ORIGINAL ARTICLE

Primary cutaneous amyloidosis: A clinico-pathological study with emphasis on polarized microscopy

Vijaya B., Bibhas Saha Dalal, Sunila, Manjunath G. V.

Department of Pathology, JSS Medical College (constituent college of JSS University), Mysore, Karnataka, India

Address for correspondence:
Dr. B. Vijaya, Department of Pathology, JSS Medical College (constituent college of JSS University), Mysore, Karnataka, India
E-mail: vijayab_jai@yahoo.co.in; .vijayabasavaraj@gmail.com

Access this article online

Website: www.ijpmonline.org

DOI: 10.4103/0377-4929.97853

Quick Response Code:

ABSTRACT

Background: Primary localized cutaneous amyloidosis (PCA) is a relatively rare condition characterized by amyloid deposition in dermis without systemic involvement. Although, histopathological examination of the lesion reveals amorphous eosinophilic deposits in papillary dermis examination of congo red stained slides under polarized light will give definitive diagnosis **Aims:** To study the clinicopathological features of cutaneous amyloidosis emphasizing the utility of polarized light in diagnosis. **Materials and Methods**: A clinicopathological study of primary cutaneous amyloidosis over a period of 8 years was undertaken. All the cases, clinically diagnosed and histopathologically proven as cutaneous amyloidosis were stained with congo red and studied under polarized light. **Results and Conclusions:** Of the 45 cases of clinically suspected amyloidosis, 32 cases were proven histopathologically as primary cutaneous amyloidosis and confirmed by congo red stain under polarized light which showed apple green birefringence. Among the two types of PCA, lichen amyloidosis was the most common variant accounting to 65.63% with pure cases of macular amyloidosis accounting for only 15.63%. Biphasic amyloidosis was seen in 18.75%. Knee was the commonest site of involvement with pruritis being the most common symptom. Histopathologically, the most common findings were hyperkeratosis, irregular acanthosis and expansion of dermal papillae by amyloid deposits showing apple green birefringence under polarized microscope with congo red staining. Although, H and E stain gives a clue for the diagnosis of amyloid nevertheless congo red staining under polarized light forms a very sensitive and definitive method for confirmation.

KEY WORDS: Apple green birefringence, primary cutaneous amyloidosis, polarized microscope

INTRODUCTION

The term amyloid is applied to extra cellular proteinaceous deposits that are resistant to proteolytic digestion and has distinctive physical properties. Deposits can be localized to a body site or can be systemic, involving several organs and tissues.[1] In primary localized cutaneous amyloidosis, deposition of amyloid occurs in previously apparently normal skin with no evidence of deposits occurring in internal organs. The etiology is unknown.[2] The term primary cutaneous amyloidosis (PCA) usually includes macular amyloidosis (MA), lichen amyloidosis (LA) and nodular amyloidosis (NA).[3]

Lichen amyloidosis and macular amyloidosis are best considered as different manifestations of the same disease process. Lichen amyloidosis is characterized by closely set, discrete, brown-red papules that often show some scaling and are most commonly located on the legs, especially the shins, although they may occur elsewhere also. Through the coalescence of papules, plaques may form on the legs. Usually the lesions of lichen amyloidosis itch severely. It is assumed by some authors that the pruritis leads to damage of keratinocytes by scratching and to subsequent production of amyloid.[1] First described by Gutmann in 1928, it is seen most frequently in Southeast Asia, China, and South America.[4] Macular amyloidosis is characterized by pruritic macules showing pigmentation with a reticulated or rippled pattern. Although, macular amyloidosis may occur anywhere on the trunk or extremities, the upper back is a fairly common site.[1]

MATERIALS AND METHODS

We undertook a 5 years retrospective study and 3 years prospective study of cutaneous amyloidosis in the department of pathology. All the cases were clinically diagnosed and histo-pathologically proven as cutaneous amyloidosis between study periods of January 2003 to December 2010. The clinical findings were retrieved from the records for retrospective study. The histopathology slides were analyzed and repeat histologic sections were taken from the paraffin blocks and were stained with congo-red and studied under polarized light. In the prospective study, all the skin

biopsies with clinical diagnosis of amyloidosis were processed routinely, stained with hematoxylin and eosin and congo-red. After staining with congo- red the slides were visualized under polarized light for apple-green birefringence. Patients proven to have cutaneous amyloidosis were subjected to undergo following tests such as X-ray spine, Bence Jones proteinuria and serum electrophoresis for M-band.

