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REVIEW ARTICLE

Primary Localized Cutaneous Amyloidosis of Keratinocyte Origin: An Update with Emphasis on Atypical Clinical Variants

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Abstract

Amyloid is a protein derived from at least 20 different substances. Once misfolded, it results in a group of cutaneous and systemic conditions. Primary localized cutaneous amyloidosis of keratinocyte origin is a very common subtype that can manifest either as lichen or macular amyloidosis, lacking systemic involvement. Lichen amyloidosis often presents as multiple hyperpigmented papules on the lower extremities whereas macular amyloidosis is classically characterized by dark brown rippled macules on the interscapular area. Review of the literature reveals that in addition to the classical presentation of primary localized cutaneous amyloidosis there exists a plethora of various manifestations that can be grouped into either geographic or morphologic categories. This review provides clinicians with the intimate knowledge of these presentations and summarizes the available treatment modalities.

Key Points

Primary localized cutaneous amyloidosis is a frequently encountered skin condition with a heterogeneous spectrum of clinical manifestations.

Classifying the clinical spectrum into geographic and morphological categories assists dermatologists in the timely recognition of the correct diagnosis.

1 Introduction

Amyloidosis refers to a group of conditions that share a common feature of abnormal deposition of eosinophilic misfolded proteins, amyloid fibrils, in various tissues [1]. It is divided into cutaneous and systemic forms based on localization but can be subgrouped based on biochemical structure [1, 2]. Primary localized cutaneous amyloidosis (PLCA) can be either keratinocyte derived in macular and lichen amyloidosis or immunoglobulin light chain derived in nodular amyloidosis. Secondary forms are also keratinocyte derived and can be seen in benign and malignant cutaneous tumors [1].

Primary localized cutaneous amyloidosis is a commonly encountered skin condition; hence, dermatologists can easily recognize the patches of skin of abnormal texture or color. Nonetheless, there are presentations that are atypical and need to be emphasized. In this review, we aim at focusing on the atypical morphology and distribution of keratinocyte-derived PLCA, to evaluate the histological features, associated differential diagnosis, and finally, to provide an updated management appraisal (Table 1).

2 Pathogenesis

Amyloid was described more than 150 years ago, initially thought to be a cellulose-like material and then discovered to be a protein, synthesized from more than 20 substances including keratin. Electron microscopy studies have shown that amyloid is made up of nonbranching fibrils that are arranged into β-pleated sheets but can also be found in alpha-helices. Amyloidosis manifests when these sheets are misfolded resulting in extracellular deposits [2].

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Table 1 Review of the available therapeutic modalities of primary localized cutaneous amyloidosis

Treatment	Considerations
Topical therapy	
Capsaicin	Anti-pruritogenic via cutaneous histamine-sensitive and mechanosensitive C and Aδ fibers Lichen amyloidosis (concentration: 8%): improvement in lesions clinically and histologically along with a reduction in pruritus Macular amyloidosis (concentration: 0.025%): no effect Notable side effects (initial burning sensation and self-limited erythema) [8] Amyloidosis cutis dyschromica: varying success [26, 59]
Corticosteroids (potent topical applied once or twice daily)	Anti-inflammatory Macular amyloidosis: no improvement [8] Lichen amyloidosis: long-term resolution in lesions and improvement in pruritus when combined with topical salicylic acid 25% ointment [56] Lichen amyloidosis (intralesional triamcinolone acetonide 10 mg/mL): improvement in pigmentation [60] Amyloidosis cutis dyschromica: varying success [26, 59] Bullous keratinic amyloidosis: mild effect on trunk lesions with poor response on extremity lesions [37]
Dimethyl sulfoxide	Penetration enhancing function and anti-inflammatory Lichen and macular amyloidosis: conflicting findings [8] Amyloidosis cutis dyschromica: varying success [26, 59] Notable side effects (contact urticaria, desquamation of skin, and burning sensation)
Hydrocolloid dressings	Mechanical prevention of scratching Lichen amyloidosis: improvement of pruritus and cosmetic appearance Recommended as first-line therapy [8]
Menthol	Cooling sensation via cold-sensitive, transient receptor, potential cation channel subfamily M member 8 in the skin and reduces pruritus via κ-opioid receptors Lichen amyloidosis: flattening of papules and almost complete resolution of pruritus [8]
Retinoids (tazarotene, tocoretinate, and tretinoin)	Induce apoptosis and stimulate macrophages assisting in the removal of the extracellular material Macular amyloidosis (tazarotene): no improvement in appearance of lesions with alleviation of pruritus Lichen and macular amyloidosis (tocoretinate): variable results Macular amyloidosis (tretinoin): minimal relief in pruritus Watch out for typical side effects [8] Amyloidosis cutis dyschromica (tazarotene): no satisfying result [61]
Tacrolimus 0.1%	Decreases T-cell activity and inflammation Lichen amyloidosis: absence of pruritus and marked decrease in thickness of plaques [62]
Vitamin D_3 analogs (calcipotriol)	Modulate keratinocyte differentiation, proliferation, and inflammation Reduction of roughness, hyperpigmentation, and itching No significant difference compared to betamethasone 17-valerate [8]
Systemic therapy	
Amitriptyline 10 mg/day	Tricyclic antidepressant indicated in neuropathic itching Lichen amyloidosis: resolution of pruritus with no change in skin lesions [8]
Cepharanthine 2 mg/day	Anti-inflammatory via reduction in radical oxygen species Lichen amyloidosis: flattening of papules when combined with topical betamethasone valerate ointment [8]
Colchicine 1 mg/day	Inhibits leukocyte function Macular amyloidosis: disappearance of pruritus and reduction in pigmentation Lichen amyloidosis: diminishment in pruritus, pigmentation, and disappearance of papules [63]
Cyclophosphamide 50 mg/day	Good response to itching, size, and hyperpigmentation Notable side effects (alopecia) Lichen amyloidosis: excellent response when combined with systemic corticosteroids [8]

