Clinicopathological Study of Primary Cutaneous Amyloidosis in a Tertiary Care Center of Eastern India Reveals Insignificant Association with Friction, Scrubbing, and Photo-Exposure: How valid is the “Keratinocyte Hypothesis”?

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Abstract
Introduction: Primary cutaneous amyloidosis (PCA) can be classified into four principal categories: macular amyloidosis, lichen amyloidosis, biphasic, and nodular amyloidosis. Some unusual variants such as widespread diffuse hyperpigmentation without papules, poikilodermalike involvement, lesions following Blaschko’s line, etc., have also been reported. However, not much data are available regarding the demography, epidemiology, clinical patterns, and distribution and histopathological findings, especially from the eastern part of India.

Aims: We conducted a cross-sectional, institution-based study to evaluate clinicopathological pattern and factors of PCA in eastern India. Materials and Methods: We recorded clinical and histopathological findings of 100 consecutive patients of PCA presenting to a tertiary care institution of Kolkata in eastern India. Results: We found female patients of PCA outnumber male (M:F = 1:1.9) with majority of patients being young adults (56%) between 20 and 40 years of age. More than half (54%) of the patients were pruritic. The severity of pruritus is significantly more associated with lichenoid and biphasic variants over macular amyloidosis. Positive family history was recorded in 17% of cases. Macular variant was the most common variant constituting 48% of the total PCA. We also found that the association with history of friction and scrubbing and photo-exposure were statistically insignificant. However, duration of the disease has statistically significant association with the disease morphology. Congo red stain showed these deposits as reddish orange substance in 28 patients out of 64 patients’ samples on which Congo red could be performed. Conclusion: Our study revealed that many concepts of pathogenesis of PCA including friction and photoexposure might have lesser importance. However, morphological types were significantly associated with the duration of the disease and symptom severity.

Key Words: Friction and scrubbing, keratinocyte hypothesis, lichen amyloidosis, macular amyloidosis, primary cutaneous amyloidosis

Introduction
Amyloidosis is the term used to describe abnormal extracellular deposition of one of the biochemically unrelated protein-rich substances (insoluble and proteolysis resistant) in the skin or other organs. The composition of such substances although formed by different types of proteins, presents one common aspect - binding to Congo red dye, having a reddish coloration in normal light or birefringent green coloration under polarized light. Tissue infiltration by these amyloid deposits occurs in a localized or systemic manner. When localized, there can be only cutaneous involvement and when systemic, it may be primary, secondary (reactive systemic) or heredofamilial. Localized or organ limited amyloidosis can be classified into cutaneous amyloidosis, endocrine, and cerebral amyloidosis.[1]

In primary cutaneous amyloidosis (PCA), there is deposition of amyloid in apparently normal skin, without the involvement of internal organs.[1] The
Primary cutaneous amyloidosis (PCA) is characterized by the deposition of amyloid material in the skin. The type of amyloid deposited in PCA is generally AL type. PCA can be divided into three main categories: macular amyloidosis, lichen or papular amyloidosis, and nodular or tumefactive amyloidosis. Coexistence of macular and papular forms is seen in some individuals, and then, it is termed biphasic amyloidosis. Some unusual variants such as widespread diffuse hyperpigmentation without papules but poikiloderma-like involvement, lesions following Blaschko's line, etc., have also been reported.

The etiology of most forms of PCA is unknown. PCA appears to be multifactorial in origin; however, environmental and genetic factors play important roles in its pathogenesis. Male and female are equally affected with a female preponderance in the nodular variant. Middle-aged adults mainly suffer. Some racial variances, familial forms, and aggravating factors such as friction, and rubbing are described in earlier literature.

The pathogenesis, also known as the “keratinocyte-theory”, is centered on inappropriate apoptosis of the keratinocytes with filamentous degeneration, which is later converted into amyloid material.

As there is not much data available regarding the demography, epidemiology, clinical patterns and distribution, and histopathological findings, especially from the eastern part of India, we conducted a cross-sectional, institution-based study to evaluate clinicopathological patterns of PCA in eastern India.

