

# A Review of Primary Cutaneous Amyloidosis

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## Abstract

Primary cutaneous amyloidosis is characterized by amyloid deposition in the skin without systemic involvement. This article reviews the three main variants of primary cutaneous amyloidosis, lichen, macular, and nodular, and briefly discusses rare forms.

## Introduction

Primary cutaneous amyloidosis (PCA) is characterized by deposition of amyloid in the skin with no extracutaneous involvement. The three main variants are lichen, macular, and nodular amyloidosis. Of these three, macular and lichen amyloidosis are most common. They are clinically distinguishable but have the same keratinocyte-derived amyloid K (AK) protein deposited in the papillary dermis, so they are often considered different manifestations of the same disease.<sup>1-3</sup> Classically, macular amyloidosis presents on the upper back as poorly demarcated, hyperpigmented macules coalescing into pruritic patches and plaques. On the lower extremities, lichen amyloidosis more often presents as discrete, hyperkeratotic papules forming larger plaques. Biphasic amyloidosis occurs when macular and lichen variants present simultaneously and has been reported in 18.75% of PCA cases.<sup>2,4,11</sup>

The nodular variant is less common and involves dermal and subcutaneous deposition of amyloid light chain (AL). AL is derived from immunoglobulin light chain material created by infiltrating plasma cells. It is the only form of primary cutaneous amyloidosis in which the amyloid deposits are of the light chain subtype. This is the same subtype found in systemic amyloidosis associated with plasma cell dyscrasias and multiple myeloma.<sup>5</sup> The nodular type is typically found on acral sites but can also appear on the face or trunk. It generally appears as single, or less commonly multiple, pink to tan, waxy papule or nodule that often hemorrhages with slight trauma.<sup>6</sup> All three variants of PCA display apple-green birefringence under polarized light due to the  $\beta$ -pleated sheet structure of the amyloid protein.<sup>2</sup>

This article reviews the three main variants of PCA along with rarely reported types. The clinical and histological presentations and the diagnosis and treatment of PCA will be discussed.

## Lichen and Macular Amyloidosis

PCA is seen most often in persons of South American, Middle Eastern or Asian ethnicities.<sup>7</sup> Most cases are sporadic, although an autosomal-dominant family history is present in up to 10% of cases. PCA is rare in children, but familial forms commonly present during the second decade of life.<sup>8</sup>

Lichen amyloidosis is most common in persons of Chinese ancestry. It typically appears as red-brown, hyperkeratotic, pruritic papules on the

shins, calves, ankles and dorsa of feet and thighs (Figure 1).<sup>4,8,9</sup> Hyperkeratotic plaques may be present and often appear similar to plaques of lichen planus, lichen simplex or nodular prurigo.<sup>8</sup> Cases of lichen amyloidosis limited to the anosacral region or the auricular concha have been documented in the literature.<sup>8</sup>

In macular amyloidosis, small, gray-brown macules may blend together to produce hyperpigmented patches. These hyperpigmented macules or patches are frequently found on the upper back and less commonly on the chest or extremities (Figure 2).<sup>10</sup> Macular amyloidosis has been described as appearing similar to fading lichenoid inflammation, post-inflammatory hyperpigmentation, and the "dirty neck" of atopic eczema.<sup>8,11</sup> Unusual variants have been described as periocular hyperpigmentation, nevoid hyperpigmentation following Blaschko's lines, and diffuse macular amyloidosis with an incontinentia pigmenti-like pattern.<sup>8,12</sup>

In both macular and lichen amyloidosis, chronic scratching in susceptible individuals is thought to contribute to the mechanism of amyloid deposition. The process of amyloid deposition involves filamentous degeneration and apoptosis of basal keratinocytes followed by conversion of filamentous masses (or colloid bodies) into amyloid material in the papillary dermis.<sup>1,8,13</sup> That lichen and macular amyloidosis have similar amyloid deposition and can occur simultaneously supports the idea they are different manifestations of a common etiology.<sup>1,8,11,14</sup> Also, new insight into amyloid diseases has shown the pathology is due not only to accumulation of fibrillar material but more so to the presence of smaller misfolded protein species, termed oligomers.<sup>21</sup> Clos et al. proposes that oligomers are formed intracellularly in the basal layer and can either cause immediate cell death and amyloid formation or be released from the basal cells into the dermis. The oligomers are then consumed and accumulate in dermal macrophages and fibroblasts, giving rise to the amyloid aggregates seen in PCA.<sup>21</sup>