Table 1 (continued)

Treatment	Considerations
Cyclosporine 300 mg/day or 100 mg/day when combined with narrow-band UVB	Reduce itching by inhibiting proinflammatory cytokines [8] Lichen amyloidosis: decrease in pruritus and complete resolution Lichen amyloidosis and atopic dermatitis: conflicting findings with nearly complete resolution of lesions and pruritus when combined with narrow-band UVB [8] and no clinical improvement [64] Notable side effects (hypertension) [8] Bullous keratinic amyloidosis (300 mg/day): improvement in pruritus and skin lesions without recurrence [36]
Retinoids (acitretin 0.5 mg/kg/day, alitretinoin 30 mg/day, etretinate 40–60 mg/day, isotretinoin 30 mg/day)	Induce apoptosis and stimulate macrophages assisting in the removal of the extracellular material Lichen amyloidosis: flattening of papules and decreased pruritus Biphasic amyloidosis (acitretin): resolution of pruritus with almost complete disappearance of lesions Watch out for typical side effects [8] Amyloidosis cutis dyschromica (acitretin): improvement in hyperpigmentation [26, 28, 61, 65] Poikiloderma-like + lichen amyloidosis (acitretin): relief from pruritus with improvement in papules and plaques [67]
Laser/light therapy	
Carbon dioxide laser (superficial and deep ablative rejuvenation mode)	Lichen and macular amyloidosis: reduction in pigmentation, thickness of lesions, itching, and amyloid deposits in repeated biopsies [8] with a higher decrease in pigmentation in the superficial ablative mode [68] Notable side effects (post-inflammatory hyperpigmentation that resolves with bleaching agent and topical corticosteroids) [68] Lichen amyloidosis: improvement of pruritus and resolution of papules when combined with topical steroids twice daily [66] Macular amyloidosis (fractional CO_2 + topical steroids + topical vitamin C > fractional CO_2): decrease in pigmentation, rippling, and lichenification as well as decrease in amyloid deposits histologically [69] Amyloidosis cutis dyschromica: varying success [26, 59]
Erbium:yttrium aluminum garnet laser	Lichen amyloidosis: almost complete clearance of lesions [8]
Narrow-band UVB	Lichen amyloidosis: complete resolution of lesions, improvement in itching, and clearance of amyloid deposits in repeated biopsy Macular amyloidosis: successful management of pruritus Biphasic amyloidosis: resolution of pruritus, decreased hyperpigmentation, and flattening of papules when combined with topical tacrolimus [8]
Pulsed dye laser	Lichen amyloidosis: decrease in pruritus and flattening of papules [70] Macular amyloidosis: improvement in pigmentation [71]
PUVA	Lichen amyloidosis: conflicting results Lichen amyloidosis: more significant improvement in the roughness and pruritus scores on the sides treated with either UVB or PUVA compared with topical corticosteroids Notable side effects (hyperpigmentation) [8]
Q-switch neodymium-doped:yttrium aluminum garnet laser	Macular amyloidosis (532 nm > 1064 nm): decrease in pigmentation [8]
Ytterbium/erbium laser	Lichen amyloidosis: improvement in pruritus and decrease in amyloid deposits on repeated biopsies Notable side effect (burning sensation) [8]
Surgical interventions	
Dermabrasion	Lichen amyloidosis: complete clearance without recurrence Notable side effects (delayed wound healing, superficial scarring, hypopigmentation, and a transient edema) [8]
Electrodesiccation	Lichen amyloidosis: complete clearance without recurrence [8]
'Scraping with the scalpel'	Lichen amyloidosis: disappearance of pruritus and acceptable to good clinical results Notable side effect (persistent pigment changes) [8]
Surgical excision	Not classified: recurrence in 6 months [8]
Transcutaneous nerve stimulation	Antipruritic effect not fully understood Macular amyloidosis: relief of pruritus [72]

Table 1 (continued)

Treatment	Considerations
Future perspectives	
IL-31	Study in mice targeting IL-31 pathway through photoablation lead to a reversal of the scratching behavior [58]
R-1-[6-[R-2-carboxy-pyrrolidin-1yl]-6-oxo-hexanoyl] pyrrolidine-2-carboxylic acid	Leads to depletion of the serum amyloid P component by competitively inhibiting the binding of serum amyloid P to amyloid fibrils. It also crosslinks serum amyloid P resulting in its clearance through the liver [57]

IL-31 interleukin-31, *PUVA* psoralen with ultraviolet A, *UVB* narrow-band ultraviolet B

Lichen amyloidosis was first recognized by Freudenthal when Congo red-positive hyaline bodies were noted within the epidermis and it was mistakenly thought to be extruded resulting in the cutaneous findings [2]. Better understanding of cutaneous amyloidosis was achieved once it was observed that the skin produced amyloid from degenerated basilar keratinocytes after exposure to psoralen and ultraviolet A [2]. Ultrastructural studies have corroborated those findings; degenerated tonofilaments were observed with amyloid filaments in some keratinocytes, implying the transformation of the degenerated filaments into amyloid [2].

