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Late-onset amyloidosis cutis dyschromica: an unusual case

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Abstract

Amyloidosis cutis dyschromica (ACD) is a rare form of primary cutaneous amyloidosis. ACD, first described by Morishima in 1970 is characterized by (i) macular, speckled, reticular hyperpigmentation with hypopigmented spots distributed extensively over the body; (ii) little or no pruritus; (iii) prepubertal onset; and (iv) focal subepidermal amyloid deposition. A 49-year-old woman presented with a 20-year history of progressive, asymptomatic, generalized mottled hyper- and hypopigmented macules all over the body. Histopathological examination of a punch biopsy specimen showed deposition of homogeneous, eosinophilic material in the papillary dermis. This amorphous, eosinophilic material was stained metachromatically with crystal violet stain and found to be compatible with amyloid. Based on the clinical and histopathological findings, the patient was diagnosed as having ACD. Amyloidosis cutis dyschromica must be considered in the differential diagnosis of patients with diffuse dyschromatosis including both hyperpigmented and hypopigmented lesions and histopathological confirmation is necessary in order to reach a correct diagnosis.

Keywords: amyloidosis, dyschromica, late-onset

Introduction

Amyloidosis cutis dyschromica (ACD) is a rare form of primary cutaneous amyloidosis. It is a chronic, progressive disease of amyloid deposition in the papillary dermis without systemic involvement. Amyloidosis cutis dyschromica, first described by Morishima in 1970 is characterized by macular, non-pruritic, speckled and reticular hyperpigmentation

with hypopigmented spots distributed extensively over the body. Onset is usually pre-pubital and histologically, focal subepidermal amyloid deposition is found [1]. Genetic factors with UVB and UVC-induced impaired DNA repair mechanisms are the main factors in the etiology of the disease [2, 4]. Various therapy options have been used in the treatment with variable success. Sunscreen, topical corticosteroids, keratolytics, dimethyl sulfoxide, capsaicin, CO₂ laser, and acitretin have all been tried in the treatment [5, 6]. Herein, a patient showing late-onset clinical and characteristic histopathological features of ACD, a rare variant of primary cutaneous amyloidosis, is reported.

Case Synopsis

A 49-year-old woman presented with a 20-year history of progressive, asymptomatic, generalized mottled hyper- and hypopigmented macules all over the body. Also, a diffuse pigmentation was noticed on the trunk and axillary region beginning a few years prior to presentation. At another facility 8 years prior, a punch biopsy had been obtained and was deemed suspicious for hypopigmented mycosis fungoides. For this reason, the patient was treated with 30 sessions of psoralen combined with ultraviolet A (PUVA). There was no response to the treatment. Another punch biopsy was obtained and reported as "macular amyloidosis." The patient was advised to use broad-spectrum sunscreens. She returned approximately eight years later and another punch biopsy was obtained because the lesions had progressed gradually to involve the entire body. The patient was born to non-consanguineous parents. She did not have

photosensitivity and reported no history of excessive sun exposure and inflammatory skin disease. She had hyperlipidemia, hypertension, and diabetes mellitus. There was a family history of hyperlipidemia and colon cancer, but there was no family member with a similar disease. Systemic examination was unremarkable. Dermatological examination revealed diffuse, band-like hyperpigmentation located on the upper quadrant of the abdomen and bilateral axillary regions, and there was generalized, mottled, varying-sized guttate hypopigmented macules ranging from 5-10mm involving the trunk and distal parts of upper and lower extremities in a symmetrical pattern (**Figure 1**). Other aspects of the dermatological examination including the hair, nails, teeth, oral mucosa, palms, and soles were normal. Routine laboratory examinations including complete blood count, urinalysis, fecal occult blood, ANA, and tests for syphilis were within normal limits, except for elevated triglyceride, 357mg/dl (normal 50-200mg/dl). Evaluation of chest X-ray, abdominal ultrasound, malignancy screening, and electrocardiogram was unremarkable. Histopathological examination of the punch biopsy specimen obtained from a guttate hypopigmented macule showed orthokeratosis in the epidermis and deposition of homogeneous, eosinophilic material in the papillary dermis (**Figure 2**). This amorphous, eosinophilic material was stained metachromatically with crystal violet stain and found to be compatible with amyloid (**Figure 3**). There was a mild inflammatory infiltrate, mostly composed of lymphocytes arranged in a perivascular fashion and sparse melanophages in the dermis. Immunohistochemical studies revealed negative staining for AE1/AE3. Based on the clinical and histopathological findings, the patient was diagnosed with ACD and scheduled for periodic follow-up.

