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Amyloidosis in the Skin

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1. Introduction
Amyloidosis is induced by deposition of amyloid proteins in various organs. Both systemic and localized type amyloidosis present with a variety of skin manifestations. Based on biochemical and immunological aspects, amyloid proteins are subdivided into several subtypes from different origins. Amyloid fibrils in primary and multiple myeloma-associated systemic amyloidosis are composed of immunoglobulin protein AL (light chain), whereas in secondary systemic amyloidosis, they are composed of a non-immunoglobulin protein (amyloid AA). In primary localized cutaneous amyloidosis, amyloid materials are derived from cytokeratin; however, in nodular primary cutaneous amyloidosis, amyloid is AL type. Dialysis-related amyloidosis is composed of β2-microglobulin.

So far, there are several reviews of skin features associated with amyloidosis [1-3]. Cutaneous amyloidosis is characterized by deposition of amyloid in the skin, which is seen in association with systemic amyloidosis and also restricted to the skin. In case of association with systemic amyloidosis, skin lesions are important as one of the extrahematologic manifestations, because cutaneous lesions may occasionally be the initial presentation of systemic amyloidosis. Representative lesions include petechiae, purpura, ecchymoses, and eyelid translucent papulonodular lesions. By contrast, amyloidosis limited to the skin is called primary localized cutaneous amyloidosis, which is clinically classified into more common macular, papular, and the rare nodular form. Also, reports of cases showing peculiar forms of cutaneous amyloidosis are seen, depending on the different races. Additionally, amyloid deposition is secondarily seen in association with skin tumors, such as basal cell carcinoma, Bowen’s disease, and other benign tumors. In this review, both primary and secondary skin lesions associated with systemic as well as cutaneous amyloidosis are discussed, making a focus on mucocutaneous manifestations.

2. Amyloid materials
Various subtypes of cutaneous amyloid are distinguished. Amyloid deposits are verified by several specific stains such as PAS, thioflavine T fluorescence, Congo red, and Dylon (Fig. 1). Light microscopy reveals amorphous materials extracellularly. Investigation by electron microscopy shows fibrillar materials (Fig. 2).

3. Systemic amyloidosis
Primary systemic amyloidosis (AL amyloidosis) is caused by plasma cell dyscrasia, and develops in 10-20% of patients with multiple myeloma. Various organs are affected such as
Fig. 1. Massive amyloid deposition with melanophages is seen in the papillary dermis in the lesional skin of lichen amyloidosis (Congo red staining). Hyperkeratosis of the overlying epidermis is also seen.

Fig. 2. Electron microscopy shows fibrillar materials consistent with amyloid (A) and normal collagen (C).
renal, cardiac, neuronal, gastrointestinal, hepatic, and splenic involvement. Skin manifestation is seen in approximately 30-40% of patients. Purpura, petechiae, and ecchymoses are induced in the skin as well as mucous membranes. Eyelid purpura is frequently seen (Fig. 3), and purpura are also seen elsewhere in the body. Purpura is caused by minor trauma, slight stimuli, or even spontaneously. Amyloid deposition is seen around the blood vessels, which causes capillary fragility. As periorbital lesions, translucent nodules, xanthomatous plaques, waxy yellowish hemorrhagic lesions are seen (Fig. 4, 5).

Fig. 3. Purpuric plaques around the bilateral eyelids

Fig. 4. Periorbital xanthomatous plaques and purpura

Other rare forms of cutaneous amyloidosis associated with systemic amyloidosis include subcutaneous nodules, whitish nodules, bullous lesions, and refractory ulcers [4, 5]. Amyloid deposition is also occasionally seen in the tongue and oral mucosa. Macroglossia is the representative sign (Fig. 6). Nail involvement is due to amyloid deposition in the nail matrix, and can be an initial manifestation of systemic amyloidosis [6]. Nail lesions present
with dystrophy, thinning, whitening, banding, striations, brittleness, onycholysis, fragility, and even anonychia (Fig. 7). Alopecia may develop when amyloid deposition occurs on the hair matrix. Scleroderma-like manifestations are rarely seen, especially on the fingers, in patients with primary systemic amyloidosis [7-9]. Skin biopsy is important for the diagnosis, because amyloid deposition can be detected even in the skin of normal appearance. Blind
aspiration biopsies from the abdominal subcutaneous fat tissues or the rectal submucosa are sometimes useful for the definitive diagnosis for systemic amyloidosis.