When it comes to lichen and macular amyloidosis, the deposited substance was identified as keratinocyte-derived amyloid using immunofluorescence studies. These deposits were immunoreactive to antikeratin antibodies but not to antibodies against A protein, prealbumin, or fibronectin, other suspected precursors [2]. As for why these deposits form, the literature emphasizes the abnormal folding of proteins in the form of β-pleated sheets resulting in their extracellular presence. As mentioned, amyloid can be present in both the β-pleated and alpha-helical structures, although the former conformation predominates and is more likely to be present in PLCA. Similar to other proteins, several factors cause amyloid to accumulate in tissue [2]. First, it is proposed that when these proteins are produced in excess amounts, they tend to clump and fold into β-pleated sheets; however, even if produced in normal amounts, these proteins can develop abnormal structures under certain conditions such as low pH or the presence of metal ions or chaperones. Normally, these defective proteins are discarded through degrading mechanisms but if this fails, amyloid can deposit in tissue. Interestingly, this process is highly variable, and a lag phase is described where certain prerequisites are actually present, but the amyloid fibrils fail to form. This process can last from weeks to years, but once the first amyloid aggregation is formed, the development of the insoluble architecture soon follows [2]. With that said, the exact pathogenesis remains unclear, but it is considered to be multifactorial with both genetic and environmental risk factors associated with keratinocyte-derived amyloid formation [3].

When assessing if certain factors predispose individuals to develop PLCA, familial forms have been described. Primary localized cutaneous amyloidosis appears to be mainly sporadic but in about 10% of patients, an autosomal dominant inheritance pattern with variable penetrance can be observed [4]. In addition, PLCA is common in southeast Asia, South America, and the middle eastern region [3]. The racial susceptibility and familial aggregation suggest that underlying genetic factors must play a role in the pathogenesis of PLCA.

To date, oncostatin M receptor-beta and interleukin (IL)-31 receptor-alpha have been implicated in familial PLCA [5]. The exact link between these proteins and disease pathogenesis is not fully understood. Both receptors are members of the IL-6 cytokine receptor family, which work by JAK/STAT, MAPK, and PI3K/Akt signal transduction pathways. These receptors, through their cytokines (IL-6, IL-11, IL-27, and IL-31, and oncostatin M), play an important role in keratinocyte differentiation, proliferation, inflammation, and apoptosis, key elements in the pathogenesis of cutaneous amyloidosis [5, 6].

Oncostatin M receptor-beta is a component of both the OSM type II receptor and the IL-31 receptor. Oncostatin M receptor-beta unites with IL-31 receptor-alpha to form the IL-31 receptor [4, 7]. Autosomal dominant and recessive mutations in the fibronectin domain of oncostatin M receptor-beta have been reported in familial PLCA [5, 7, 8]. These studies suggest that missense mutations lead to aberrant IL-31 signaling, which is directly related to the clinical symptom of itch [7, 8]. The latter is plausible

because IL-31 is also implicated in pruritic skin conditions such as prurigo nodularis. In addition, the IL-31 inhibitor, nemolizumab has been demonstrated to be useful in treating chronic pruritus in atopic dermatitis [6, 9].

In families with PLCA, aberrant IL-31 signaling may also cause downstream failure to induce expression of monocyte chemotactic protein-1. Monocyte chemotactic protein-1 is important in the recruitment of immune cells such as monocytes, which subsequently differentiate into macrophages when inflammation or injury is detected. The absence of monocyte chemotactic protein-1 results in failure to initiate the proper innate immunity response needed to establish a scavenging system and to clear cellular debris [10].

Further confirming the involvement of genetic factors, PLCA has been associated with syndromes such as pachyonychia congenita, familial palmoplantar keratoderma, and multiple endocrine neoplasia type 2A (MEN2A) [11, 12]. The strongest association has been noted with MEN2A; a rare autosomal dominant syndrome characterized by medullary thyroid carcinoma, pheochromocytoma, and parathyroid tumors. This disorder is related to a germline mutation of the RET protooncogene, located on chromosome 10 [12]. Efforts to map the predisposing gene failed to provide direct evidence implicating RET in the pathogenesis of PLCA, but patients affected by this syndrome frequently report neurological itching on the upper back, even prior to the development of PLCA; a vital screening sign of this disorder. Review of the reported cases revealed that MEN2A-related PLCA seems to be more common in women and is the second most common manifestation of MEN2A, preceded only by medullary thyroid carcinoma [13]. As not all MEN2A patients have cutaneous amyloidosis, it is reasonable to assume that the gene of familial PLCA is separate but linked to the MEN 2A locus in the pericentromeric region of chromosome 10 [12].

3 Classical Clinical Variants

Classically, PLCA is divided into macular and lichen (Fig. 1), nonetheless, it is important to note that these entities represent the ends of a clinical spectrum. In fact, some lesions exhibit features of both macular and lichen amyloidosis, which is termed "biphasic amyloidosis" [1, 2, 14].

Macular amyloidosis is characterized by hyperpigmented grayish-brown patches either in a rippled or confluent pattern. The former being more evident upon stretching of the skin. This condition affects most commonly the upper back, especially the scapular area, followed by the extensor surfaces of the extremities. It is often accompanied by pruritus, but it can also be asymptomatic. Pruritus may even precede clinically evident lesions. In biphasic amyloidosis, papular lesions are seen on a background of hyperpigmentation [1, 2, 14].

Lichen amyloidosis is the most common form of PLCA. Initially, it presents as firm, discrete, hyperkeratotic, matchhead to pea-sized, skin-colored or hyperpigmented, dome-shaped or hemispheric papules [14]. Later on, the lesions coalesce into plaques with a rippled pattern. An asymmetric distribution is occasionally noted early on. With time, the lesions progress to a symmetric pattern. The most common site involves the pretibial area but other extensor surfaces, such as thighs and forearms, can be affected.