Case Discussion

Primary cutaneous amyloidosis is characterized by the cutaneous deposition of amyloid materials in the absence of other cutaneous diseases and amyloidosis includes three major forms; macular amyloidosis, lichen amyloidosis, and the rare

nodular amyloidosis. Also, there are other rare forms such as poikiloderma-like, bullous, vitiliginous, and anosacral amyloidosis, in addition to amyloidosis cutis dyschromica [7, 9]. Macular amyloidosis is



Figure 1. Diffuse, band-like hyperpigmentation located on the upper quadrant of the abdomen, and generalized, mottled, varying-sized guttate hypopigmented macules ranging from 5-10mm involving the trunk.

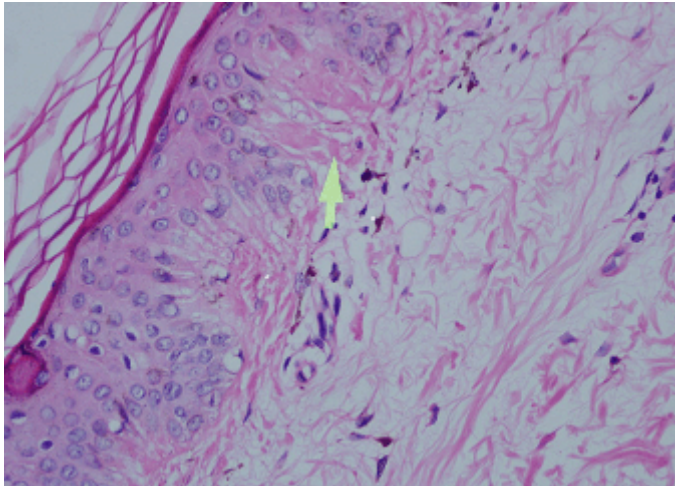


Figure 2. Orthokeratosis in the epidermis and deposition of homogeneous, eosinophilic material in the papillary dermis (arrow). H&E, 200x.

characterized by typical brownish patches with a reticular or rippled pattern, involving the upper back and extremities. Lichen amyloidosis presents with persistent pruritic hyperpigmented papules or plaques especially on the extremities and upper back. Sometimes macular and lichen amyloidosis can be seen concomitantly; this condition is called biphasic amyloidosis [7].

Amyloidosis cutis dyschromica, an uncommon variant of primary cutaneous amyloidosis, is characterized by non-pruritic reticular hyperpigmentation checkered with hypopigmented macules all over the body. Amyloidosis cutis dyschromica is more common in Asian countries and

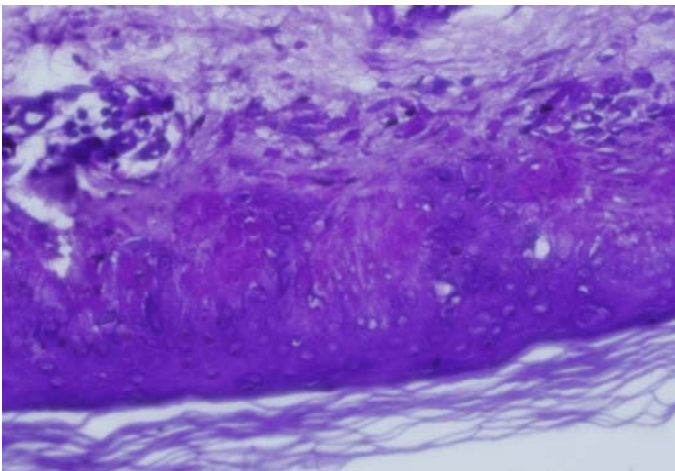


Figure 3. The deposits in the papillary dermis stain metachromatically with crystal violet stain, 200x.

has female predominance [10], and is assumed to be a familial disorder. A genetic predisposition and excessive sun exposure are the major responsible factors in the etiology of the disease. Although its pathogenesis still remains unclear, defective DNA repair in keratinocytes after UVB and UVC damage may play a role in the etiology [11, 12]. There are several hypotheses about amyloid deposition mechanisms. It has been suggested that repeated damage by sun exposure with impaired DNA repair mechanisms results in keratinocyte destruction and triggers apoptosis. The presence of melanophages in the superficial dermis also suggests damage to the basal epidermis. Amyloid deposition in the superficial dermis occurs owing to phagocytosis of cytokeratin by histiocytes and fibroblasts. It is also assumed that as a result of apoptosis, damaged keratinocytes may turn directly into amyloid depositions [13-15].

