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# EPIDEMIOLOGY, CLINICAL AND HISTOPATHOLOGICAL PROFILE OF PATIENTS WITH PRIMARY LOCALIZED CUTANEOUS AMYLOIDOSIS (PLCA) IN A TERTIARY CARE HOSPITAL IN MUMBAI

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**ABSTRACT**

**Background:** Primary localized cutaneous amyloidosis (PLCA) is one of the common pigmentary disorders in dermatology.

**Aims:** To study epidemiological and clinical profile of patients with PLCA. To study utility of H & E stain, Thioflavin-T stain & direct immunofluorescence (DIF) for demonstration of amyloid deposits.

**Methods:** Patients of both sexes, aged 18 to 65 years were included. Detailed history & clinical examination was followed by skin biopsy for H& E stain, Thioflavin-T stain and DIF studies.

**Results:** Sixty-five patients with clinical diagnosis of PLCA were studied. Mean age of presentation was 38.76 years with female preponderance. Macular amyloidosis (84.61%) was the commonest type followed by lichen amyloidosis (50%). Amyloid was demonstrated by H&E stain in 63.07 % of the cases, by Thioflavin-T stain in 64.61 % of the cases and by DIF in 44.61 % of the cases.

**Conclusions:** H& E stain was found to be equally effective for diagnosis of PLCA compared to special stains.

**KEYWORDS :** Macular. lichen amyloidosis, Thioflavin T stain, DIF

## INTRODUCTION:

Primary localized cutaneous amyloidosis (PLCA) is characterized by the deposition of extracellular amyloid, a particular fibrillar substance in the skin without evidence of amyloid deposits in the internal organs. This entity is classified into; papular or lichen amyloidosis(most common), the macular type and the nodular type with systemic evolution.[1]

Lichen amyloidosis is seen in the elderly (50 to 60 years) with male preponderance. It is more common in persons of Chinese ancestry [2] and characterized by an eruption of itchy, hyperkeratotic and reddish brown papules over the shins, feet, thighs, calves and ankles.[Figure 1a] Macular amyloidosis is common in middle aged and elderly females. It is more prevalent among Central and South Americans, Middle Eastern and Asians and is characterized by symmetrical, brownish macules, with typical rippled, reticulate hyperpigmentation. The lesions are moderately itchy, distributed over the upper extremity, upper back, legs and occasionally on the chest and buttocks.[1] [Figure 1b]

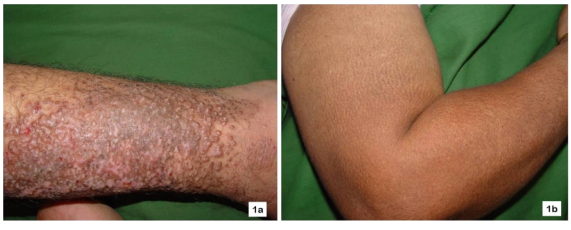

**Figure 1a: Lichen amyloidosis Figure 1b: Macular amyloidosis**

Macular and lichen amyloidosis usually do not evolve into a systemic form and both can coexist in the same patient i.e. biphasic amyloidosis. The diagnosis is usually clinical but can be confirmed by demonstration of amyloid histologically with various stains like Congo red(with or without polarizing microscope) , crystal violet, Periodic acid Schiff (PAS) , fluorescent dyes, Thioflavin-T and Thioflavin-S.

Efficacy of Haematoxylin & eosin (H & E) stain is less, as the deposits are smaller and easily be missed. Direct immunofluorescence has revealed immunoglobulin M (IgM) and C3 positivity in few reported studies. [3]

Though the exact etiology of PLCA is unknown but the role of friction and chronic itching is strongly suspected and observed in the previous studies.

## MATERIAL AND METHODS:

This descriptive study was conducted in the tertiary care hospital in Mumbai after receiving approval from institutional ethic committee. Patients of both the sexes with clinical diagnosis of PLCA and age above 18 years were included in the study after informed consent.

Objectives were to study epidemiology and clinical profile of patients with PLCA, to study findings of H&E stain, Thioflavin-T stain and direct immunofluorescence (DIF) for demonstration of amyloid. A detailed clinical history & examination was followed by two skin biopsies with 4 mm punch from the lesional skin. One biopsy was sent for haematoxylin & eosin and Thioflavin T stain and the other was sent for direct immunofluorescence in Michel's medium. Laboratory investigations including blood sugar, thyroid profile and ultrasonography of abdomen and pelvis to look for associated systemic disorders were also done.

## DIAGNOSIS BY HISTOPATHOLOGY AND DIF:

Presence of eosinophilic amorphous globular deposits in the dilated dermal papillae with pigmentary incontinence on H& E stain was considered diagnostic features of PLCA. Sections showing yellowish green deposits of amyloid in papillary dermis when stained with Thioflavin T were considered diagnostic of PLCA. While fluorescent deposits in papillary dermis by DIF were considered diagnostic of PLCA.