4 Differential Diagnosis

Notalgia paresthetica shows a significant overlap with macular amyloidosis and should be entertained in the differential diagnosis. The former presents on the upper back and can have a rippled hyperpigmentation [15]. On histology, notalgia paresthetica demonstrates scattered melanophages but no amyloid deposits. When macular amyloidosis adopts a more diffuse form, it should be differentiated from post-inflammatory hyperpigmentation [16]. Other conditions to be ruled out are atrophic lichen planus [17],

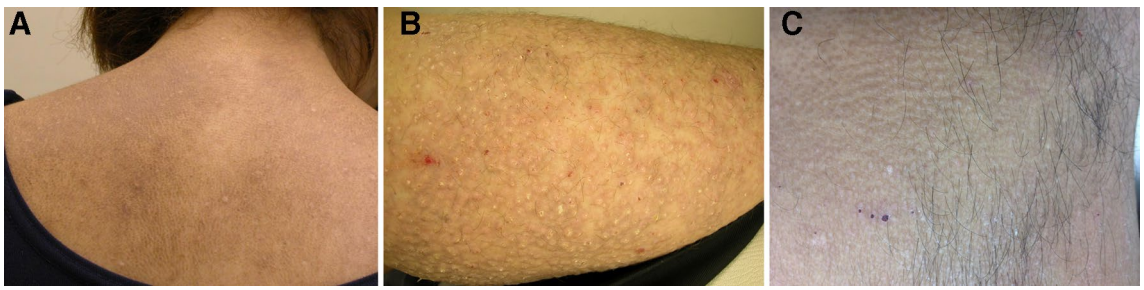

Fig. 1 Cutaneous amyloidosis: classical macular (**A**), lichen (**B**), and both macular and lichen amyloid (**C**) together

Table 2 Differential diagnosis of clinical variants of PLCA

Condition	Clinical presentation	Pathology presentation	Comments
Macular amyloidosis			
Atrophic lichen planus	Coalescence of papules into large plaques with an atrophic center and residual hyperpigmentation [17]	Hyperkeratosis without parakeratosis Focal hypergranulosis Irregular acanthosis with a "sawtooth" appearance Vacuolar degeneration of the basal cell layer Band-like lymphocytic infiltrate at the dermal-epidermal junction [17]	Commonly seen in intertriginous areas and the lower extremities unlike PLCA [17]
Drug-induced hyperpigmentation	Nonspecific and variable acquired pigmentation Frequently seen on sun-exposed areas [19]	Variable according to the molecule [19]	Main culprits are nonsteroidal anti-inflammatory drugs, antimalarials, amiodarone, cytotoxic drugs, tetracyclines, heavy metals, and psychotropic drugs [19]
Erythema dyschromicum perstans	Slowly progressive symmetric round or oval shaped slate-gray to blue-brown macules and patches following skin cleavage lines [18]	Variable depending on phase of lesion Active: vacuolization of the basal layer, colloid bodies, mild lichenoid lymphocytic infiltrate Inactive: pigment incontinence with dermal melanophages [18]	Commonly seen on neck, trunk, and proximal arms Seen in patients with skin types III and IV [18]
Frictional melanosis	Rippled pattern of brown pigmented patches with symmetric distribution [20]	Increased basal layer pigmentation Acanthotic epidermis Condensation of collagen, pigment incontinence [20]	Chronic friction is a key player in the pathogenesis [20]
Notalgia paresthetica	Rippled hyperpigmentation on the upper back Intense pruritus over scapular area [15]	Scattered dermal melanophages [15]	
Post-inflammatory hyperpigmentation	Asymptomatic hyperpigmented macules and patches with a range in color Epidermal: tan to dark brown Dermal: gray-blue to gray-brown [16]	Epidermal: increased pigment in keratinocytes Dermal: increased pigment in dermal melanophages [16]	Epidermal post-inflammatory hyperpigmentation fades more rapidly than the dermal counterpart [16]
Lichen amyloidosis			
Lichen simplex chronicus	Well-defined pruritic hyperpigmented lichenified plaques with "leathery" appearance [22]	Hyperkeratosis Acanthosis with irregular elongation of rete ridges Hypergranulosis Vertically oriented collagen bundles in the papillary dermis [22]	Secondary to chronic scratching or rubbing Commonly seen on posterolateral neck, occipital scalp, anogenital region, forearms, and shins [22]
Papular mucinosis	Multiple waxy papules, may coalesce into plaques [21]	Acid glycosaminoglycan deposition in the papillary dermis [21]	
Hypertrophic lichen planus	Intensely pruritic thick hyperkeratotic plaques [17]	Hyperkeratosis without parakeratosis Focal hypergranulosis Irregular acanthosis with a "sawtooth" appearance Vacuolar degeneration of the basal cell layer Band-like lymphocytic infiltrate at the dermal-epidermal junction [17]	Commonly seen on the shins or dorsal aspect of the feet [17]

Table 2 (continued)

Condition	Clinical presentation	Pathology presentation	Comments
Pretibial myxedema	Hyperpigmentation, non-pitting edema, nodules, and plaques over the anterior legs and dorsa of the feet [21]	Increased hyaluronic acid and chondroitin sulfates in dermis Compression of dermal lymphatics Fragmentation of collagen fibers Lymphocytic infiltrate in early stages [21]	Associated with Graves' disease [21]
Prurigo simplex/nodularis	Multiple pruritic skin-colored to hyperpigmented papulonodules with varying degrees of central scale, crust, or erosion [22]	Marked epidermal hyperplasia Compact hyperkeratosis [22]	Commonly seen on extensor surfaces, upper back, lumbosacral area, and buttocks Mid-upper back is typically spared ("butterfly sign") [22]
Colloid millium	Multiple skin-colored to gray-brown papules [23]	Amorphous, eosinophilic, granular deposits in the superficial dermis [23]	Commonly seen on sun exposed sites (e.g., face, dorsal aspect of hands and forearms) [23]
Elephantiasis nostras verrucosa	Papules, verrucous lesions, enlargement, and woody fibrosis [21]	Pseudoepitheliomatous hyperplasia Dilated lymphatic vessels [21]	Commonly seen on the lower extremities Sequela of chronic non-filarial lymphedema [21]

PLCA primary localized cutaneous amyloidosis

erythema dyschromicum perstans [18], drug-induced pigmentation [19], and frictional melanosis (Table 2) [20].