Fig. 7. Fingernails of a patient with systemic amyloidosis showing longitudinal ridging and splitting

4. Localized amyloidosis

Primary localized cutaneous amyloidosis (PLCA) is defined by deposition of amyloid in previously normal skin with no evidence of deposits in internal organs, and classified into more common macular, papular, and the rare nodular form. PLCA may be induced by chronic stimuli or minor trauma [10].

Lichen amyloidosis is frequently seen on the dorsal aspect of the lower legs and forearms, which is characterized by pruritic, firm, hyperkeratotic, reddish-brown papules or nodules (Fig. 8). Main component of amyloid in lichen amyloidosis is considered to be cytokeratin, suggesting that amyloid deposits may be derived from degenerated epithelial cells. Macular amyloidosis is predominantly localized on the upper back, and characterized by dark pigmented macules with a rippled pattern of pigmentation (Fig. 9). In severe cases, macular amyloidosis involves all over the back (Fig. 10). Lichen amyloidosis and macular amyloidosis are occasionally seen in a single patient, and is known as biphasic forms.

Unique features of macular amyloidosis are rarely seen on the upper back or exterior aspects of upper extremities. Lesions are pigmented, discrete spotty papules and not presented hyperkeratotic papules like lichen amyloidosis (Fig. 11). Those lesions are induced by prolonged scratching or rubbing with various objects such as bath sponges, brushes, towels, plant sticks and leaves, which resulted in keratinocyte degeneration. The same clinical entity includes friction amyloidosis, friction melanosis, and towel melanosis [11]. Friction amyloidosis is induced by long-term use of a nylon towel or scrub brush over
Fig. 8. Lichen amyloidosis on the lower leg

Fig. 9. Macular amyloidosis on the upper back
Fig. 10. Widespread primary cutaneous localized amyloidosis (macular form)

Fig. 11. Pigmented papular form of macular amyloidosis on the upper back (insert: higher magnification)
the bony regions such as the arms, forearms, clavicle, scapula, and neck [12, 13]. Amyloid deposits in the skin may be derived from degenerated epithelial keratinocytes [14], possibly through filamentous degeneration or apoptosis [15]. Histological investigation by amyloid stain show deposition of amorphous materials in the papillary dermis. Amyloid is usually detected unassociated with hair follicles, but rarely recognized around the follicles (Fig. 12). Nodular amyloidosis presents with a single or multiple nodules on the face, trunk and extremities [16, 17], which sometimes develop following trauma (Fig. 13). Also, periorbital small, waxy nodules are multiply seen. In the nodular type, amyloid is originated from AL protein by local plasma cells, and modified β2-microglobulin is also shown to be a component of amyloid fibrils [18]. Apart from other types, amyloid materials are situated up to in the deep dermis. Plasma cell infiltration is prominent within or peripheral areas of the amyloid materials (Fig. 14). Although patients with nodular amyloidosis may develop systemic amyloidosis after long-term follow-up, recent papers indicate that the ratio is lower than previously reported [16]. In the series of 16 cases of nodular amyloidosis, 2 patients had Sjögren’s syndrome, 2 had diabetes mellitus, and 3 had liver disease. In particular, association with Sjögren’s syndrome is remarkable [19].

PLCA usually is unassociated with systemic disorders; however, a few cases of HCV-related amyloidosis have been reported [20, 21], one of which was biphasic PLCA [20]. Nodular lesions showing the surface atrophy are described as amyloidosis cutis nodularis atrophicans.

