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Cutaneous Amyloidosis: A Pilot Study at a Teaching Hospital in New Delhi

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Abstract:

Background: *Amyloidosis is characterized by the deposition of polymeric fibrillar proteins in the extracellular compartment in tissues and organs ultimately leading to damage with functional compromise. Cutaneous amyloidosis is clinically classified into more common macular, papular, and the rarer nodular form. The present study was undertaken with the aim to histopathologically analyze and characterize clinically diagnosed amyloid cases.*

Methods:*The present study was a retrospective analysis of skin biopsies conducted over a one year period. Data on the age and presenting clinical features were retrieved from the accompanying laboratory request forms or patients records wherever available. All skin biopsies with a histologic diagnosis of amyloid were retrieved and reviewed, the pattern of amyloid deposition identified and classified. Special stains including Congo Red stain was done in all the cases.*

Results: *Histopathological confirmation of cutaneous amyloidosis was seen in nine out of fourteen cases and was confirmed by positive Congo-red stain under polarized light. Out of this seven were females and two were males. Majority of the lesions were of macular type. In all the nine cases, family history was negative and no evidence of systemic involvement was noted, either clinically or based upon the lab investigations.*

Conclusions: *In this pilot study of 9 cases, histologically diagnosed as cutaneous amyloidosis we noted a female preponderance in young and middle-aged persons. Macular amyloidosis was the most common form and the most common site of involvement, the upper extremity and the inter-scapular/back region.*

Keywords: *Cutaneous, amyloidosis, macular, lichen.*

Introduction:

Amyloidosis is characterized by the deposition of polymeric fibrillar proteins in the extracellular compartment in tissues and organs, ultimately leading to damage with functional compromise.[1] The term "amyloid" (starch-like) was first coined in 1854 by Virchow who observed its resemblance to starch or cellulose.[2] It has systemic and localized forms, depending on whether the amyloid deposition is localized to one organ system or multiple organs. Both systemic and localized types present with a variety of skin manifestations.

Amyloidosis limited to the skin is called primary localized cutaneous amyloidosis, and is clinically classified into more common macular, lichenoid, and the rarer nodular form. On the other hand, deposition of amyloid in the skin is also seen in association with systemic amyloidosis. Cutaneous lesions may occasionally be the initial presentation of systemic amyloidosis and hence carries significance. Representative lesions include papulonodular lesions, petechiae, purpura, and even ecchymoses.[3]

We undertook a study to analyze the types and frequency of cutaneous amyloidosis in the patient population attending the Dermatology Out Patients Department over a one-year period from Janu-ary 2014 to December 2014.

Methods:

The present study was conducted at the Hakeem Abdul Hameed Centenary Hospital, New Delhi over a one-year period. This hospital caters to the population from the nearby slums and the adjoining areas around this hospital in New Delhi. This was a retrospective analysis of 14 cases which were clinically diagnosed as cutaneous amyloidosis and the skin biopsies sent to our department for histological confirmation. Data on the age and presenting clinical features were retrieved from the accompanying laboratory

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request forms or patients records where ever available.

All skin biopsies with a histologic diagnosis of amyloid were retrieved and reviewed, the pattern of amyloid deposition identified and classified (9/14). The sections were stained with hematoxylin and eosin stain (H&E). Special stains included Congo-red stain was done in all the cases. The clinical presentation including the age of the patient and the histology were correlated. Other skin biopsies clinically labelled as cutaneous amyloid but not confirmed histologically were also reviewed (5/14).

Results:

This retrospective search of medical records showed that a total of fourteen skin biopsies with a clinical diagnosis of amyloidosis were received in the Department of Pathology during the study period Histopathological confirmation of cutaneous amyloidosis was seen in nine out of these four-teen cases and was confirmed by positive Congo-red stain under polarized light. Among these, seven were females and two were males. Mean Age of patients with cutaneous amyloidosis was 36.5 years and the age range of patients with cutaneous amyloidosis was 25 years to 52 years.

Clinical history regarding the duration of the skin lesion, its onset and progression, provoking factors if any and history of sun exposure were elicited in each case. The duration of the lesions ranged from 1 year to 20 years and pruritus was the presenting complaint in 7/9 cases. All the nine patients who were from a low socio economic strata of society gave a positive history of sun exposure. No concomitant cutaneous skin lesion was identified histologically in any of these nine confirmed cases of amyloidosis. The site of involvement was the interscapular area or back in seven out of nine cases whereas in eight cases multiple sites like the back, upper extremity, lower extremity and the trunk were involved (Table I) In six of the patients the presenting skin lesions which were biopsied were pigmented macules, whereas in three patients lichenified papules were seen. Patients with pruritic, brownish, rippled or reticulate hyperpigmented macular lesions, were classified as 'macular amyloidosis'. These lesions were characterized by a change in surface color, without elevation or depression and, were therefore, non palpable. On the other hand, patients with persistent, pruritic, papular eruptions were classified as lichenoid amyloidosis. These lesions were circumscribed, solid elevations of skin and a visible and palpable thickening of skin with accentuated skin markings, varying in size from a pinhead to one centimetre (Table II).