**Materials and Methods**

This is an institution based, cross-sectional study conducted on consecutive patients of PCA from November 2014 to January 2016. All cases clinically diagnosed as cutaneous amyloidosis and consented to take part in the study were included in the study. Due permission was obtained from the Institutional Ethics Committee. Detailed history and clinical examination were noted in a case record form which included demographic profile, clinical characteristics, and type with a special mention of lifestyle factors such as scrubbing, friction, sun exposure, and atopic background. Skin biopsy was done with a 3 mm sterile skin biopsy punch with standard aseptic precautions, and the histopathology sections were stained with both hematoxylin and eosin stain and Congo red stain. Congo red-stained sections were visualized under polarized microscopy for apple green birefringence. All data were analyzed by SPSS statistical software version 20 (Tulsa, Oklahoma: StatSoft Inc., 2001).

**Results and Analysis**

Among the 8870 new outpatient department (OPD) patients screened, we were able to recruit 100 patients with PCA fulfilling the inclusion and exclusion criteria. Females outnumbered males with a 1.9:1 ratio [Table 1]. Majority of our patients were young adults with 46% belonging to the age group of 20–39 years. Middle aged and older (above 40 year) constituted 39% of our study population. The mean age at presentation was 38.35±13.7 [Table 1].

Out of 100 patients of PCA, 48 patients were of macular variety (48%), 22 patients were of lichen amyloidosis (22%), and biphasic amyloidosis was seen in 30 (30%) patients [Table 1 and Figures 1-3]. Macular, biphasic, and lichenoid, all three varieties of PCA were most common in 30–39 years of age group. There was no statistical difference in age at presentation between the three types of PCA (P=0.058) when analyzed by one-way ANOVA [Table 1].

All three types of PCA were common in females with no statistical significance of gender difference (P=0.408) [Table 1]. Pigmented macules with rippled pattern were seen in all cases of macular amyloidosis. Pigmented papules were seen in all cases of lichen amyloidosis and biphasic amyloidosis.

All patients had involvement of >1 site. Lower limb (75%) was the most commonly affected site followed by upper limb (65%), neck (31%), upper back (19%) and least commonly involved site was face constituting 10% of all cases. Generalized involvement was seen in three cases of which two were macular variant and one was biphasic type [Table 2].

Majority of the patients were homemakers accounting for 47 (47%) cases; 6 (6%) were farmer; 13 (13%) were student; and the remaining 34 (34%) were pursuing other professions. There was statistically significant difference between occupation and type of the PCA [Table 1].

Majority of the patients with cutaneous amyloidosis had duration between 1 and 5 years (62%); duration <1 year was seen in 17% of patients and 21% had duration >5 years. Mean duration of disease of different types of
PCA was 35.9 months, 44.9 months, and 62.4 months for macular, lichenoid, and bipolar PCA, respectively. Costal Wallis ANOVA found this statistically significant [Table 1].

A total of 46 patients were asymptomatic and 54 were symptomatic. In macular amyloidosis, 13 were symptomatic. In both lichen and biphasic forms, most of the patients were symptomatic (P=0.001) [Table 1].

Only 21 (21%) gave history of using scrub during bathing and 79 (79%) patients did not give any history of chronic friction (P=0.063) [Table 1].

Positive family history was recorded in total 17 (17%) cases; 12 (25%) cases of macular amyloidosis, 2 (6.7%) cases of biphasic, and 3 (13.6%) cases of lichen amyloidosis had positive family history (P=0.99).

Only 24 (24%) patients had a history of significant photo exposure and the remaining 76 (76%) had occasional insignificant sun exposure [Table 3].

Histopathological examination of hematoxylin and eosin-stained sections of lichen amyloidosis showed hyperkeratosis, papillomatosis, mild acanthosis, and elongated rete ridges. There was an expansion of dermal papillae with globular deposits of eosinophilic, 