In addition to the characteristic features seen by the naked eye, Chuang et al. did a study on the dermoscopic features of 35 cases of PCA. The most common finding was a brown or white central hub surrounded by various patterns of pigmentation. Of the 18 cases of macular amyloidosis in the study, eleven patients showed white central hubs, four patients showed brown hubs, and three showed both.<sup>4</sup> The 17 cases of lichen amyloidosis displayed whitish central hubs or whitish scar-like centers surrounded by



Figure 1. Hyperkeratotic, hyperpigmented papules and plaques on bilateral shins of a patient with lichen amyloidosis.



Figure 2. Hyperpigmented patch on the upper back of a patient with macular amyloidosis.

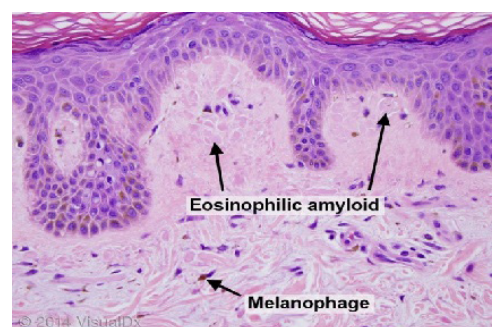


Figure 3. Histological features of amorphous, eosinophilic amyloid deposited in the dermis.

brown dots or a white rim. Of the cases with whitish central hubs, half also had the whitish scar-like pattern for some lesions. This study helped demonstrate that dermoscopy may assist in achieving an accurate diagnosis of PCA, but more studies are needed to delineate the clinical usefulness of dermoscopy.

While the diagnosis of macular and lichen amyloidosis relies on clinical identification of characteristic skin findings, definitive diagnosis requires histological confirmation.<sup>7</sup> On hematoxylin and eosin (H&E) stain, both macular and lichen amyloidoses demonstrate pink amyloid deposits in the papillary dermis (**Figure 3**). Histologies are similar as well, but lichen amyloidosis typically has more amyloid deposited. Lichen amyloidosis also commonly has secondary effects from rubbing, causing it to demonstrate irregular acanthosis, hypergranulosis, and hyperkeratosis of the epidermis, features similar to macular amyloidosis and lichen simplex chronicus.<sup>7</sup> Other common features seen on H&E include pigment loss, fissuring of the amyloid deposits, and extravasation of red blood cells.

The amyloid may be seen with several stains, including methyl violet, crystal violet, thioflavin T and Congo red. Congo red is one of the most common staining techniques, as amyloid shows a characteristic apple green birefringence when viewed under polarized light. An H&E stain may give suspicion for amyloid diagnosis, but Congo-red staining under polarized light has proved sensitive and definitive.<sup>2</sup> Vijaya et al. helped demonstrate the importance of Congo red in a study of 45 cases of suspected amyloidosis. The results showed that most patients tested positive for apple-green birefringence under polarized light.<sup>11</sup> The labelling of cytokeratin (CK) 5 might also be useful in the diagnosis of both lichen and macular amyloidoses.<sup>1,13</sup> Studies by Huilgol et al. and Apaydin et al. suggest CK 5 might be involved as a common precursor in amyloid formation.