Once lichen amyloidosis is encountered, careful consideration should be given to lichen simplex chronicus and hypertrophic lichen planus. Both are characterized by chronic pruritic plaques often on the shins. However, histologically, none of these entities exhibit amyloid deposition. Other conditions to be entertained include papular mucinosis [21], pretibial myxedema [21], prurigo simplex/nodularis [22], colloid millium [14, 23], and elephantiasis nostras verrucosa (Table 2) [21]. The term "frictional amyloidosis" has been coined to describe a subgroup of patients in whom friction is the culprit to the production of macular and lichenoid lesions [2, 8, 24].

5 Histological Findings

Both macular and lichen amyloidosis display amyloid deposits restricted to the upper dermis, particularly the papillary dermis (Fig. 2). The special stains routinely employed in the detection of amyloid deposits are Congo red and Crystal violet [2, 25]. It is important to note that other stains might be used such as Thioflavin T, periodic-acid-Schiff method, and Sirius red to detect amyloid deposits [2, 25]. In lichen amyloidosis, the amyloid deposits may expand the papillae and displace the elongated rete ridges laterally. Features of chronic rubbing, such as acanthosis and orthohyperkeratosis, can be seen in the epidermis. These features are more pronounced in lichen amyloidosis compared with macular amyloidosis [2, 25].

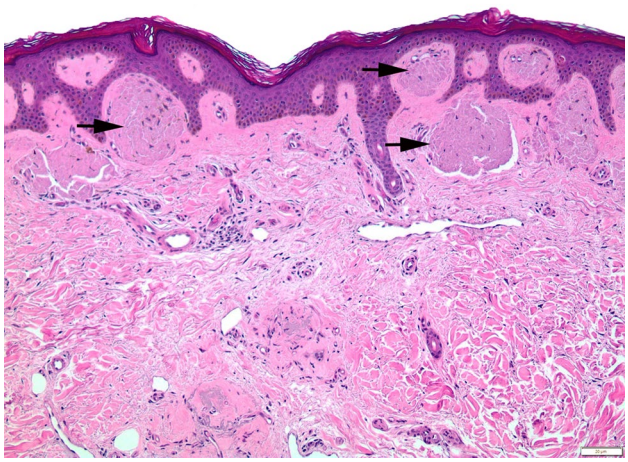

Fig. 2 Cutaneous amyloidosis: classical histopathology showing deposits (*arrows*) in the papillary dermis (hematoxylin and eosin ×200)

6 Atypical Clinical Variants Based on Morphology

6.1 Amyloidosis Cutis Dyschromica

Amyloidosis cutis dyschromica has been reported as a rare form of PLCA (Fig. 3A). It is characterized by the presence of (1) reticular hyperpigmentation with hypopigmented macules distributed extensively, (2) minimal or no itching, (3) onset before puberty, and (4) focal subepidermal amyloid deposition [26]. It has been found to be a familial disorder with unknown pathogenesis. Environmental factors, particularly sun exposure, have been proposed as the underlying cause [26]. Some reports have highlighted the loss of glycoprotein nonmetastatic gene B as a possible etiology, in addition to associations with various disorders such as systemic sclerosis, systemic lupus erythematosus, and familial Mediterranean fever [27–29].

The differential diagnosis includes dyschromatosis universalis hereditaria [30], poikiloderma-like amyloidosis, and xeroderma pigmentosum (Table 3) [26, 31]. Amyloidosis cutis dyschromica can be distinguished from dyschromatosis universalis hereditarian histologically. Additional clinical features, such as poikilodermic lesions, short stature, and palmo-plantar keratoderma, point towards poikiloderma-like amyloidosis instead of amyloidosis cutis dyschromica [32]. A differentiating factor between xeroderma pigmentosum and amyloidosis cutis dyschromica is the marked photosensitivity present in the former.

6.2 Poikiloderma-Like Amyloidosis

Poikiloderma-like amyloidosis has been frequently reported in the literature (Fig. 3B). Two clinical forms have been described: the ordinary type and the poikiloderma-like cutaneous amyloidosis syndrome [32, 33]. The ordinary type presents with poikilodermatous lesions, and lichenoid papules, with or without blisters with an adult onset [32]. Poikiloderma-like cutaneous amyloidosis syndrome has an earlier onset and presents with multiple features including (1) poikilodermatous skin lesions, (2) lichenoid papules, (3) cutaneous amyloid deposits in the pigmented and lichenoid lesions, (4) light sensitivity, (5) short stature, and (6) other features such as blister formation or palmoplantar keratosis [33]. Based on the clinical presentation, it can be confused with true poikiloderma conditions such as poikiloderma atrophica vasculare [34], mycosis fungoides [35], connective tissue disorders, or genodermatoses (Table 4). This highlights the importance of a skin biopsy to be able to distinguish poikiloderma-like amyloidosis from the above-mentioned entities.

