Study on epidemiology of cutaneous amyloidosis in northern India and effectiveness of dimethylsulphoxide in cutaneous amyloidosis

Arvind Krishna, Bhola Nath[1], G. G. Dhir[3], Ranjeeta Kumari[2], Virendra Budhiraja[4], Kalpana Singh[5]

Department of Skin and VD, Subharti Medical College, [1]Department of Community Medicine, G.G.S. Medical College, BFUHS, Faridkot, [2]AIIMS, Rishikesh, [3]Department of Skin and VD, S. N. Medical College, Agra, [4]Department of Anatomy, Subharti Medical College, Meerut, [5]Department of Pathology, S. N. Medical College, Agra, India

ABSTRACT

Context: Amyloidosis, which is characterized by the extracellular deposition of a proteinaceous substance, is usually associated with considerable tissue dysfunction. However, the etiology of the disease remains uncertain and the treatment disappointing. **Aim:** 1. To know the epidemiology of cutaneous amyloidosis 2. To evaluate the effect of dimethylsulphoxide on cutaneous amyloidosis. **Settings and Design:** Data was collected from patients attending the Outpatient Department (OPD) over a period of one year. **Material and Methods:** Patients were screened on the basis of signs and symptoms and then confirmed histologically. A total of 62 patients who were suspected to be suffering from amyloidosis on the basis of clinical signs and symptoms and 38 patients who were further confirmed histopathologically underwent the treatment. **Statistical Analysis Used:** Chi-square test was used for testing the significance of proportions. **Results:** 63.15 percent of the patients had macular amyloidosis and the interscapular area was the most common area involved (52.63%). Pruritus, pigmentation, and papules responded excellently to dimethylsulphoxide after one month of treatment. **Conclusions:** Cutaneous amyloidosis is a disease found in middle-aged persons, with a female preponderance, and dimethylsulphoxide seems to be an effective therapy.

Key words: Cutaneous amyloidosis, dimethylsulphoxide, pigmentation, pruritis

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Address for correspondence:
Dr. Arvind Krishna, Department of Skin and VD, NH-58, Subhartipuram, Subharti Medical College, Meerut, India
E-mail: jeeta21@yahoo.com

INTRODUCTION

Amyloidosis is a disease of the skin characterized by extracellular deposition of a proteinaceous substance, and is usually associated with considerable tissue dysfunction. Two types of cutaneous amyloidosis have been observed. One is primary localized cutaneous amyloidosis (PLCA), without any deposits in the internal organs and the other is secondary cutaneous amyloidosis. Various subtypes of PLCA are recognized, including the more common macular and papular (lichen amyloidosis) types and the rare nodular form. Macular amyloidosis is rare in Europe and North America, but is much more common in Central and South America, the Middle East, and Asia.[1-6] The etiology of PLCA remains unknown.[1] In general, the treatment of PLCA has been disappointing. Various treatment modalities have been evaluated, but have proven to be of limited use.[7]

The present study was therefore undertaken to study the epidemiology of primary cutaneous amyloidosis in the patients attending the Outpatient Department (OPD) of the Skin Department of a medical college in north India and to evaluate the effect of dimethylsulphoxide (DMSO) on primary localized cutaneous amyloidosis.

MATERIALS AND METHODS

The study group comprised patients attending the OPD of the Skin Department of a medical college for over a period of 12 months, from 1 July, 2002 to 30 June, 2003. All the patients suspected to be suffering from cutaneous amyloidosis on the basis of clinical symptoms and signs were included in the study, after obtaining an informed written consent from them. A total of 62 patients were suspected to be suffering from amyloidosis, while 38 patients were confirmed histopathologically and underwent the treatment. Patients having any systemic disease, pregnant and lactating women or patients less than 18 years of age were excluded from the study. Patients with pruritic, brownish, rippled or reticulate hyperpigmented macular lesions, commonly distributed over

the back or chest, were classified as 'macular amyloidosis'. Patients with persistent, pruritic, papular eruptions on their shins, extensor aspect of their thighs, forearms, and upper arms were classified as 'lichen or papular amyloidosis', while patients having both the lesions were grouped under 'biphasic amyloidosis'. Confirmation of the diagnosis was done by a histopathological examination of the biopsy specimen from the suspected lesion.

Details regarding the occupation of the patient, duration of illness, progression of disease, habit of scratching or rubbing the area, use of pumice stone, attempt to forcefully remove the pigmentation, and family history, were elucidated. The exact morphology and distribution of the lesion were also recorded. Socioeconomic status was classified on the basis of the Kuppuswamy classification. Classes I and II were grouped as the upper class, Class III as the middle, and Classes IV and V as the lower class. Ethical clearance was obtained from the ethical committee of the college.

