Primary Localized Cutaneous Amyloidosis: A Retrospective Study of an Uncommon Skin Disease in the Largest Tertiary Care Center in Switzerland

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Keywords

Primary localized cutaneous amyloidosis · Lichen amyloidosis · Macular amyloidosis · Amyloid · Phototherapy · Topical corticosteroids

Abstract

Background: Primary localized cutaneous amyloidosis (PLCA) is defined by the deposition of amyloid protein in the skin without systemic involvement. There are four subtypes of PLCA: lichen amyloidosis (LA), macular amyloidosis (MA), biphasic amyloidosis (BA), and nodular amyloidosis (NA). PLCA occurs most frequently in Latin Americans and Asians. Treatment is not standardized. **Objectives:** To identify subtypes, demographic and clinical features and treatment efficacy in patients with histopathologically confirmed PLCA. **Materials and Methods:** Data of PLCA patients were extracted from the electronic hospital database and included if diagnosis of PLCA was histopathologically confirmed and if sufficient information regarding treatment and follow-up was available. The evaluation of the treatment efficacy was based on a novel score to assess the reduction of itch and skin lesions. **Results:** In this retrospective, monocentric

study, 37 cases of PLCA diagnosed between 2000 and 2020 were included (21 females) with a mean age of 52 years. LA was the most frequent subtype found in 21 patients (56.8%), followed by MA in 10 patients (28%) and BA in 6 patients (16.2%). No cases of NA were included. 22 patients (59.4%) had skin phototype II or III. Regarding treatment, a combination of UVA1 phototherapy with high-potency topical corticosteroids seemed to show the highest efficacy with complete clearance of symptoms in 4 patients (10.8%). A substantial improvement of symptoms was found in 5 patients (12.7%) treated with high-potency topical corticosteroids alone or in combination either with UVA1 or bath PUVA or monotherapy with UVA1 phototherapy or capsaicin (0.075%) cream. Low-/medium-potency topical corticosteroids alone or in combination with UVBnb (311 nm) phototherapy showed a lower efficacy. **Conclusion:** Our data show that PLCA is a rare disease in central Europe but can also be expected in a predominantly Caucasian population. The best treatment response was achieved with a combination of UVA1 phototherapy and high-potency topical corticosteroids.

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Introduction

Primary localized cutaneous amyloidosis (PLCA) is a rare skin disease characterized by the deposition of amyloid in the dermis without systemic involvement. Amyloid is an extracellular proteinaceous material which can accumulate in the skin and other organs. Amyloid in PLCA is derived from keratin peptides of necrotic keratinocytes and not, as in systemic forms of amyloidosis, from immunoglobulin or serum protein deposits [1]. The etiopathology of PLCA is not known. It has been hypothesized that signaling abnormalities via the oncostatin M-type II receptor and/or the interleukin (IL)-31 receptor lead to keratinocyte apoptosis and subsequent amyloid deposition and pruritus [2, 3]. Furthermore, point mutations in the IL-31 receptor A gene have been found in a hereditary form of PLCA [4]. It is assumed that the deposition of filamentous material secondary to intense scratching induced by pruritogenic processes leads to amyloid formation in the skin. Chronic scratching, as for example seen in atopic dermatitis, may promote damage to keratinocytes resulting in localized amyloid formation [5].

PLCA is thought to occur most frequently in individuals of Latin American or Asian origin [6]. Data on PLCA regarding demography, epidemiology, clinical patterns, and histopathological findings in Caucasians, however, is limited. Therefore, we retrospectively analyzed clinical patterns and treatment efficacy of PLCA in a tertiary care center in Switzerland.

Subtypes and Clinical Manifestation

There are four subtypes of PLCA: lichen amyloidosis (LA), macular amyloidosis (MA), and nodular amyloidosis (NA). A joint manifestation of LA and MA is called biphasic amyloidosis (BA) [7].

LA is the most frequent subtype of PLCA. It is characterized by multiple, localized or generalized, grouped papules with a predilection for the shins (Fig. 1). MA is characterized by multiple brown-greyish macules with a reticulated or rippled pattern and has a predilection for the upper back (Fig. 2). NA is the rarest form of PLCA and presents as firm pink to brown nodules preferentially involving the extremities. Nodule size varies from a few millimeters to centimeters and may coalesce to plaques [8, 9]. Amyloid in NA is caused by light-chain amyloid synthesized by monoclonal plasma cells localized in the skin [8, 9]. Previous studies have shown that up to 22% of patients with NA have underlying Sjögren syndrome [10].

Fig. 1. Lichen amyloidosis manifesting as symmetrically distributed, hyperpigmented papules with central denting on both shins (male, 39 years, phototype V).

Histopathology

The key finding in PLCA is the deposition of pink, amorphous globular material in the papillary dermis. Additionally, increased pigmentation of the basal layer and scattered melanophages can be found. LA is characterized by marked acanthosis and hyperkeratosis. Typical histological findings of LA are shown in Figure 3.