RESULTS

Forty five skin biopsies with a clinical diagnosis of amyloidosis were received in the department of pathology between 2003 and 2010. Of these, 32 cases displayed features of cutaneous amyloidosis on histopathology and were confirmed by congo-red stain under polarized light. In all cases, family history was negative and there was no evidence of systemic involvement clinically or with available laboratory investigations.

Of the 32 cases, 22 were males and 10 were females with a male to female ratio of 2.2:1. The age range was between 19 to 68 years with a mean age of 43.88 years. The duration of lesions ranged from 2 months to 10 years. Pruritis was the presenting symptom in 20 cases. (62.5%) Knee and shin were the commonest sites of involvement. Twenty one patients (65.63%) had multiple sites of involvement including knee, shin, elbow, back and the chest. The involvement of the knee and shin were seen in 22 patients (69.23%), followed by elbow in 8 cases (34.38%) and the back and chest in 10 cases (31.25%).

Lichenified papules [Figure 1] and pigmented macules [Figure 2] were the commonest lesions observed. Lichenified papules were seen in 21 patients (65.63%), pigmented macules in 5 cases (15.63%) and lichenified papules with pigmented macules in 6 patients (18.75%). No patients had any manifestations of systemic involvement.

Histopathological examination of haematoxylin and eosin stained sections of lichen amyloidosis showed hyperkeratosis, papillomatosis, mild acanthosis and elongated reteridges. There was expansion of dermal papillae with globular deposits of eosinophilic, amorphous acellular material. [Figure 3] Congo red stain showed these deposits as reddish orange substance. Visualization of congo-red stained slides under polarized light showed apple-green birefringence of the deposits confirming the presence of amyloid [Figures 4 and 5]. Two cases showed deposits of amyloid extending into upper dermis from the papillary dermis. A few cases showed a mild degree of perivascular lymphocytic infiltration in the upper dermis. Cases of macular amyloidosis showed amyloid deposits with no significant epidermal changes. No case of nodular amyloidosis was observed.

During the study period, there was a case of lichen planus pigmentoses which showed amyloid deposits in the papillary dermis. Histopathological features showed orthokeratosis, thinning of epidermis, basal cell vacuolar degeneration and diffuse mild degree of lymphocytic infiltration in the upper dermis with perivascular accentuation. Plenty of dermal melanophages were noted. Along with these features, papillary dermis showed deposits of amorphous eosinophilic acellular material which was confirmed to be amyloid on congo-red stain visualized under polarized light. This represents a case of secondary amyloidosis. Two cases showed ill-defined eosinophilic scanty deposits in the upper dermis which raised a suspicion of amyloid on routine histopathological staining. But, congo-red stain did not show apple-green birefringence in the eosinophilic deposits and cutaneous amyloidosis was ruled out. The histopathological diagnoses offered in those cases which were not proved to be amyoidosis were as follows: Frictional melanosis, hypertrophic lichen planus, spongiotic reaction pattern, psoriasi-form reaction pattern and scleromyxedema.

DISCUSSION

Rokintansky gave the first description of amyloidosis in 1842.[5] Amyloid deposits are characterized by amorphous, eosinophilic, acellular material on routine hematoxylin and eosin staining.

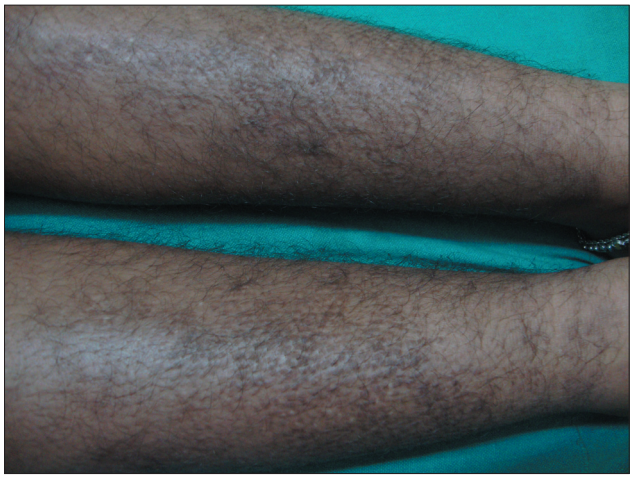

Figure 1: Lichen amyloidosis showing lichenified papules on the lower limbs

Figure 2: Macular amyloidosis showing pigmented macules in rippled pattern on the back