## RESULTS:

Sixty-five patients of PLCA were studied. Most patients in our study were in the 4$^{th}$ and 5$^{th}$ decade with mean age of 39.30 years. Female to male ratio was 7.1:1. Mean duration of illness was 2.4 years. Family history was present in 4 of 65 patients (6.25 %).

History of pruritus was present in 78.48 % of all patients of PLCA, 74.54% of patients of with macular amyloidosis and almost 100% patients with lichen and biphasic amyloidosis.

History of friction was present in 76.92% patients of PLCA, 72.72 % patients with macular and 100% patients with lichen and biphasic amyloidosis. The materials used for scrubbing the skin included towel, nylon brush and loofah, pumice stone, coconut shell, and comb.

Macular amyloidosis was seen in 55 /65 patients, lichen amyloidosis in 6/65 patients and biphasic amyloidosis in 4/65 patients.

Distribution: Upper extremities were the most common site affected in PLCA followed by legs. Upper extremities i.e. arm and forearm was affected in 40/55 patients with macular type and leg was affected in 6/6 patients and 4/4 patients with lichen and biphasic type respectively.

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Diabetes mellitus was present in 20 % of patients. Other associated illness seen were diffuse facial hyperpigmentation and hypothyroidism.

**STAINING TECHNIQUES:**

amyloid deposits were demonstrated by H& E stain in 41/65 (63.07%) of patients,[figure 2a] by Thioflavin-T stain in 42/65 (64.61% ) of patients [figure 2b]and by DIF in 29/65 (44.61%) 103 patients.[Figure 2c] In 32% of the patients none of the staining technique was positive.

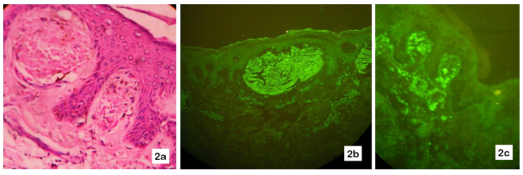


**Figure 2:** (2a)Pink, amoprhous globular deposits of amyloid in the dilated dermal papilla with
pigmentary incontinence, H & E stain, 400X, (2b) Yellowish green deposits of amyloid in papillary
dermis under immunofluorescence microscope, Thioflavin T stain, 400X
(2c): Fluorescent deposits of amyloid in papillary dermis by Direct immunofluorescence (DIF), 400X

**Positivity of staining technique for demonstration of amyloid deposits in different types of amyloidosis is depicted in Table 1.**

**Table 1: Positivity of staining technique for demonstration of amyloid deposits**

| Types of amyloidosis | Hand E | Thioflavin T | DIF |
|---|---|---|---|
| Macular | 32/55 (58.18 %) | 33/55 (60 %) | 22/55 (40%) |
| Lichen | 5/6 (83.33 %) | 5/6 (83.33 %) | 4/6 (66.66 %) |
| Biphasic | 4/4 (100 %) | 4/4 (100 %) | 3/4 (75%) |
| **Total** | **41/65 (63.07%)** | **42/65 (64.61%)** | **29/65 (44.61 %)** |

In 32% of the patients none of the staining technique were positive.

Of the 46.15% patients showing positive results with DIF, IgA antibody showed maximum positivity (96.66%) followed by IgM (90%), C3(86.66%), IgG (60%) and fibrinogen (56.66%). Positivity of fibrinogen by DIF in patients of PLCA was almost similar to IgG antibody.

Biopsies from leg revealed maximum positivity by all 3 staining techniques (H& E stain & Thioflavin T stain: 20/23 (86.95%) and DIF: 16/23 (69.56 %) compared to biopsies from arm and back. [Figure 3]

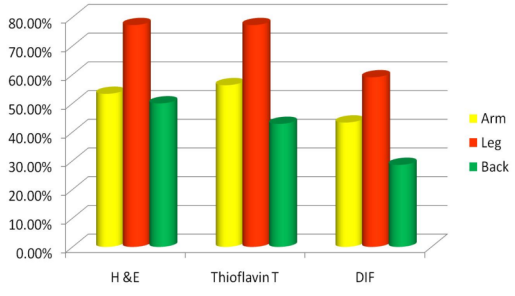


**Figure 3: Positivity of staining techniques in biopsy sites from arm, leg and back**

Ultrasonography of abdomen and pelvis to look for associated diseases of reproductive tract and hormonal disorders revealed uterine fibroid and simple ovarian cyst in only 2 patients.