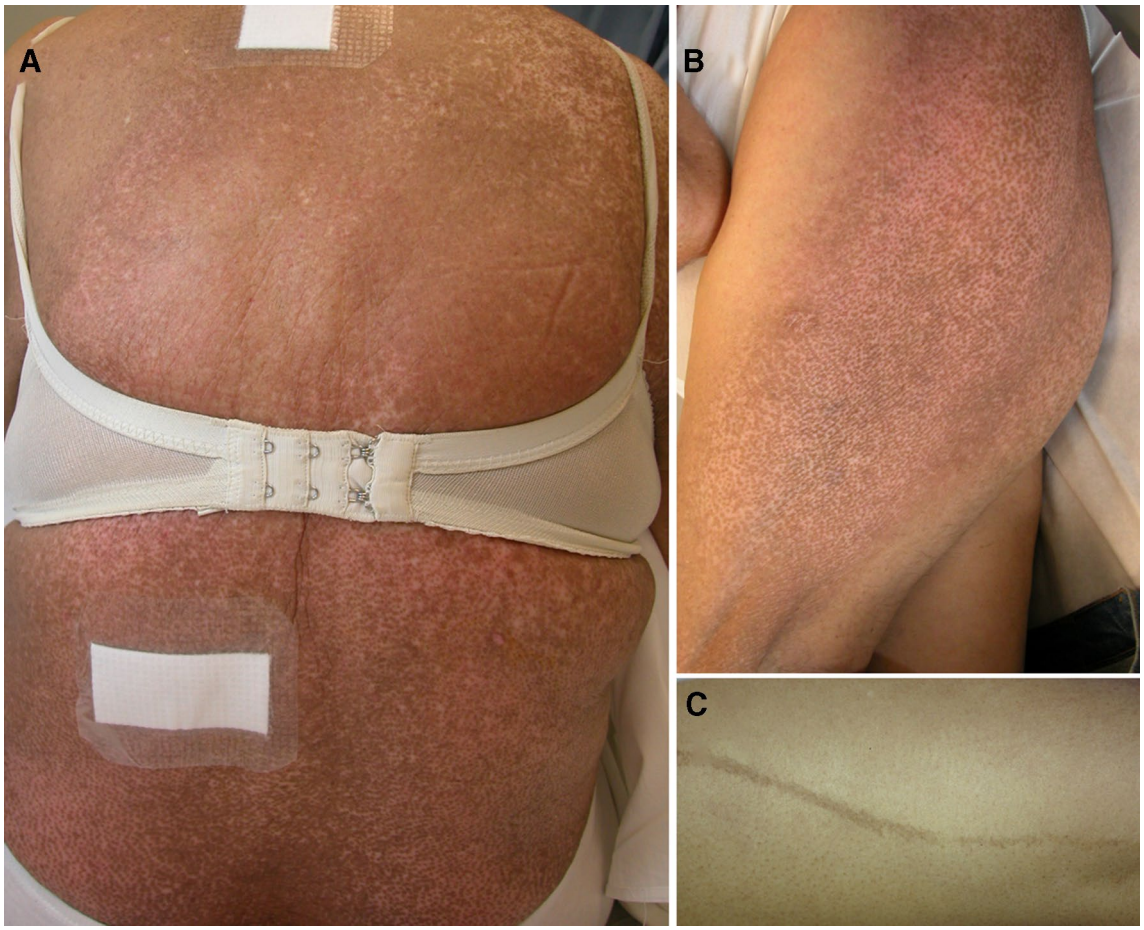

Fig. 3 Cutaneous amyloidosis: dyschromic (**A**), poikilodermatous (**B**), and linear (**C**) presentations

Table 3 Differential diagnosis of clinical variants of amyloidosis cutis dyschromica

Condition	Clinical presentation	Pathology presentation	Comments
Dyschromatosis universalis hereditaria	Generalized hyperpigmented and hypopigmented macules Apparent in early childhood [30]	Hyperpigmented: focal increase in the melanin content of the basal layer Hypopigmented: focal decrease in the melanin content of the basal layer [30]	Mostly reported in Japanese patients [30]
Xeroderma pigmentosum	Solar lentigines Marked photosensitivity Premature actinic damage Early onset of all major skin malignancies [31]	Variable depending on lesion biopsied [31]	Ocular and neurological abnormalities [31]

6.3 Bullous Amyloidosis (Keratinic Variant)

A bullous variant of lichen amyloidosis has been described in a few case reports [36–38]. Cases presented with pruritic lichenoid papules and vesicles. Based on the clinicopathological findings, a diagnosis of lichen amyloidosis was established. Note that familial forms of bullous amyloidosis were observed emphasizing the importance of genetic factors in the pathogenesis of PLCA [37]. Bullous amyloidosis without systemic involvement is a rare entity. Actually, most cases (88%) [38] described as bullous amyloidosis were later diagnosed as systemic amyloidosis [37]; therefore, careful attention should be given to patients presenting with bullous lesions.