After confirmation of the diagnosis by histopathology and staining, all the patients were prescribed 100% topical DMSO, twice daily, and regularly examined every month, for three months. We presumed that the patients did not miss any of the doses, as there was no means to confirm it. The patients were not prescribed any antihistamines, non-steroidal anti-inflammatory drugs (NSAIDs) or any topical or systemic corticosteroid. There were no dropouts in the study and each and every patient attended the three-month-long study.

The response to the treatment was graded into three categories. Complete abolition of pruritus or pigmentation or complete flattening of papules was regarded as an 'excellent response', decrease in pruritus, pigmentation or partial flattening of papules was graded as a 'partial response,' and no or negligible decrease in pruritus, pigmentation or flattening of papules was labeled as 'no response'.

The data was compiled and analyzed using Microsoft Excel for Windows. Discrete data was analyzed using Pearson's Chi-square test for proportions. The Chi-square trend was used to evaluate the effect of the drug after one, two and three months of treatment. Two tailed p-values were considered, and a p-value less than 0.05 was considered significant.

RESULTS

A total of 62 patients were suspected to be suffering from amyloidosis on the basis of clinical signs and symptoms. Thirty-eight patients were confirmed histopathologically, after examination of their biopsy specimens. Two-thirds of the patients with histologically confirmed amyloidosis were classified as macular amyloidosis, while 23 percent and 13 percent were identified as papular and biphasic amyloidosis, respectively.

The most common site affected by cutaneous amyloidosis was the interscapular area or the back. (52.63%) [Table 1].

Among the patients attending the Skin OPD, cutaneous amyloidosis was more commonly found among the females, unmarried people, urban dwellers, and in the patients in the age group of 40 – 49 years. None of the patients suffering from amyloidosis belonged to the higher socioeconomic class [Table 2].

The most common age of onset of the disease among patients diagnosed with having cutaneous amyloidosis was from 30 to 39 years of age. A history of chronic friction or rubbing was more common among patients suffering from biphasic amyloidosis, although it did not differ significantly in the other two groups. A family history of the disease was more common in patients with macular and biphasic amyloidosis [Table 3].

The effect of DMSO on pruritus, pigmentation, and papules was excellent in the initial one month (P value < 0.0001). Thereafter, the symptoms improved, but not as significantly as compared to the previous month [Table 4, Figures 1 and 2].

The side effects of DMSO reported by the patients included desquamation of the skin and a burning sensation [Table 5].

DISCUSSION

The present study was an attempt to study the epidemiology of PLCA and the effectiveness of DMSO on the lesions. An analysis of cutaneous amyloidosis cases during a one-year period yielded a total of 62 patients, with signs and symptoms suggestive of cutaneous amyloidosis, of which 38 were histologically confirmed. A similar study conducted in Jakarta, Indonesia, which yielded 78 cases during a period of five years.[8] Also Black and Wilson detected 21 cases of macular amyloidosis over a period of 12 years.[9] This indicated a higher prevalence of the disease in our setting or a higher level of reporting of the condition.

The predominance of macular lesions of PLCA found in our study was in accordance with that reported by other workers

Table 1: Classification of cutaneous amyloidosis

Characteristic	No. of Patients	Percentage
Type		
Macular Amyloidosis	24	63.15
Papular Amyloidosis	9	23.68
Biphasic Amyloidosis	5	13.16
Site Affected		
Interscapular area / Back	20	52.63
Shins	9	23.68
Multiple area involvement	9	23.68

in Indonesia, London, Turkey, and India.[8-11] On the other hand a study done in Kuala Lumpur revealed a different picture, with the most common form being papular amyloidosis, which in our study was exclusively found in only 23.7% of the cases. PLCA has been found to affect the Chinese more frequently than the other major ethnic groups, but macular amyloidosis is more common than expected among Indians.[12] We did not find any case of nodular amyloidosis in our study, a finding supported by other studies.[8-11] These differences in racial susceptibility suggest that genetic factors might play a role in the etiology and pathogenesis of cutaneous amyloidosis.

Table 2: Sociodemographic characteristics of patients with primary localized cutaneous amyloidosis

Sociodemographic characteristics	No. of Patients (38)	Percentage
Gender		
Male	11	28.95
Female	27	71.05
Age Group (years)		
20 – 29	5	13.16
30 – 39	9	23.68
40 – 49	13	34.21
50 – 59	11	28.95
Locality		
Rural	15	39.47
Urban	23	60.53
Marital status		
Married	34	89.47
Unmarried	4	10.53
Socioeconomic class		
Lower Class	20	52.63
Middle Class	18	47.37
Higher Class	0	0

The most common area of involvement was reported to be the interscapular area or the back, which could be due to the fact that macular amyloidosis, which was the most common variety, reported in our study, was found usually on the interscapular areas or the back. The distribution reported was similar to that reported by Djuanda *et al* and Leonforte.[10,13]