Table-I

Distribution of cases according to site of lesion

Site of Lesion	Frequency	Percentage
Upper extremity	8	88.8
Lower extremity	3	33.3
Interscapular area/Back	7	77.7
Multiple areas of involvement	8	88.8

Table-II

Distribution of cases according to type of amyloidosis

Type of amyloidosis	Frequency	Percentage
Macular amyloidosis	6	66.66%
Lichen amyloidosis	3	33.33%
Total	9	100%

Table-III

Histological Diagnoses of 14 cases clinically diagnosed as Cutaneous amyloid

Histological Diagnoses	Numbers (Total - 14 cases)
Macular Amyloidosis	6
Lichen Amyloidosis	3
Lichen simplex chronicus	3
Hypertrophic lichen planus	2

In all the nine cases, family history was negative and no evidence of systemic involvement was noted, either clinically or based upon the laboratory investigations. Histopathological examination of hematoxylin and eosin stained sections of lichen amyloidosis showed hyperkeratosis, acanthosis, papillomatosis, and elongated rete ridges in three cases. The dermal papillae were expanded with globular deposits of an amorphous, eosinophilic, hyaline, acellular substance (Figure 1) Congo red staining showed these deposits as a brick red colored substance (Figure 2) Visualization of Congo-red stained slides under polarized light showed apple-green birefringence of the deposits confirming the presence of amyloid. A thin band of compressed collagen was noted

between these deposits and the overlying epidermis, while at some places sub epidermal clefting above the deposits was seen. A mild degree of perivascular lymphocytic infiltration in the upper dermis was seen in some cases. Cases of macular amyloidosis showed similar amyloid deposits but with no significant epidermal changes in six cases. No case of nodular amyloidosis was observed in this study. The final diagnoses offered in those cases not histologically proven to be amyloidosis was lichen simplex chronicus in three cases and hypertrophic lichen planus in two cases respectively (Table III)

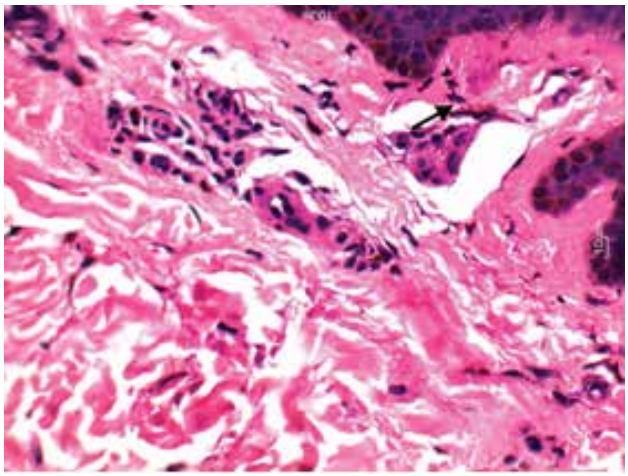

Figure 1: Amorphous acellular material in the dermal papillae. (H&E, 40X)

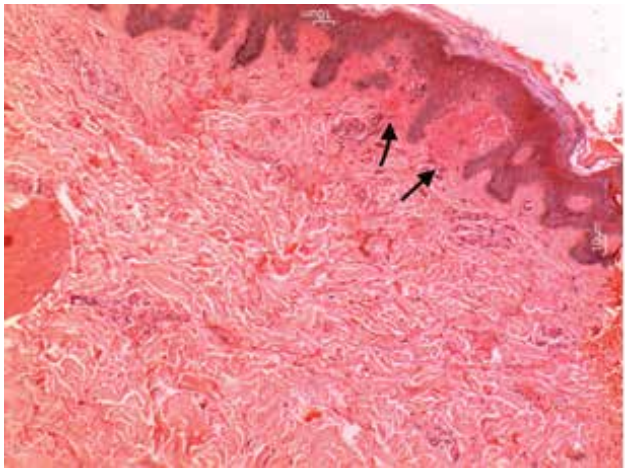

Figure 2: Brick red colored substance deposits on Congo-red staining, 20X).