Table 4 Differential diagnosis of poikiloderma-like amyloidosis

Condition	Clinical presentation	Pathology presentation	Comments
Mycosis fungoides	Variable from patch to plaque and final tumor stage [35]	Varies depending on stage of the disease Lymphocytic lichenoid infiltrate Epidermotropism Pautrier microabscesses CD3+, CD4+ and CD8 cell infiltrate on immunohistochemical staining [35]	
Poikiloderma atrophica vasculare	Asymptomatic or mildly itchy, variably erythematous, round, or irregularly shaped patches, coalescing into net-like patterned lesions [34]	Epidermal atrophy Telangiectasia Pigment incontinence Focal dense band-like lymphocytic infiltrate CD8+ cell infiltrate on immunohistochemical staining [34]	Might be considered as a rare variant of early-stage mycosis fungoides [34]

6.4 Incontinentia Pigmenti Like

Macular amyloidosis has masqueraded as incontinentia pigmenti in several reports [39–43]. Patients would present in early infancy with diffuse Blaschkoid-arranged brownish patches that were initially erythematous. The lack of pruritus is a common feature of this entity [41]. It is important to note that vesicle or bulla formation is uncommon in this subtype; however, it has been reported [39]. Intriguingly, a familial inheritance of incontinentia pigmenti-like cutaneous amyloidosis has been suggested but not fully elucidated [40, 42].

6.5 Linear

Patients with linear macular amyloidosis exhibit a localized Blaschko-linear macular hyperpigmentation distribution [44] (Fig. 3C). The major clinical differential diagnosis to be entertained is nevoid hyperpigmentation. Furthermore, several acquired dermatoses distributed in a Blaschko-linear pattern should be considered such as psoriasis, lichen planus, and lichen striatus.

6.6 Nevoid

A case of asymmetric hyperpigmentation limited to the left side half of the body suggested a possible nevoid origin [45]. Therefore, it is important to keep in mind PLCA as a diagnosis in cases displaying bizarre patterns of hyperpigmentation.

6.7 Nodular Amyloidosis (Keratinic Variant)

Although the material in nodular amyloidosis is derived from immunoglobulin light-chains amyloid, an unusual type of nodular keratinocyte-derived amyloid has been reported with no systemic involvement [46]. The lesions displayed are numerous nodules coalescing into plaques on the lower extremities. Skin biopsy reveals typical characteristics of PLCA. Moreover, lipid chromatography tandem mass spectrometry analysis confirmed that the deposition was keratinocyte derived [46]. By being able to establish that the amyloid is keratinocyte derived, one can avoid an extensive systemic work-up. The differential diagnosis includes nodular amyloidosis [46], cutaneous lymphoid hyperplasia [47], pretibial myxedema [21], sarcoidosis [48], and granuloma annulare [49] (Table 5). All these conditions have distinctive histopathological findings.

7 Atypical Variants of Amyloidosis Based on Distribution

The atypical variants of PLCA have been observed in unusual distributions such as on the ears, the anosacral area, and the face as well as a diffuse pattern.

7.1 Ear

Skin-colored pruritic papules on the ear were misdiagnosed as contact dermatitis unresponsive to topical corticosteroids. This prompted physicians to further evaluate the case with a skin biopsy, leading to the diagnoses of a variant of lichen amyloidosis of the auricular concha [50]. It is interesting to note that, although pruritus usually precedes the skin lesions in lichen amyloidosis [51], it was not found in half of the patients with the auricular concha involved. Moreover, using immunohistochemistry procedures, the amyloid expressed cytokeratin 34βE12, suggesting that the amyloid in amyloidosis of the ear is keratinocyte derived [52].

7.2 Anosacral

Although anosacral cutaneous amyloidosis was previously thought to be correlated with older age, patients developing the disease before the age of 60 years challenge this

Table 5 Differential diagnosis of nodular amyloidosis (keratinic variant)

Condition	Clinical presentation	Pathology presentation	Comments
Cutaneous lymphoid hyperplasia	Single erythematous to violaceous nodule or plaque [47]	Variable divided into T cells and B cells Mixed lymphocytic dermal infiltrate, plasma cells, and eosinophils Reactive germinal centers [47]	Commonly seen on the face and upper trunk Triggers identified include arthropod bites, vaccinations, tattoos, and drugs [47]
Granuloma annulare	Papules coalescing into annular plaques Seen in children and young adults [49]	Palisading granulomatous dermatitis Focal degeneration of collagen and elastin Mucin deposition [49]	Commonly seen on acral sites [49]
Nodular amyloidosis	Waxy nodules or infiltrated plaques [46]	Amyloid (immunoglobulin γ light chains) deposits in dermis, subcutis, and blood vessels Perivascular infiltrate of plasma cells [46]	Commonly seen on trunk and extremities Can rarely progress to systemic amyloidosis [46]
Pretibial myxedema	Hyperpigmentation, non-pitting edema, nodules, and plaques over the anterior legs and dorsa of the feet [21]	Increased hyaluronic acid and chondroitin sulfates in dermis Compression of dermal lymphatics Fragmentation of collagen fibers Lymphocytic infiltrate in early stages [21]	Associated with Graves' disease [21]
Sarcoidosis	Erythematous to violaceous papules and plaques [48]	Non-caseating epithelioid granulomas Minimal or absent lymphocytic infiltrate [48]	Commonly seen on face as well as tattoos or scars Associated with erythema nodosum Systemic granulomatous disorder that commonly involves the lungs "Apple jelly" color on diascopy [48]

assumption [53]. It can easily be misdiagnosed as the clinical presentation is inconsistent [54]. Some patients showed also skin lesions on other parts of the body, whereas others presented with a solitary brownish scaly plaque in the gluteal area only [54]. Because of its wide clinical presentation, the differential diagnosis should include lichen simplex chronicus, post-inflammatory hyperpigmentation, senile gluteal dermatosis, or erythrasma [53].

7.3 Face

A single report of macular amyloidosis affecting the temple of patients has been recorded [55]. It was described as multiple discrete brownish macules on the temple that coalesced into a reticular pattern. Because of its uncommon location, lichen planus pigmentosus or other dyschromic dermatoses involving the face should be considered as well [55].