The female preponderance of cutaneous amyloidosis was overwhelming and was in accordance with the findings of other research studies carried out in Indonesia, India, Malaysia, and South America.[10-13]

Preponderance of the patients was found to be in the age group of 40 – 60 years, which was similar to studies done by Djuanda *et al.* and Looi.[10,12] The age of onset of the disease was also 30 – 50 years, and the patients seemed to report within a short period of onset of the disease. The urban predominance of the cases could be because of the fact that patients coming to the Medical College for treatment usually came from the nearby urban areas. The disease seemed to be more prevalent among the married and patients belonging to the lower class. Age could act as a confounder in the association found between marriage and cutaneous amyloidosis.

Wong reported the role of chronic friction in cutaneous amyloidosis.[1] Scratching has been known to produce traumatic and pressure changes such as excoriation, inflammation, pigmentation, and finally lichenification in the human skin. We observed that a history of chronic friction or rubbing of the lesion was present in 14 out of 38 patients. Three hours of experimental scratching over a period of three days has been reported to produce focal hyperpigmentation of the black skin, followed by hyperkeratosis induction and initial damage to the keratinocytes leading to initiation of an early stage of macular amyloidosis.[1] Goulden *et al*. also reported an association of

Table 3: Etiology of Cutaneous Amyloidosis

Characteristics	Age Group	No. of patients	Percentage	χ^2 value, *P*-value
Age of Onset	10 – 19	2	5.26	
	20 – 29	7	18.42	
	30 – 39	12	31.58	
	40 – 49	11	28.95	
	50 – 59	6	15.79	
History of Chronic friction / rubbing the lesion	Macular Amyloidosis (n = 24)	9	37.50	0.16, 1.00*
	Biphasic Amyloidosis (n = 5)	2	40.00	0.11, 0.73†
	Papular Amyloidosis (n = 9)	3	33.33	0.03, 1.00‡
Family History	Macular Amyloidosis (24)	5	20.83	0.32, 1.00*
	Biphasic Amyloidosis (5)	1	20.00	0.12, 1.00†
	Papular Amyloidosis (9)	1	11.11	0.02, 1.00‡

*Association between Macular and Biphasic amyloidosis, †Association between Biphasic and Papular amyloidosis, ‡Association between Macular and Papular amyloidosis

Table 4: Effectiveness of DMSO on cutaneous amyloidosis after one, two, and three months of treatment

Duration of Treatment	Excellent response No. (%)	Partial Response No. (%)	No Response No. (%)	χ^2 value, *P* value
Response of Dimethyl sulfoxide on Pruritus				
Start of treatment	0	0	38	46.78, <0.0001*
After one month	22 (57.89)	9 (23.68)	7 (18.42)	0.84, 0.36†
After two months	26 (68.42)	7 (18.42)	5 (13.16)	0.11, 0.74‡
After three months	27 (71.05)	7 (18.42.)	4 (10.53)	1.56, 0.21§
Response of Dimethyl sulfoxide on Pigmentation				
Start of treatment	0	0	38	21.81, < 0.0001*
After one month	8 (21.05)	11 (28.95)	19 (50.00)	0.51, 0.47†
After two months	10 (26.32)	12 (31.58)	16 (42.10)	1.01, 0.31‡
After three months	12 (31.58)	15 (39.47)	11 (28.95)	2.96, 0.08§
Response of Dimethyl sulfoxide on Papules				
Start of treatment	0	0	38	25.66, < 0.0001*
After one month	3 (21.43)	6 (42.86)	5 (35.71)	1.00, 0.31†
After two months	5 (35.71)	6 (42.86)	3 (21.43)	0.59, 0.44‡
After three months	7 (50.00)	5 (35.71)	2 (14.29)	2.94, 0.08§

*Chi-square trend values from the start of treatment to the first month, †Chi-square trend values from the first month to the second month, ‡Chi-square trend values from the second month to the third month, §Chi-square trend values from the first to the third month