**DISCUSSION:**

Primary localized cutaneous amyloidosis (PLCA), is one of the common pigmentary dermatoses in Indian patients. Previously few studies have evaluated the epidemiology and histopathology profile of the patients with PLCA but there is paucity of literature on the utility of thioflavin T stain and direct immunofluorescence in the histopathological diagnosis of PLCA.

Majority of patients in our study belonged to age group of 31 to 40 yrs with mean age of presentation of 39.30 years, which is almost similar to other reported studies. [3,4,5]

Female preponderance was noted in our study (M: F ratio 1:7.1) and was higher compared to other studies. [6,7].

There was a significant difference in sex distribution in different types of PLCA. Macular subtype showed female preponderance and lichen subtype showed male preponderance. This finding was comparable to the studies conducted by Rasi et al and Eswaramoorthy et al [8,9].

The mean duration of illness in our study was 2.4 years which was comparable to the reported studies.[10, 11] Family history was present in 6.25 % of the patients compared to 9.3 % reported study.[9]

History of pruritus was present in 78.48 % of all patients of PLCA, 74.54% of patients of macular amyloidosis and almost 100% patients of lichen and biphasic amyloidosis. This finding is also similar to study reported by Leonforte et al. [12]

History of friction was present 76.92% of patients with PLCA.

In our study PLCA was associated with other cutaneous and systemic disease. Diabetes mellitus was seen in 20 % patients. It was more common in macular subtype of PLCA. The other associated disorders included hypothyroidism, urticaria, melasma, allergic contact dermatitis and prurigo. Many of these disorders are known to be associated with prolonged intractable itching, which could be contributing factor in the etiopathogenesis of PLCA. Reported association of macular amyloidosis include chronic urticaria, acne vulgaris, generalized xerosis, hypothyroidism, hypertension and idiopathic hirsutism. [13]

Diffuse facial hyperpigmentation was observed in 5 patients of macular amyloidosis with extensive cutaneous involvement. This association has already been described as an unusual variant in two cases by Wang et al. [14]

Macular amyloidosis was the most common type (84.61 %) in our study followed by lichen amyloidosis (9.23 %). The distribution of PLCA in our study varied according to type of PLCA. Simultaneous involvement of arms, forearms, back and leg was the most common presentation in patients of macular amyloidosis, while leg was most commonly affected in patients of lichen amyloidosis. Biphasic amyloidosis showed lesions of macular amyloidosis on arms, forearms, back and lesions of lichen amyloidosis on legs.

Diagnosis in our study was confirmed by histopathology(H & E stain), special stain like Thioflavin T and Direct immunofluorescnce technique.

Our findings were comparable to study conducted by Salim et al [3] which showed positivity of 93.33 % by H&E and Mysore et al which showed positivity of 30% by H&E and 60% by Thioflavin T for demonstration of amyloid.[10]

In our study, DIF was positive in 29/65 (44.61 %) of cases with deposits of amyloid are visualized as fluorescent deposits in the papillary dermis and in few cases the deposits were also seen in upper and mid dermis. Demonstration of fibrinogen on DIF in PLCA has not been reported in any of the previous studies but our study showed positivity of fibrinogen almost similar to that of IgG antibody.

Immunoglobulin positivity in our study showed following results: IgA>IgM >C3 >IgG>F. Other colleagues found different results as IgM >C3 >IgA >IgG (Salim et) [3], IgG>C3 (Habermann et al) [15], IgM>C3 (MacDonald) [16].

Comparison of staining techniques with subtype of amyloidosis revealed H & E and Thioflavin T were almost equally effective in demonstration of amyloid in all subtypes of PLCA compared to DIF. All 3 techniques showed higher positivity in biphasic and lichen amyloidosis compared to macular amyloidosis which could be attributed to presence of larger deposits in these 2 subtypes.

Correlation of staining method with biopsy site revealed that maximum positivity for amyloid obtained when the biopsies were taken from the leg compared to other sites.

Limitation of our study included unequal sample size in all 3 types of PLCA. Hence the utility of H& E stain, Thioflavin T and DIF could not be studied in the individual type of amyloid.

## CONCLUSION:

PLCA is a common pigmentary disorder in dermatology. Diagnosis is usually clinical but sometimes may require histopathological confirmation. Difficulty in demonstration of amyloid in skin biopsy specimens could be due to smaller deposit, difficulty in differentiating the deposit from collagen or inappropriate biopsy site. Special stains like Thioflavin T and DIF techniques can be more useful as the deposits appear more prominent but it requires a specialized set up and trained personnel that can add to the cost.

Present study refocuses on the epidemiology of PLCA and utility of various staining techniques like H& E stain, Thioflavin T stain and DIF for the diagnosis of PLCA. Our study also highlights the importance of H & E stain in demonstration of amyloid if biopsy is taken from the appropriate site.

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