing of lesional tissue, focusing on disrupted eccrine gland development and keratinization pathways (41, 42). In vivo systems and patient-derived organoids may help clarify the downstream effects of these mutations and their potential to trigger secondary neoplastic transformation. Spatial transcriptomics also offers a promising tool to map aberrant signaling pathways and cellular interactions within lesional microenvironments, which may uncover novel molecular targets (43, 44). Incorporating molecular profiling into diagnostic workflows may improve subtype classification, inform prognosis, and guide genetic counseling, especially for patients with congenital or widespread disease.

Surveillance and Clinical Management Protocols

Surveillance strategies should evolve in tandem with these molecular insights, especially given PEODDN's variable clinical course and potential for malignant transformation. Although traditionally regarded as benign, several case reports have documented squamous cell carcinoma arising within longstanding lesions (45-47). Evidence-based monitoring protocols should combine dermatologic imaging techniques—such as dermoscopy or reflectance confocal microscopy—with symptom tracking and periodic biopsy to guide intervention thresholds. Because many lesions follow a Blaschkoid distribution, suggestive of early embryonic mosaicism, systemic evaluation is warranted in congenital or extensive presentations to identify possible extracutaneous involvement (9, 11). Quality-of-life assessments should be incorporated into routine care, as PEODDN may cause pruritus, pain, or psychosocial distress depending on location and extent. AI-assisted

image analysis and digital lesion tracking may further enhance surveillance accuracy and reduce interobserver variability. Ultimately, interdisciplinary collaboration across dermatology, genetics, oncology, and pathology will be essential to develop comprehensive surveillance algorithms that reflect both clinical variability and emerging molecular insights.

7. Discussion

Molecular

The extremely uncommon adnexal hamartoma known as Porokeratotic Eccrine Ostial and Dermal Duct Nevus (PEODDN) is characterized by aberrant keratinization surrounding eccrine acrosyringia. It frequently manifests as linear or whorled patterns that follow the lines of Blaschko. PEODDN, which was formerly thought to be a benign congenital or early-onset disease, is now understood to be a postzygotic mosaic condition, mostly caused by somatic mutations in GJB2. The idea of embryonic mosaicism is supported by the finding of connexin-26 mutations limited to lesional tissue, which explains both the localized distribution and the broad range of clinical phenotypes, from solitary filiform papules to systematized dermal involvement across multiple body segments. These molecular insights have also shifted the clinical understanding of PEODDN, suggesting potential reproductive implications, particularly in patients harboring compound germline and somatic mutations.

Clinical Evidence

The majority of PEODDN lesions are stable and asymptomatic, and conservative treatment is frequently used. For isolated, asymptomatic lesions, observation with recurring follow-up is suitable. Although long-term recurrence rates are unclear, ablative CO2 laser therapy and surgical excision have shown promising results for lesions that are symptomatic or cosmetically problematic. The potential for molecularly guided interventions is shown by newly developed targeted medications such topical flufenamic acid, which inhibits connexin hemichannels. Developmental delay, hyperthyroidism, and sensory polyneuropathy are examples of extracutaneous symptoms that suggest the clinical spectrum may be wider than previously thought.

8. Case-Based Reports and Oncogenic Potential

Squamous cell carcinoma in situ and even metastatic squamous cell carcinoma originating inside long-standing or widespread PEODDN lesions have been reported in case reports, however they are uncommon. PEODDN may act as a precursor in a multi-step tumorigenesis pathway involving dysregulated gap-junction signaling and impaired keratinocyte differentiation. Malignant progression seems more likely in the context of chronic ulceration, widespread distribution, or presumed second-hit genetic events.

9. Recommendations and Future Directions

Advanced diagnostic techniques including dermoscopy, reflectance confocal microscopy, and digital lesion tracking should be used in surveillance regimens to maximize patient care and reduce the risk of cancer. For developing or ulcerated lesions, especially those with systematized or congenital distribution patterns, a low threshold for biopsy is advised. Reducing recognition disparities requires more skin-of-color photos to be included in training materials and diagnostic datasets. To create evidence-based risk stratification tools, improve diagnostic frameworks, and direct targeted therapies, long-term, multi-institutional cooperation and longitudinal data gathering will be essential. Precise diagnosis and better long-term results for individuals with PEODDN will require a multidisciplinary approach encompassing dermatology, pathology, clinical genetics, and oncology.

Authors Declare No Conflict of Interest

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