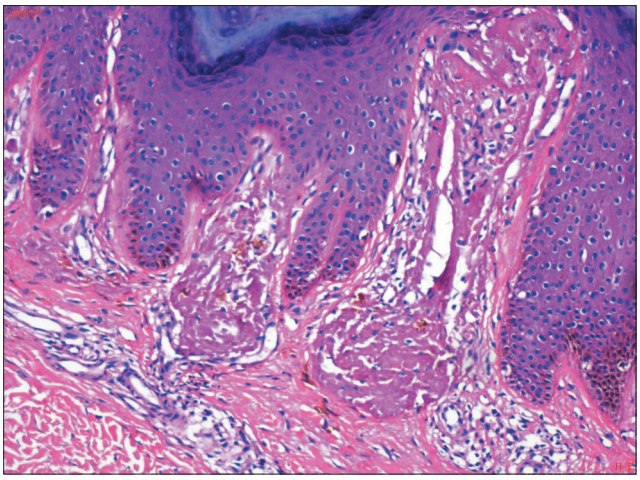

Figure 3: Photomicrograph of lichen amyloidosis showing acanthotic epidermis with deposits of amyloid in the papillary dermis. (Hematoxylin and eosin, ×100)

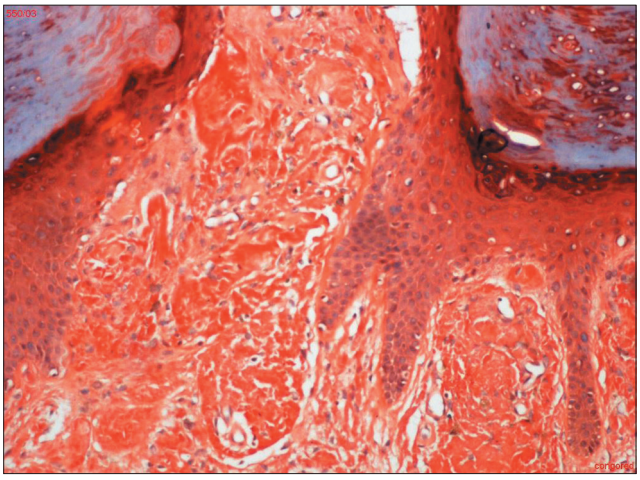

Figure 4: Photomicrograph of lichen amyloidosis showing orange-red deposits of amyloid in papillary dermis. (Congo red stain, ×200)

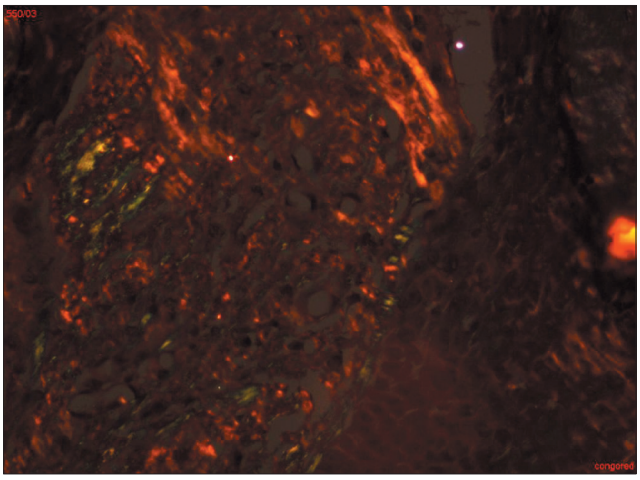

Figure 5: Photomicrograph of lichen amyloidosis showing apple green birefringence of the amyloid deposits under polarized light. (Congo red stain under polarized light, ×400)

The congo-red stain gives an orange-red staining reaction to these deposits, which show apple-green birefringence when visualised under polarised light which is the most confirmatory test. The staining characteristics result from the cross-beta-pleated sheet conformation of the polypeptide backbones of the amyloid fibrils. These fibrils are ultra structurally 8 to 12 nm in width and of indeterminate length.[1] Chemically, there are more than 16 different amyloids.[1,5]

Amyloidosis can be systemic or localized. Primary localized cutaneous amyloidosis is defined as localized amyloidosis of the skin without evidence of systemic involvement. It is of 3 clinical types: Lichen amyloidosis, macular amyloidosis and nodular or tumefactive amyloidosis. Macular and papular forms may co-exist in the same patient; this is known as biphasic amyloidosis.[5] Nodular amyloidosis is a rare condition. Secondary cutaneous amyloidosis is characterized by the presence of amyloid in the stroma of various cutaneous tumors such as basal cell carcinoma, squamous cell carcinoma, nevocellular nevi and a few adnexal tumours.[6] Secondary cutaneous amyloid deposits are also seen in seborrheic and actinic keratosis, Bowen's disease, porokeratosis, skin treated with UVA radiation after the ingestion of psoralens. [6] Lichenoid amyloidosis can arise in a setting of macular amyloidosis, presumably due to scratching. When treated by intralesional injection of steroids, the lichenoid lesions can become macular.[1]