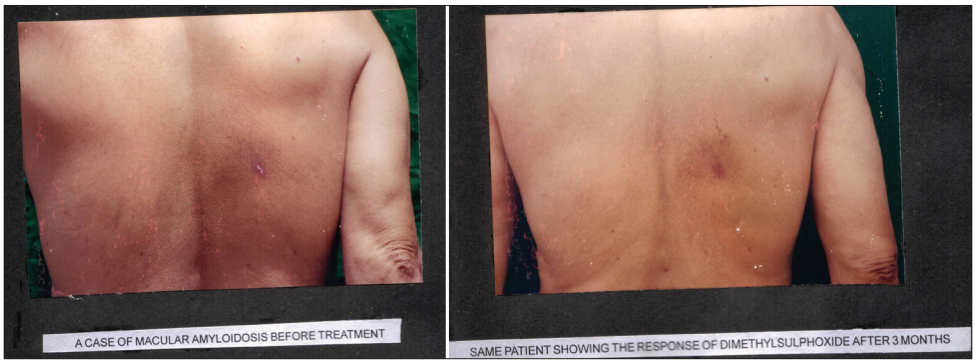

Figure 1: Pre and Post treatment photographs of a case of Macular Amyloisdosis

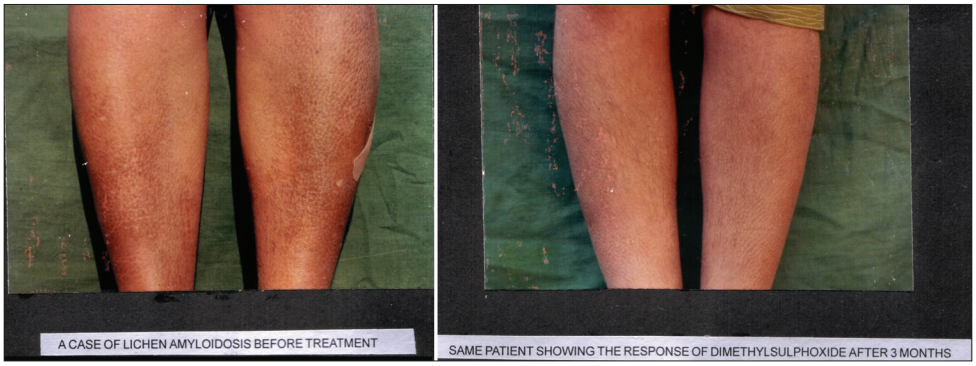

Figure 2: Pre and Post treatment photographs of a case of Lichen Amyloisdosis

macular amyloidosis with notalgia paresthetica.[14] Leonforte JF also dismantled the hitherto accepted fact that macular amyloidosis is a primary condition and stated that it is secondary to scratching initiated by pruriginous diseases.[13] However, Eswaramoorthy *et al.* could not find a direct correlation between macular amyloidosis and friction to the skin, but still stated that these factors may play a collective role in the genesis of macular amyloidosis.[11]

A familial association of cutaneous amyloidosis was reported in seven patients in our study, which corroborates with the findings of other research workers.[11,15] Rajgopalan *et al.* found cutaneous

Table 5: Side effects of the drug

Side Effects	No. of patients	Percentage
Desquamation	2	5.26
Burning Sensation	5	13.16
Contact Urticaria	0	0

amyloidosis in members of four successive generations, suggesting an autosomal dominant mode of transmission.[16] Desouza reported four siblings with localized cutaneous amyloidosis.[17] However, Looi LM reported that most cases of primary cutaneous amyloidosis did not have a familial basis.[12]

Of the various therapeutic modalities with variable success, the most encouraging and beneficial effect had been observed with topical dimethylsulphoxide (DMSO) therapy. Highly successful results were obtained in macular and lichen amyloidosis cases over a short treatment period with concentrations between 10 and 100%.[18-20] Pruritus disappeared within a week and remarkable flattening of papular lesions was achieved in 2 – 16 weeks of therapy. However, histopathological examinations have revealed no decrease in amyloid deposits.

Treatment with 100% DMSO twice daily for three months resulted in complete relief from pruritus in 71% of the patients, complete disappearance of pigmentation in 31.5%, and complete remission of papules in 50% of the cases. Ozkaya-Bayazit observed that the mean time required for the disappearance of pruritus was 4.1 weeks of treatment with 100% DMSO once daily. They also observed that response to pigmentation was visible in 50% and flattening of papules in more than 70% of the cases after 6.5 months of treatment. [8] Similarly, Pandhi R *et al*. observed a decrease in pruritus score, but not a complete disappearance in any of the patients treated with 100% DMSO after 12 weeks of treatment. Also, complete remission of pigmentation was observed in only 24% of the patients and flattening of papules in only 16.6% of the cases.[21]

Side effects of the local application of DMSO, as reported in other studies, include a burning sensation and desquamation and contact urticaria. However, contact urticaria has not been reported in our study.

CONCLUSION

Cutaneous amyloidosis is a disease of middle-aged persons with a female preponderance. Macular amyloidosis is the most common form and the most common area affected is the interscapular area. Friction plays an important part in the development and progression of the disease. Dimethylsulphoxide is beneficial in reducing the pruritus and pigmentation, as well as decreasing the size of the papules. However, the etiology of amyloidosis remains unclear and population-based studies would prove to be of great benefit in evaluating the exact etiology of amyloidosis. Also well-controlled studies are needed to evaluate the effect of DMSO on cutaneous amyloidosis.

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