| Table 1: Demography of primary cutaneous amyloidosis |
|-----------------------------------------------------|
| **Number of patients, n (%)**                        |
| Macular amyloidosis | 48 (48%) | 22 (22%) | 30 (30%) | 100 (100%) |
| Lichen amyloidosis | 35.43±14.83 | 39.36±12.40 | 42.86±11.39 | 38.35±13.7 |
| Biphasic amyloidosis | 62.4 months | 44.9 months | 30.4 months | 39.87±40.26 |
| **Gender distribution, n (%)**                       |
| Male | 14 (29.2) | 10 (45.5) | 10 (33.3) | 34 (34) |
| Female | 34 (70.8) | 12 (54.5) | 20 (66.7) | 66 (66) |
| **Occupation, n (%)**                                |
| Homemaker | 19 (39.6) | 11 (50) | 17 (56.7) | 47 (47) |
| Agriculturist | 4 (8.3) | 0 | 2 (6.7) | 6 (6) |
| Student | 12 (25) | 1 (4.5) | 0 | 13 (13) |
| Others | 13 (27.1) | 10 (45.5) | 11 (36.6) | 34 (34) |
| **Duration of disease in months (mean±SD)**          |
| Macular amyloidosis | 35.93±35.66 | 44.95±45.65 | 62.4±57.86 | 39.87±40.26 |
| Lichen amyloidosis | 0.048 (by Costal Wallis ANOVA) |
| Biphasic amyloidosis | 0.058 (by one-way ANOVA) |
| **Symptom (itching), n (%)**                         |
| Symptomatic | 13 (27.1) | 17 (77.3) | 24 (80) | 54 (54) |
| Asymptomatic | 35 (72.9) | 5 (22.7) | 6 (20) | 46 (46) |
| **History of friction/scrub, n (%)**                 |
| 14 (29.2) | 1 (4.5) | 6 (20) | 21 (21) | 0.063 (by χ²) |
| Positive family history, n (%)                       |
| 12 (25) | 3 (13.6) | 2 (6.7) | 17 (17) | 0.99 (by χ²) |
| Significant photo exposure, n (%)                    |
| 17 (35.4) | 1 (4.5) | 6 (20) | 24 (24) | 0.63 (by χ²) |
| History of atopy, n (%)                              |
| 6 (12.5) | 2 (9.1) | 5 (16.7) | 13 (13) | 0.717 (by χ²) |
| History of generalized dry skin, n (%)               |
| 21 (43.8) | 11 (50) | 14 (46.7) | 46 (46) | 0.885 (by χ²) |

*SD: Standard deviation*
amorphous acellular material. Macular amyloidosis showed amorphous deposits in the upper dermis without significant epidermal changes. Congo red stain showed these deposits as reddish orange substance in 28 samples out of 64 samples on which Congo red could be performed [Table 3 and Figures 4-6].

Twenty cases (20%) had history of preexisting dermatoses including eczema, generalized dryness, and atopy [Figure 2]. Some had associated systemic diseases including diabetes mellitus, hypothyroidism, hypertension, liver dysfunction; however, none of these associations was significant [Table 4].

Discussion

Amyloidosis can either be localized or systemic. The various forms of localized cutaneous amyloidosis are macular, lichen, and nodular. Sometimes, the features of LA and MA coincide and are known as biphasic amyloidosis.[4] 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 nevus and a few adnexal tumors. Secondary cutaneous amyloid deposits are also seen in seborrheic and actinic keratoses, Bowen’s disease, porokeratosis, skin treated with UVA radiation after the ingestion of psoralens.[5]

During the course of the study, there were 100 new patients with a diagnosis of cutaneous amyloidosis among 8870 new patients who attended the skin OPD.

Hence, the prevalence of cutaneous amyloidosis was 1.13% among the patients attending the skin OPD.

In the present study of 100 cases of PCA, macular amyloidosis was most common (48%), followed by biphasic amyloidosis (30%) and lichen amyloidosis (22%). In a study by Vijaya et al., lichen amyloidosis

| Table 2: Comparative distribution of cutaneous lesions of different primary cutaneous amyloidosis |
|-------------------------------------------------|---------------------------------|-----------------|-----------------|
|                               | Macular amyloidosis | Lichen amyloidosis | Biphasic amyloidosis |
| Upper limb                     | 30 (62.5)          | 14 (63.6)         | 21 (70)           |
| Lower limb                     | 32 (66.6)          | 19 (86.4)         | 24 (80)           |
| Upper back                     | 21 (43.75)         | 10 (45.45)        | 15 (50)           |
| Abdomen                        | 8 (16.7)           | 4 (18.9)          | 7 (23.30)         |
| Neck                            | 18 (37.5)          | 3 (13.6)          | 10 (33.33)        |
| Face                            | 10 (20.8)          | 0                 | 0                |
| Generalized                    | 2 (4.17)           | 0                 | 1 (3.33)          |

| Table 3: Histopathological features of primary cutaneous amyloidosis |
|---------------------------------------------------------------------|
| Features                        | n (%)             |
| Hematoxylin and eosin stain (n=74)                               |
| Hyperkeratosis                | 52 (70.3)         |
| Acanthosis                    | 60 (81.1)         |
| Amorphous deposits            | 32 (43.2)         |
| Congo red positivity         |                  |
| Positive                      | 28 (45.2)         |
| Negative                      | 34 (54.8)         |