Lichen amyloidosis was first described by Gutmann in 1928.[1] It is seen most frequently in South East Asia, China, and South America. Lichen amyloidosis is the commonest type of primary cutaneous amyloidosis. Its etiology is unknown but chronic irritation to the skin has been proposed as an etiological factor. [6] However, there are examples where in cutaneous amyloidosis was not associated with scratching and chronic irritation was not the causal factor.[7,8] Amyloid deposits have also been shown to contain disulfide bonds, which are present in keratin. Based on this finding and on those of ultra structural studies, cutaneous amyloid deposits are thought to be derived from degenerated keratin peptides of apoptotic keratinocytes transformed into amyloid fibrils by dermal macrophages and fibroblasts.[4,9] A working hypothesis is that the epidermal trauma induced by long term scratching and rubbing seen in associated chronic diseases results in keratinocyte degradation and formation of amyloid.[4,10] Cutaneous amyloidosis is thought to be caused by a filamentous degeneration of keratin-type intermediate filaments with subsequent apotosis and conversion of filamentous masses into amyloid material.[11] Additionally, immunofluorescence studies with antikeratin antiserum have shown intense staining of the amyloid for the antikeratin antibody.[1,12] Direct immunofluorescence studies have shown fluorescence with immunoglobulins and complement in the papillary amyloid deposits chiefly with IgM and C3.[13,14]

Lichen amyloidosis and macular amyloidosis show deposits of amyloid that are limited to the papillary dermis. Most of the amyloid is situated within the dermal papillae. Although, the deposits usually are smaller in macular amyloidosis than in lichen

amyloidosis, differentiation of the two on the basis of the amount of amyloid is not possible.[1,15] The two conditions actually differ only in the appearance of the epidermis, which is hyperplastic and hyperkeratotic in lichen amyloidosis.[1] In the present study, LA was the more common variant at 61.54%, macular amyloidosis accounting for 15.38% and bi-phasic amyloidosis at 23.08%. These findings are consistent with the study by Wang et al where LA was the most common clinical variant (67%) with pure cases of macular amyloidosis being only 8% which were often associated with lichenoid lesions to form biphasic amyloidosis, accounting to 25% in their series.[16]

We found a male preponderance with a mean age of involvement of 43.88 years and pruritis being the most common symptom in 20 cases (62.5%). In case of LA, the pretibial area is the commonest site of involvement as observed in our study with duration of 2 months to 10 years. [5,17,18]

The clinical differential diagnosis of LA includes lichen simplex chronicus and lichen planus.[4] Clinically macular amyloidosis, should be differentiated from post inflammatory hyper pigmentation, frictional melanosis, resolving lichen planus or neurodermatitis.[2] The histopathological features help in resolving the differential diagnosis. Although, amyloid can be suspected on routine hematoxylin and eosin stain, it has to be confirmed by visualising congo-red stained slides under polarised light for apple-green birefringence. Eosinophilic deposits can also be due to hyalinised collagen. Two cases showed ill-defined eosinophilic deposits in the upper dermis, which aroused a suspicion of amyloid on routine histopathological staining. However, congo-red staining and visualization under polarised light did not show apple-green birefringence. The sensitivity of congo-red staining in detection of amyloid was 100% in our study.

Many studies have attempted to define the chemical nature of the dermal amyloid deposits in primary localized cutaneous amyloidosis (PLCA). Immunohistochemical techniques have showed that the amyloid deposits did not bind antibodies to AA, prealbumin or fibronectin. Although, there are studies demonstrating the frequent presence of immunoglobulin in deposits of macular and papular PLCA, there is no evidence that the amyloid fibrils are composed of protein AL. Despite the fact that previous studies have identified keratin-like material in deposits of macular and papular PLCA, the exact nature of the amyloid fibril protein in these conditions, and the mechanism by which tonofilaments of necrotic keratinocytes are transformed into amyloid material in the papillary dermis, remain uncertain.[19]

Lichen amyloidosis has been reported in association with several skin disorders, including atopic dermatitis,[20] lichen planus,[21] and mycosis fungoides.[22] In this study, we encountered histopathological evidence of cutaneous amyloidosis in a case of lichen planus pigmentosus. Apart from the histological features of lichen planus pigmentoses, there were deposits of amorphous eosinophilic material in the papillary dermis which was proved as amyloid by congo-red staining visualised under polarised light. As far as we know, this was the first case of lichen planus pigmentoses associated with cutaneous amyloidosis.