Additionally, other unusual variants of PLCA have been reported depending on genetic, racial, and environmental factors. Those include poikiloderma-like appearance, reticular

Fig. 12. Amyloid deposition around the hair follicle in the papillary dermis in the lesional skin of macular amyloidosis (Congo red)
Fig. 13. Nodular amyloidosis on the chin

Fig. 14. Plasma cell infiltration in the lesional skin of nodular amyloidosis
form, hypopigmented, widespread diffuse pigmentation, incontinentia pigmenti-like pattern, homogenous pigmented patched, and amyloidosis cutis dyschromia [22-30]. Also, eczematous lesions [31, 32] and bullous lesions mimicking bullous pemphigoid [33] have been reported. Rare sites include ear, nose, and cheek [34-38]. Anosacral cutaneous amyloidosis is frequently seen in Asian elderly people, and hyperkeratotic, pigmented plaques are located on the bilateral outer area of the anus (Fig. 15).

Fig. 15. Anosacral amyloidosis

Therapeutic modalities for cutaneous amyloidosis remain a challenge, although topical application of corticosteroids and dimethylsulfoxide (DMSO), phototherapy, and laser treatment are selected.

5. Secondary amyloidosis associated with various disorders

An association of cutaneous amyloidosis with various disorders (i.e. inflammatory disorders, autoimmune disorders, and tumors) has been reported. Amyloid deposition is occasionally seen associated with chronic inflammation, and secondary cutaneous amyloid deposition is sometimes seen in patients with atopic dermatitis [39]. Chronic stimuli by frequent scratching may play a triggering role in amyloid production from keratinocytes. Additionally, secondary amyloid deposition associated with inflammatory disorders, such as psoriasis [40] or disseminated superficial porokeratosis [41] have been reported. Connective tissue diseases or collagen vascular diseases have been rarely seen, such as systemic sclerosis, lupus erythematosus, Sjögren’s syndrome, rheumatoid arthritis, dermatomyositis, Behchet’s disease, scleroderma, sarcoidosis, and so on [42-47]. Association of PLCA with various autoimmune disorders suggests that underlying immune-mediated factors may be implicated [47].
Secondary amyloid deposition is occasionally associated with both benign and malignant skin tumors such as melanocytic naevi, seborrheic keratosis, calcifying epithelioma, dermatofibroma, solar keratosis, Bowen’s disease, basal cell carcinoma, trichoepithelioma, and so on [48-56]. Although an epidermal origin of amyloid in secondary cutaneous amyloidosis, particularly in association with skin tumors of epithelial cell origin, is suggested in several conditions, degenerating naevus cells may contribute to the amyloid production [55]. A previous report showed amyloid deposition in Bowen’s disease treated with radiotherapy [53]. It is suggested that any insult to the skin leading to degenerative cell changes could result in amyloid deposition.

6. Dialysis-related amyloidosis

In dialysis-related amyloidosis, skin manifestations often present with cutaneous or subcutaneous nodules [57, 58]. Bilateral subcutaneous masses are seen on the buttocks (Fig. 16), which are sometimes painful on sitting. Extensive deposition of β2-microglobulin amyloid is seen in the dermis to subcutis, occasionally associated with local calcification.

Fig. 16. Dialysis-related amyloidosis on the buttocks

7. References


Amyloidosis in the Skin


Amyloidosis is a benign, slowly progressive condition characterized by the presence of extracellular fibrillar proteins in various organs and tissues. It has systemic or localized forms. Both systemic and localized amyloidosis have been a point of interest for many researchers and there have been a growing number of case reports in the literature for the last decade. The aim of this book is to help the reader become familiar with the presentation, diagnosis and treatment modalities of systemic and localized amyloidosis of specific organs or systems and also cover the latest advancements in therapy.

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