Figure 4: Macular amyloidosis (H and E, ×100)

Figure 5: Lichen amyloidosis (H and E, ×100)

Figure 6: Macular amyloidosis (Congo red, ×100)
was the most common variant (65.63%), with macular amyloidosis accounting for only 15.63% and biphasic amyloidosis seen in 18.75%.\[^6\] Another study reported that 90% of the cases were macular amyloidosis while only 10% were lichen amyloidosis.\[^7\] One similar study found macular amyloidosis in 74.13% of patients and lichen amyloidosis in 25.86%.\[^8\] A study in Malaysia on PCA showed that only 26% were macular amyloidosis while 74% were lichen amyloidosis.\[^9\] A recent study done in south India showed lichen amyloidosis as the frequently encountered type (61.54%).\[^1\]

The occurrence of macular amyloidosis being more common than lichen amyloidosis in the present study was in concurrence with some studies\[^7,8\] but was not in concordance with some other studies.\[^6,9\] These results showed that there could be considerable regional variation in the occurrence which might be due to local cultural practice.

In our study, majority of the patients belong to the age group of young adults, with age 30–39 years constituting 35% followed by 20–29 years at 21%. The mean age was 38.35±13.7. Our finding corroborated with a study of cutaneous amyloidosis which noted the commonly affected age group to be 30–39 years as in the present study. However, the severity of itching was significantly high in biphasic and lichen amyloidosis when compared to macular variant (P<0.01). Other workers also observed the same. A recent study from India showed 32% were asymptomatic and 68% were symptomatic which was similar to the present study.\[^15\]

Mechanical trauma, such as friction, scrubbing or that induced by nylon fibers and bristles, has been considered in the etiology of cutaneous amyloidosis and has been reported under various names, such as friction amyloidosis, towel melanosis, and nylon clothes friction dermatitis.\[^14\]

Only 21 (21%) of our patients gave history of using scrub during bathing or any kind of regular mechanical trauma or friction and 79 (79%) patients denied any history of chronic friction. In a study on macular amyloidosis, 15% of patients had a history of using scrubber.\[^7\] In one study from India, the role of scrub was seen in 30.76% of the patients, whereas Rasi et al. reported that in their study only 4% had a history of chronic friction.\[^13\] In another study from south India, 46% of the patients gave a history of using nylon scrubs or towels.\[^10\] Our findings as well as findings of some other studies have put a serious question mark on the “keratinocyte hypothesis” of origin of PCA.

Family history was not significantly associated with PCA. In the present study, positive family history

### Table 4: Associated conditions with primary cutaneous amyloidosis

| Condition                      | Number of patients (%) |
|--------------------------------|------------------------|
| Diabetes                       | 4 (4)                  |
| Hypertension                   | 4 (4)                  |
| Hypothyroidism                 | 2 (2)                  |
| Liver dysfunction              | 3 (3)                  |
| Kidney dysfunction             | 2 (2)                  |
| Tuberculosis                   | 1 (1)                  |
| Malignancy                     | 1 (1)                  |
| Preexisting dermatoses         | 20 (20)                |
was noted in 17 (17%) patients. In 2005, a study on lichen amyloidosis showed that 20% of cases had a positive family history.\[18,19\] In another study on macular amyloidosis, family history was found in 10% cases.\[20,21\] The overall positive family history of 17% in this study was similar to other studies, an observation that showed genetic predisposition and racial factor might contribute to a minor role in the occurrence of PCA.\[22-24\]

Of the total 100 patients, only 24 (24%) had a history of regular sun exposure whereas the majority of the patients of all three forms of PCA denied regular sun exposure.