Numerous treatments for PCA aim to either relieve itch or remove amyloid deposits in the papillary dermis.<sup>8,15</sup> Treatment of macular and lichen amyloidoses also involves reducing friction to the skin.<sup>15</sup> Identifying the cause of rubbing, whether it be habit, pruritus, neuropathy, or a combination of these, may be of benefit. Therapies include topical or intralesional corticosteroids, capsaicin, topical lidocaine, topical calcineurin inhibitors (specifically 0.1% tacrolimus), calcipotriol, topical dimethylsulphoxide, phototherapy (broadband and narrowband UVB, psoralen plus UVA photochemotherapy with oral acitretin), oral retinoids (acitretin), cyclosporine, pulsed dexamethasone-cyclophosphamide, acyclovir and interferon-alpha, dermabrasion, Nd:YAG laser, pulsed dye laser, CO2 laser and hydrocolloid dressings.<sup>8,10,15</sup> The large array of treatment options demonstrates the difficulty in managing PCA.<sup>8</sup>

Frolich et al. describe an interesting treatment option in a case of a 67-year-old Caucasian female with therapy-resistant pruritus in lichen amyloidosis on her upper back. After 26 years of pruritus, this patient responded to menthol therapy.<sup>15</sup> The mechanism of antipruritic action in this patient was not clear, but the authors offered some possible explanations. For instance, patients sometimes report relief of their chronic pruritus with cool showers or cool packs, and when menthol is applied to the skin, a cooling sensation occurs due to menthol chemically triggering cold sensitive TRPM8 receptors in the skin.<sup>15</sup> Studies have shown that menthol diffuses through the stratum corneum and increases drug diffusion and separation. Also, it has been demonstrated that menthol selectively activates K-opioid receptors, which may help explain its antipruritic effects.<sup>15</sup>

Another new treatment option targets IL-31 and oncostatin M receptor b (OSMRb). Tanaka et al. discuss the involvement of these receptors in mechanisms of pruritus in familial PCA. Missense mutations have been identified in OSMRb, an interleukin (IL)-6 family cytokine receptor, and interleukin 31 receptor A (IL31RA) in patients with familial PCA.<sup>8</sup> Tanaka et al. propose that signaling abnormalities from these receptors could lead to keratinocyte apoptosis, subsequent amyloid accumulation, and changes in the number of cutaneous nerves, leading to pruritus.<sup>8</sup> Additional research is necessary to further understand and develop treatments aimed at these receptors.

## Nodular Amyloidosis

Primary cutaneous nodular amyloidosis (PCNA) is very rare, with approximately 60 cases recorded in the medical literature up to 1994.<sup>16</sup> In contrast to lichen and macular amyloidoses, nodular amyloidosis shows no predilection for certain ethnic groups.<sup>17</sup> Recent studies indicate nodular amyloidosis occurs equally in both genders and most commonly impacts patients between 50 years and 60 years of age.<sup>5,18,19</sup> It typically presents as single or, less commonly, multiple pink to yellowish brown, waxy nodules ranging from several millimeters to several centimeters in size.<sup>8,17,20</sup>

While a definitive cause of PCNA is unknown, it is understood that amyloid deposits in nodular amyloidosis originate from immunoglobulin light chains secreted by local plasma cells.<sup>6</sup> The pathophysiology involves plasma-cell infiltration of the skin followed by monoclonal AL amyloid deposition in the dermis, subcutis, and around the blood vessels and nerve sheaths.<sup>5,19,20</sup> The literature hypothesizes that PCNA is a form of plasmacytoma or plasma-cell dyscrasia.<sup>6,21</sup>

PCNA nodules most often appear on the face, scalp, acral areas and genitalia (**Figure 4**).<sup>5,8</sup> There are documented cases of nodular amyloidosis occurring in other areas of the body, however, such as the upper back and plantar surface of the foot (**Figure 5**).<sup>22</sup> PCNA lesions may resemble large bullae, and the epidermis may appear atrophic or anetodermic; the nodules may be quite friable, contain superficial telangiectasias, or hemorrhage as a result of perivascular amyloid deposition.<sup>22,23</sup> Terushkin et al. report a case of amyloidosis involving AL amyloid that appeared bruise-like and was not nodular in nature. A histopathological diagnosis of PCNA was proposed for this lesion.<sup>9</sup>

PCNA has been associated with autoimmune connective-tissue disorders including primary biliary cirrhosis, systemic lupus erythematosus, Sjögren's syndrome, systemic sclerosis, and rheumatoid arthritis.<sup>19,20</sup> Sjögren's syndrome is a chronic, lymphoproliferative autoimmune disease found in a significant number of PCNA cases.<sup>16</sup> Results in a retrospective study by Meijer et al. supported PCNA with Sjögren's syndrome as a distinct clinical entity. This was based on four interrelated factors, including the type of AL amyloid involved, the localized deposition of AL amyloid, the presence of light chain-restricted plasma cells near the amyloid deposits, and the relationship with Sjögren's syndrome.<sup>16</sup>

Summers and Kendrick described a case of a 69-year-old woman with prior history of CREST (calcinosis, Raynaud phenomenon, esophageal motility disorders, sclerodactyly, and telangiectasia)



Figure 4. Tan to pink, waxy nodules on the scalp and face of a patient with nodular amyloidosis.