Primary cutaneous amyloidosis is a persistent and pruritic dermatosis, most common site of involvement being the shins. The treatment of primary cutaneous amyloidosis is disappointing.[2] H and E stain gives a clue for the diagnosis of amyloid but congo-red staining under polarized light is a very sensitive and definitive method to confirm and rule out other clinically similar conditions.

ACKNOWLEDGMENT

The authors sincerely thank the faculty of department of dermatology for their constant support.

REFERENCES

1. Maize J, Maize Jr J, Metcalf J. Metabolic Diseases of the Skin. In: Elder, David E, Elenitsas R, Johnson, Bernett L, Murphy, et al, editors. Lever's Histopathology of the Skin, 9th ed. Philadelphia: Lippincott Williams and Wilkins; 2004. p. 436-41.
2. Padhiar B, Karia U, Shah B. Primary cutaneous amyloidosis. Indian J Dermatol Venereol Leprol 1997;63:105-6.
3. Li WM. Histopathology of primary cutaneous amyloidoses and systemic amyloidosis. Clin Dermatol 1990;8:30-5.
4. Behr FD, Levine N, Bangert J. Lichen Amyloidosis associated with atopic dermatitis. Arch Dermatol 2001;137:553-5.
5. Salim T, Shenoi SD, Balachandran C, Mehta VR. Lichen Amyloidosus: A study of clinical, histopathologic and immunological findings in 30 cases. Indian J Dermatol Venerol Leprol 2005;71:166-9.
6. Weedon D. Cutaneous deposits. In: Weedon D, editors. Skin Pathology. 2nd ed. Philadelphia: Churchill Livingstone; 2005. p. 429-34.
7. Ramírez-Santos A, Labandeira J, Monteagudo B, Toribio J. Lichen amyloidosus without itching indicates that it is not secondary to chronic scratching. Acta Derm Venereol 2006;86:561-2.
8. Wolfgang W, Imke W, Matthias B, Carlos DC. Lichen Amylodosus. A consequence of scratching. J Am Acad Dermatol 1997;37:923-8.
9. Kumakiri M, Hashimoto K. Histogenesis of primary localized cutaneous amyloidosis. J Invest Dermatol 1979;73:150-62.
10. Wong C, Lin C. Friction amyloidosis. Int J Dermatol 1988;27:302-7.
11. Wei-Min Li MB. Histopathology of primary cutaneous amyloidosis and systemic amyloidosis. Clin Dermatol 1990;8:30-5.
12. Masu S, Hosokawa M, Seiji M. Amyloid in localized cutaneous amyloidosis: Immunofluorescence studies with anti-keratin antiserum. Acta Derm Venereol 1981;61:381-4.
13. Salim T, Shiny SD, Balachandran C, Mehta V. Lichen amyloidosis: A study of clinical, histopathology and immunofluorescence findings in 30 cases Indian J Dermatol Venerol Leprol 2005;71:166-9.
14. MacDonald DM, Black MM, Ramnarain N. Immunofluorescence studies in primary localized cutaneous amyloidosis. Br J Dermatol 1996;96:635-41.
15. Brownstein MH, Hashimoto K. Macular amyloidosis. Arch Dermatol 1972;106:50-7.
16. Wang WJ, Chang YT, Huang CY, Lee DD. Clinical and histopathological characteristics of primary cutaneous amyloidosis in 794 Chinese patients. Zhonghua Yi Xue Za Zhi 2001;64:101-7.
17. Wong C. Lichen amyloidosis: A relatively common skin disorder in Taiwan. Arch Dermatol 1974;110:43840.
18. Tay CH, Dacosta JL. Lichen amyloidosis: Clinical study of 40 cases. Br J Dermatol 1970;82:129-37.
19. Breathnach SM, Bhogal B, De Beer FC, Black MM, Pepys MB. Primary localized cutaneous amyloidosis: Dermal amyloid deposits do not

bind antibodies to amyloid a protein, prealbumin or fibronectin. Br J Dermatol 1982;107:453-9.
20. Shanon J. Cutaneous amyloidosis associated with atopic disorders. Dermatologica 1970;141:297-302.
21. Hongcharu W, Baldassano M, Gonzalez E. Generalized lichen amyloidosis associated with chronic lichen planus. J Am Acad Dermatol 2000;43:346-8.
22. Romero L, Kantor G, Levin M, Vonderheid E. Localized cutaneous amyloidosis associated with mycosis fungicides. J Am Acad Dermatol 1997;37:124-7.

How to cite this article: Vijaya B, Dalal BS, S, Manjunath GV. Primary cutaneous amyloidosis: A clinico-pathological study with emphasis on polarized microscopy. Indian J Pathol Microbiol 2012;55:170-4.
Source of Support: Nil, **Conflict of Interest:** None declared.