**Conclusion**

PCA is a condition, which is often easy to recognize but difficult to treat as we have very less understanding of the etiopathological factors associated with the disease. Our study showed that the disease was most common in its macular form in young adult females, usually without any precipitating factors. The disease is chronic in nature and presentation to qualified dermatologist may be delayed by months or years as it is often asymptomatic or mildly pruritic especially in its macular form. However, most interesting findings coming out of our study is that the recurrent friction through scrubbing, etc., and regular photo exposure, which are often blamed to be causative factors for the disease process, may not be significantly involved. However, further longitudinal studies are required to find out genetic or personal or cultural factors responsible for the disease causation.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Padhiar B, Karia U, Shah B. Primary cutaneous amyloidosis. Indian J Dermatol Venereol Leprol 1997;63:105-6.
2. Sarkany RP, Breathnach SM, Morris AA, Weismann K, Flynn PD. Metabolic and nutritional disorders. In: Burns T, Breathnach S, Cox N, Griffiths C, editors. Rook's Textbook of Dermatology. 8th ed. Singapore: Wiley-Blackwell; 2010. p. 59.1-103.
3. Glenner GG. Amyloid deposits and amyloidosis: The beta-fibrilloides (second of two parts). N Engl J Med 1980;302:1333-43.
4. Kibbi AG, Rubeiz NG, Zaynoun ST, Kurban AK. Primary localized cutaneous amyloidosis. Int J Dermatol 1992;31:95-8.
5. Weedon D, editor. Cutaneous deposits. In: Skin Pathology. 2nd ed. Philadelphia: Churchill Livingstone; 2005. p. 429-34.
6. Vijaya B, Dalal BS, Sunila, Manjunath GV. Primary cutaneous amyloidosis: A clinicopathological study with emphasis on polarized microscopy. Indian J Pathol Microbiol 2012;55:170-4.
7. al-Ratrouj JT, Satti MB. Primary localized cutaneous amyloidosis: A clinicopathologic study from Saudi Arabia. Int J Dermatol 1997;36:428-34.
8. Kibbi AB, Rubeiz NG. Primary localized cutaneous amyloidosis. Int J Dermatol 1989;31:95-6.
9. Looi LM. Primary localized cutaneous amyloidosis in Malaysians. Australas J Dermatol 1991;32:39-44.
10. Panicker V, Jagadeesan V, Anjaneyan G, Lekshmi S, Eappen M, Sreedevan V, et al. A clinicopathological study of primary localised cutaneous amyloidosis. Int J Res Dermatol 2017;3:470-4.
11. Black MM, Jones EW. Macular amyloidosis. A study of 21 cases with special reference to the role of the epidermis in its histogenesis. Br J Dermatol 1971;84:199-209.
12. Looi LM. The pattern of amyloidosis in Malaysia. Malays J Pathol 1994;16:11-3.
13. Rasi A, Khatami A, Javaheri SM. Macular amyloidosis: An assessment of prevalence, sex, and age. Int J Dermatol 2004;43:898-9.
14. Black MM. The role of the epidermis in the histopathogenesis of lichen amyloidosus. Histochemical correlations. Br J Dermatol 1971;85:524-30.
15. Kilaparty K, Maripati L. Clinicoepidemiological and histopathological study of cutaneous amyloidosis with histopathological correlation. Int J Adv Med 2016;3:731-6.
16. Siragusa M, Ferri R, Cavallari V, Schepis C. Friction melanosis, friction amyloidosis, macular amyloidosis, towel melanosis: Many names for the same clinical entity. Eur J Dermatol 2001;11:545-8.
17. Sumitra S, Yesudian P. Friction amyloidosis: A variant or an etiologic factor in amyloidosis cutis? Int J Dermatol 1993;32:422-3.
18. Salim T, Shenoi SD, Balachandran C, Mehta VR. Lichen amyloidosus: A study of clinical, histopathologic and immunofluorescence findings in 30 cases. Indian J Dermatol Venereol Leprol 2005;71:166-9.
19. Tay CH, Dacosta JL. Lichen amyloidosis. Clinical study of 40 cases. Br J Dermatol 1970;82:129-36.
20. Taheri R. Prevalence of macular amyloidosis in North Iran. Indian J Dermatol 2007;52:192-3.
21. Bandhlish A, Aggarwal A, Koranne RV. A clinico-epidemiological study of macular amyloidosis from north India. Indian J Dermatol 2012;57:269-74.
22. Tafarel JR, Lemos LB, Oliveira PM, Lanzoni VP, Ferraz ML. Cutaneous amyloidosis associated with primary biliary cirrhosis. Eur J Gastroenterol Hepatol 2007;19:603-5.
23. Kurban AK, Malak JA, Afifi AK, Mire J. Primary localized macular cutaneous amyloidosis: Histochecmistry and electron microscopy. Br J Dermatol 1971;85:52-60.
24. Rajagopalan K, Tay CH. Familial lichen amyloidosis. Report of 19 cases in 4 generations of a Chinese family in Malaysia. Br J Dermatol 1972;87:123-9.