Figure 5. Tan to pink, waxy nodules on the upper back of a patient with nodular amyloidosis.

syndrome, type 2 diabetes mellitus, and fatty liver, who presented with a brown papule on the left shin. The initial biopsy indicated macular and lichen amyloidosis with involvement of the papillary dermis. Over the next three years, more than 20 yellow, waxy nodules developed on her bilateral lower extremities, ranging in size from 1 cm to 4 cm. Biopsies stained positive for amyloid extending from the superficial papillary dermis to the subcutaneous tissue, results consistent with nodular amyloidosis. This is thought to be the first published case examining an association between PCNA and systemic sclerosis, including the CREST variant of limited cutaneous systemic sclerosis.<sup>10</sup>

Traumatic injury to tissue is recognized as a triggering factor of PCNA in some cases. Dong Yoon Lee et al. described a tumefactive nodule consistent with PCNA on the scalp of a 50-year-old Korean man with a history of repeated head trauma from a soccer ball.<sup>6</sup> Kalajian et al. described another patient who presented with a three-year history of a posttraumatic, slow-growing nodule on the chin caused by a thrown beer can. This nodule was consistent with PCNA and eventually began

to enlarge and develop additional nodules.<sup>18</sup> These articles demonstrate that trauma may be an inciting event for PCNA.

The diagnosis and differentiation of nodular amyloidosis is established via tissue biopsy, radiographic examination, and evaluation of immunoglobulins to detect latent paraproteinemia and systemic disease.<sup>24</sup> Since the amyloid fibrils are deposited from the dermis to subcutaneous tissue, as well as within blood vessel walls, biopsy specimens should include full-thickness skin into subcutaneous fat.

The amyloid chains involved in PCNA are indistinguishable from those deposited in the skin and other tissues in primary systemic amyloidosis.<sup>20</sup> Thorough work-up and close follow-up is recommended, since up to 7% of PCNA patients will eventually develop systemic involvement. It is also essential to exclude systemic involvement, because up to 40% of patients with primary systemic amyloidosis will present with identical cutaneous findings to those seen in PCNA.<sup>20</sup> Physical exam findings such as periorbital purpura, macroglossia, carpal tunnel syndrome and nail dystrophy secondary to amyloid deposition all point to systemic involvement. Initial lab tests should include a CBC, CMP and urinalysis. A urine and serum protein electrophoresis can be ordered to rule out multiple myeloma and other monoclonal gammopathies. An electrocardiogram, echocardiogram and chest X-ray can provide further evidence of an infiltrative process in the heart and lungs. Biopsies of the abdominal fat pad, oral or rectal mucosa, liver, muscle, bone or transverse carpal ligament can be performed if clinical suspicion points to systemic involvement.<sup>16</sup> Paraproteinemia in patients with PCNA may also indicate progression to systemic amyloidosis.<sup>24</sup> Annual follow-up studies should be performed to monitor for progression. The advancement of PCNA to systemic amyloidosis, however, is uncommon, particularly if no clinical or laboratory evidence for systemic disease is present at the time of diagnosis.<sup>5</sup>

Treatment of PCNA is individualized and based upon clinical presentation. Surgical removal, dermabrasion, carbon dioxide laser, pulsed dye laser, and destruction of the lesions by electrodesiccation and curettage have resulted in variable success.<sup>16,17</sup>