Discussion:

Amyloidosis refers to an abnormal extracellular deposition of fibrillar proteins which occurs in a range of inherited and inflammatory disorders. These fibrillar proteins are chemically unrelated but share the same physical ultrastructure of the characteristic cross-β-pleated sheet conformation and also the staining characteristics.[4] The histologic diagnosis of amyloid is almost wholly based on its staining characteristics. The most common staining technique uses the dye Congo red, which under ordinary light imparts a brick red color to amyloid deposits. Under polarized light the Congo red-stained amyloid shows the characteristic apple-green birefringence. Amyloid also stains metachromatically with crystal violet and methyl violet stains.[5] Many workers have used cotton dyes like pagoda red, RIT scarlet no 5 and RIT cardinal red no 9 which stain amyloid better. Unlike Congo red stain, these cotton dyes do not stain conditions like solar elastosis and colloid milium, and are therefore regarded as being more specific.[6] Furthermore, direct immu nofluorescence has shown immunoglobulin G, IgM and compliment C3 in the amyloid deposits.[4,7]

Primary localized cutaneous amyloidosis is defined as localized amyloidosis of the skin without evidence of systemic involvement. Three clinical types are described: lichen amyloidosis, macular amyloidosis and nodular / tumefactive amyloidosis. The term biphasic amyloidosis has been used when both lichen and macular forms coexist in the same patient. Amyloid deposition is also seen in a wide range of cutaneous lesions when it is labelled as secondary cutaneous amyloidosis. Amyloid has been identified in basal cell carcinoma. Less commonly, it has been reported in squamous cell carcinoma, adnexal tumors such as cylindroma, pilomatrixoma and trichoblastoma, in seborrheic and actinic keratosis, porokeratosis and even Bowen's disease.[8] In this pilot study of 9 histologically proven cases of dermal amyloidosis, two thirds of the patients, i.e. 6/9 cases were reported as macular amyloidosis while one third of the patients i.e 3/9 cases were classified as lichen amyloidosis. There were no cases of biphasic amyloidosis in this study. Macular amyloidosis is recognized to be predominantly localized on the upper back, and characterized by spotty pigmented macules and a rippled pattern of pigmentation as was seen in six of our cases. Lichen amyloidosis, on the other hand, is frequently seen on the dorsal aspect of the lower legs and forearms, characterized by pruritic, firm, hyperkeratotic, reddish brown papules, a finding which was seen in three patients in this study. A comparative analysis of case series of cutaneous amyloidosis in literature is presented at Table IV.

Table-IV

Comparative analysis of case series of cutaneous amyloidosis in literature

Author and Year of report	Macular amyloid	Lichen amyloid	Biphasic amyloid
Looi LM et al 1999	28.2%	74.1%	0%
Vijaya B et al 2012	15.63%	65.63%	18.75%
Krishna et al 2012[15]	64%	23%	13%
Kilaparty et al 2016[16]	74%	18%	8%
Present study	66.66%	33.33%	0%

The majority of cases of cutaneous amyloidosis were represented by the macular variant, a finding which was also recorded by other workers in India and South east Asia.[9,10] Looi, in his study reported that macular amyloidosis is more common than expected among Indians.[11] On the other hand, a study from South India found lichen amyloidosis to be the more common variant in their study of primary cutaneous amyloidosis.[12]

A female preponderance was noted in our study similar to previous studies on cutaneous amyloidosis.[9,10,11] It has been proposed that trauma to the skin due to long standing pruritus leads to scratching, keratinocyte degradation and ultimately laying down of amyloid.[13] Pruritus as the chief clinical presentation was seen in 7/9 cases in this study. Padhiar et al have described how frictional melanosis and resolving lichen planus are differentiated from macular amyloidosis.[14] Frictional melanosis has been described in thinly built persons who typically give a history of using a brush/washing agent. Common locations include bony prominences like the shins and also the upper back, thus often clinically mistaken for cutaneous amyloidosis. The clinical differential diagnosis of lichen amyloidosis includes chronic inflammatory dermatological conditions like lichen planus and lichen simplex chronicus. Histopathological examination and special stains help to arrive at a final diagnosis In 5/14 cases in this study, the clinical diagnosis of cutaneous amyloidosis was excluded by careful application of histopathological techniques and special staining procedures.

Conclusions:

Cutaneous amyloidosis is a disease of young to middle-aged persons with a female preponderance. Macular amyloidosis is the most common form and the most common site of involvement is the upper extremity and the interscapular/back region. Clinical and histopathological examination supplemented by special staining procedures is helpful in detection of majority of cases.

Conflict of interest: None.

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