Histopathologically, ACD is characterized by deposition of acellular, amorphous, eosinophilic material, which stains metachromatically with crystal violet stain in the papillary dermis. A mild inflammatory infiltrate, mostly composed of lymphocytes arranged in a perivascular fashion and sparse melanophages, is found in the dermis [2]. The deposition in the papillary dermis stains positively with Congo red and reveals apple-green birefringence under polarized light. Qiao et al. reported that immunohistochemically, these deposits stain strongly with cytokeratin 34 β E12 and cytokeratin 5/6. However, they have negative or faintly positive staining for pan-cytokeratin AE1/AE3 [10].

Dyschromatosis universalis hereditaria, xeroderma pigmentosum, poikiloderma-like amyloidosis, idiopathic guttate hypomelanosis, and progressive macular hypomelanosis must be considered in the differential diagnosis and histopathological examination should be made to confirm the diagnosis. Amyloid deposition is not detected in these diseases other than poikiloderma-like amyloidosis. Poikiloderma-like amyloidosis is differentiated by poikilodermic changes such as lichenoid papules, blisters, atrophy, and telangiectasia. Photosensitivity, palmoplantar

keratoderma, and short stature are reported in these cases [1, 11, 12].

Avoiding excessive sun exposure and using a broad-spectrum sun protector are the essential principles in the treatment. Topical corticosteroids, keratolytics, capsaicin, dimethyl sulfoxide, and CO₂ laser have been used in the treatment of ACD with variable success. Retinoids have also been reported as effective. Retinoids are believed to induce apoptosis of damaged keratinocytes and therefore prevent transformation of degenerated basal keratinocytes into amyloid. Retinoids may also stimulate phagocytosis of the amyloid deposits by macrophages [1]. Both these effects may downregulate amyloid formation so acitretin may be a promising drug for treating the disease [16].

The postpubertal onset of ACD had been observed in our patient. Cases of ACD with postpubertal onset were rarely reported in the literature [10]. Since familial cases have been reported suggesting a genetic predisposition, other family members were evaluated and there were no family members with similar disease. All other investigations were within normal range and no systemic involvement was detected in the patient. Other clinical characteristics of the patient and histopathological features such as deposition of amorphous, eosinophilic amyloid material in the papillary dermis support the diagnosis of ACD. Although immunohistochemical results and literature reports strongly support an epidermal origin of the amyloid, in our case, the biopsy specimen revealed negative staining for cytokeratin AE1/AE3. These broad-spectrum anti-cytokeratin antibodies were positive in two of the cases in the literature [4, 6]. On the other hand, another study reported that all the six cases showed immunohistochemical positivity for

cytokeratin 34 β E12 and cytokeratin 5/6, but negative or faintly positive staining for pan-cytokeratin AE1/AE3 [10]. Further studies are also needed to show the staining profile of the amyloid. Our patient had been treated with 30 sessions PUVA because of her initial diagnosis of hypopigmented mycosis fungoides. This treatment with UVA radiation caused progression of the lesions all over the body. Although the etiology of ACD is not yet fully clarified, it is widely accepted that excessive sun exposure, namely UVB and UVC damage to keratinocytes, play a major role in the pathogenesis. It can be suggested that UVA may also trigger and exacerbate the course of ACD. Acitretin therapy was planned but could not be started because the patient had hyperlipidemia even though she had been taking fenofibrate. She was advised to use broad-spectrum sunscreens including UVA protection.

Conclusion

Amyloidosis cutis dyschromica, which is a rare disease characterized by primary involvement of the skin, must be considered in the differential diagnosis of patients with diffuse dyschromatosis including both hyperpigmented and hypopigmented macules. Histopathological confirmation should be made in order to reach a correct diagnosis. Amyloidosis cutis dyschromica is assumed to be a familial disorder; therefore evaluation of other family members is important. Sunscreen, topical corticosteroids, keratolytics, dimethyl sulfoxide, capsaicin, CO₂ laser, and acitretin have all been used successfully in the treatment.

Potential conflicts of interest

The authors declare no conflicts of interests.

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