## Rare Variants of Primary Cutaneous Amyloidosis

Several cases of rare variants of PCA have been reported. Papular amyloidosis of the auricular concha was first reported in 1988 and is considered an uncommon variant.<sup>18</sup> Four adult patients were described with newly formed papules of the auricle that were unassociated with lesions elsewhere. Neff et al. described a similar case of auricular concha amyloidosis in 2010. The histopathology of both studies demonstrated nodular deposits of amyloid in the papillary dermis.<sup>18</sup> One study performed immunoperoxidase staining, which demonstrated positive antikeratin antibody EKH4, confirming the keratinocyte origin of the amyloid.<sup>18</sup>

Amyloidosis cutis dyschromica, another rare variant, was first described in a young female in 1970. In 2011, Garg et al. performed an extensive review of literature and detected only 20 case reports of amyloidosis cutis dyschromica

worldwide.<sup>25</sup> The disease is characterized by speckled reticular hyperpigmentation with hypopigmented macules vastly dispersed. Minimal or no itching may be present, and onset is usually before puberty. Histopathology demonstrated focal amyloid deposition in the papillary dermis. Genetic predisposition and environmental factors, particularly a large amount of sun exposure, have been proposed as the underlying cause.<sup>25</sup>

Bullous amyloidosis is another rare form of PCA. The literature suggests 88% of bullous amyloidosis cases have systemic involvement.<sup>3</sup> There may also be a genetic component, as one report notes a family in which eight members were affected within two generations.<sup>14</sup> The lesions in this variant exhibit subepidermal blisters and are often described as being intermixed with hyperkeratotic papules of lichen amyloidosis. A case by Chandran et al., however, reported the bullae and erosions to be isolated.<sup>3</sup> While the mechanism of bullae formation is unclear, it is believed that trauma or rubbing is the primary precipitating factor.<sup>14</sup>

Uncommon presentations of diffuse macular amyloidosis include nevoid-like hyperpigmentation, widespread diffuse pigmentation, poikiloderma-like presentation, and an incontinentia pigmenti-like pattern.<sup>3</sup> Wan et al. reported a case of unusually diffuse macular amyloidosis with an incontinentia pigmenti-like pattern in a 28-year-old woman. She presented with diffuse nonpuritic hyperpigmentation that followed Blaschko lines and had been present since early childhood.<sup>12</sup> Skin biopsy confirmed amorphous deposits of eosinophilic material consistent with amyloidosis.<sup>6</sup>

Another example, described by Chandran et al., involved a 27-year-old Chinese woman with primary localized cutaneous amyloidosis with lichen, poikiloderma-like, dyschromic and bullous variants. All of the subtypes occurred in isolation from one another, and no associations with systemic involvement were identified. Biopsies were taken from each distinct morphology, which included lichenoid papules on the shin, poikiloderma in the axilla, a blister on the knee, an erythematous annular plaque on the temple and a pigmented macule on the hip. All demonstrated the characteristic amyloid deposition found in PCA, stained positive for Congo red and showed apple-green birefringence under polarized light.<sup>16</sup>

## Discussion

As demonstrated in this review, PCA can have a wide range of clinical presentation. Hyperkeratotic pruritic papules on the shins that coalesce into plaques are characteristic of lichen PCA. Hyperpigmented pruritic macules on the upper back that coalesce into patches are characteristic of macular PCA. Biphase amyloidosis involves lichen and macular PCA occurring simultaneously. Nodular PCA characteristically presents as single to multiple, tan to pink waxy nodules on acral areas of the body. Less-common variants have a wide array of presentations, including bullous, poikiloderma-like, dyschromic, incontinentia pigmenti-like, and nevoid-like patterns.

While lichen and macular PCA are the most common presentations, nodular and the uncommon variants of PCA should be included in a differential diagnosis for cases that present similarly to the ones mentioned in this review. Biopsy of the lesion and histological identification of amorphous

eosinophilic material in the dermis, along with apple-green birefringence under polarized light, are diagnostic of PCA. The treatment options for PCA are vast, and none has proven ideal.<sup>7</sup>

## Conclusion

Primary cutaneous amyloidosis mainly presents in lichen, macular, or nodular variants, but other variants have also been reported. The diagnosis involves both clinical and histological analyses. Treatment aims at relieving itching or removing amyloid deposition, but no effective treatment is currently available.

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