7.4 Diffuse

Diffuse reticulated rippled hyperpigmentation over the body (Fig. 4) and nails with mucosal involvement raised a possibility of a new entity of PLCA that does not fit previous types [32]. This variant was labeled as an atypical presentation of PLCA with some overlapping features of amyloidosis cutis dyschromica and poikiloderma-like amyloidosis. Other entities such as dermatopathia pigmentosa reticularis and Naegeli–Franceschetti–Jadassohn syndrome should be included in the differential diagnosis.

8 Therapeutic Modalities

The literature regarding PLCA treatment is scarce and limited to case series and case reports [8]. Despite the multitude of treatment options, no gold standard has been established as none are curative or uniformly effective and most therapies aim at breaking the itch-scratch cycle (Table 1) [8, 26, 28, 36, 37, 56–72]. Mild cases of PLCA respond, to some extent, to potent topical corticosteroids with an added benefit when given under occlusion or combined with a keratolytic agent [56]. Patients should be encouraged to avoid chronic friction, for example with towels and brushes, as they have been identified as potential precipitating or aggravating factors [8, 24]. Hydrocolloid dressings can serve as a mechanical barrier to protect the involved sites [8].

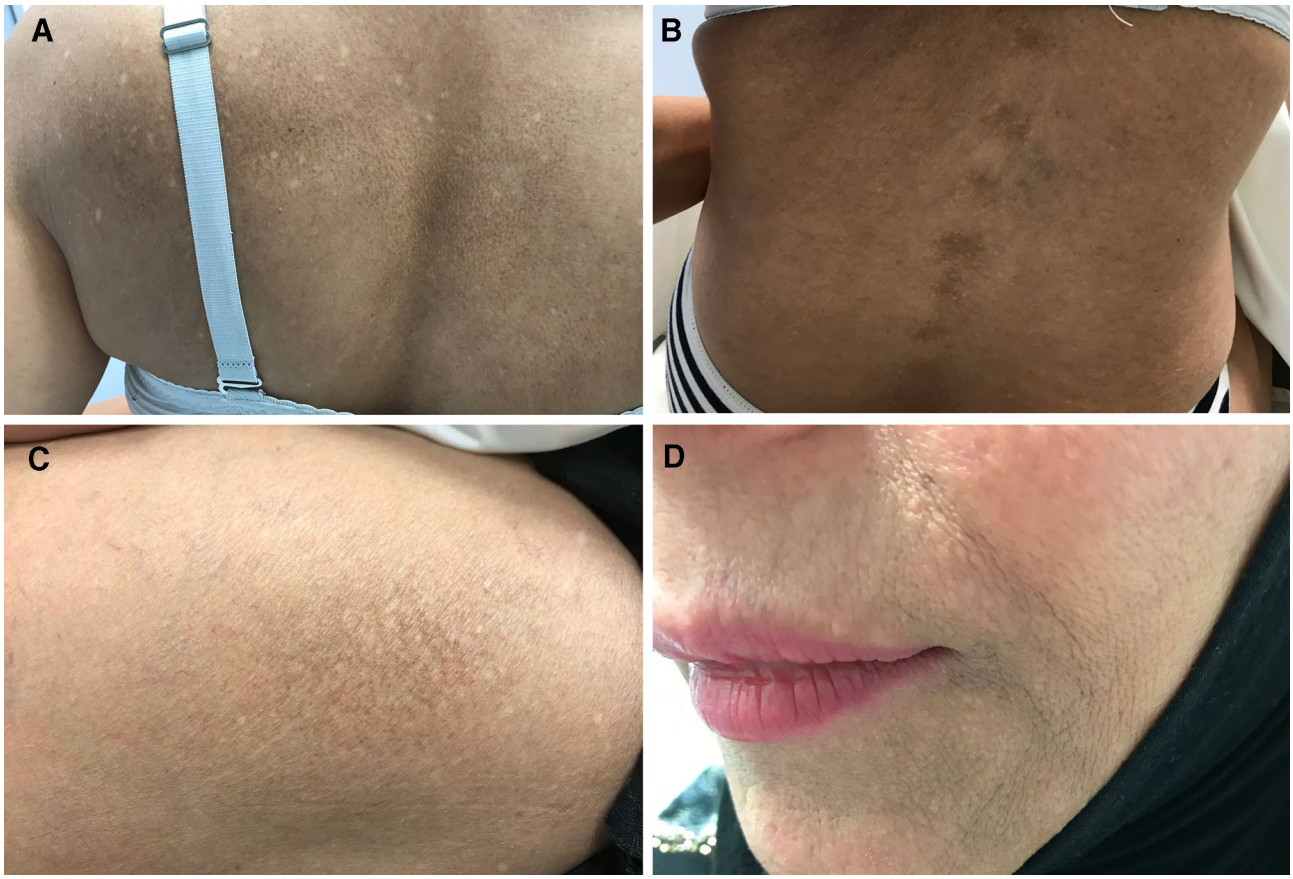

Fig. 4 Diffuse cutaneous amyloidosis case with involvement of the trunk (**A**, **B**), extremities (**C**), and face (**D**)

9 Conclusions

Primary localized cutaneous amyloidosis is a common disorder with well-known presentations easily discernable from other skin conditions. However, some forms of PLCA exhibit an atypical presentation whether in morphology or location. A physician's awareness of specific PLCA manifestations provides an opportunity to establish early diagnosis and avoid unnecessary diagnostic testing. Hence, this review aims at providing physicians with the spectrum of PLCA cutaneous variants with emphasis on the atypical variants and to summarize available therapeutic options.

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