For better visualization of the amyloid, special stains (congo red or pagoda) can be used (Fig. 4). Immunohistochemical staining with cytokeratin 5/6 (CK5/6) confirms the epidermal origin of the amyloid deposits in PLCA.

Materials and Methods

Patient Characteristics and Data Acquisition

After ethical approval (BASEC Nr.: 2019-02410), the electronic hospital database was searched for patients ≥ 18 years old, treated at the Department of Dermatology at the University Hospital Zurich in the last 20 years (January 1, 2000, to December 31, 2020).

The following keywords were used to identify all patients diagnosed with PLCA: “Lichen amyloidosis,” “lichen amyloidosis,” “macular amyloidosis,” “nodular amyloidosis,” “primary cutaneous amyloidosis,” “biphasic amyloidosis.” Seventy-nine patients were identified using these criteria.

Out of these 79 patients, 42 patients had to be excluded from the present study because they did not meet the following inclusion criteria: (1) histologically confirmed diagnosis of PLCA, (2) availability of follow-up information for at least 3 months after diagnosis, (3) availability of information and photographic material regarding treatment response, (4) age > 18 years (Fig. 5). In total, 9 patients with NA were identified. They either did not meet above-mentioned inclusion criteria or had concomitant mono-

Fig. 2. Interscapular macular amyloidosis with hyperpigmentation (woman, 59 years, phototype III).

clonal gammopathy, and therefore amyloid deposits in the skin were interpreted as secondary to systemic disease. The following clinical information about the patients was extracted from the electronic database: age, sex, skin phototype (Fitzpatrick's scale I–VI), geographical region of origin, comorbidities, personal history of atopy, family history of PLCA, type of PLCA and treatment modalities (including treatment duration and treatment efficacy).

Treatment Efficacy

Treatment efficacy was assessed based on information available in the patients' medical records. To standardize treatment efficacy, we used a simple score to retrospectively assess treatment efficacy and reduction of itch: A score from 0 to 3 was applied to separately measure the itch and the reduction of skin changes including scaling, induration, hyperkeratosis, redness: 0 = no effect on itch or skin, 1 = mild improvement of itch or skin, 2 = good improvement of itch or skin, 3 = very good improvement or complete resolution of itch or skin. The final score was calculated as the sum of both scores; a maximum score of 6 signified very good improvement or complete resolution of itch and skin changes. A minimal score 0 meant no treatment effect at all. The treatment efficacy score (TES) was established following a shared decision-making process by C.G. and I.K.

Histopathology

All histopathology specimens were reviewed by a board certified dermatopathologist (I.K.). Special stains (congo-red or pagoda stain) were performed in all cases; immunohistochemistry staining for CK5/6 was available in some cases.

Statistical Analyses

Descriptive analyses were performed using standard parameters (absolute and relative frequencies, means). Missing data were not imputed. Analyses were performed using IBM SPSS Statistics (IBM SPSS Statistics for Mac, Version 26.0; IBM Corp., Armonk, NY, USA).

Fig. 3. Globular eosinophilic deposits (=amyloid) in the tips of the dermal papillae in LA. H&E stain. ×400.

Fig. 4. Congo red stain highlighting globular orange-red deposits (=amyloid) in the tips of the dermal papillae in LA. ×400.

Results

Patient Characteristics

A total of 37 patients with histopathologically confirmed PLCA and sufficient clinical information on follow-up and treatment were included in this study. Twenty-one patients (56.8%) were female and 16 (43.2%) male. The mean age was 52 years (range: 29–90 years). Twenty-one patients (56.8%) presented with LA, 6 (16.2%) with BA and 10 (27%) with MA. Zero cases of NA were diagnosed. Eleven patients (29.7%) were classified as skin phototype II, 11 patients (29.7%) phototype III, 11 patients (29.7%) phototype IV, and 4 patients (10.8%) as phototype V. Skin phototype I and VI were not represented in the study.

Fig. 5. Flowchart of the methods: inclusion criteria.

Table 1. Patient characteristics ($n = 37$)

Characteristics	n (%)
Gender	
Female	21 (56.8)
Male	16 (43.2)
Age, mean (range), years	52 (29-90)
Skin phototypes	
I	0
II	11 (29.7)
III	11 (29.7)
IV	11 (29.7)
V	4 (10.8)
VI	0
Clinical subtype	
LA	21 (56.8)
MA	10 (27)
BA	6 (16.2)
Localization	
Lower legs	15 (40.5)
Back/interscapular	15 (40.5)
Lower legs and arms	2 (5.4)
Mandibular	2 (5.4)
Lower arms	1 (2.7)
Abdomen	1 (2.7)
Generalized	1 (2.7)
Comorbidities	
Atopy	8 (21.6)
Thyroid disease	3 (8.1)

The regions of origin (“ethnicity”) of all included patients were as follows: Central Europe: 15 patients (40.5%); Mediterranean countries: 8 patients (21.6%); China/Southeast Asia/India/Sri Lanka/Mongolia: 10 patients (27%); Middle East: 4 patients (10.8%). Patients from cen-

Table 2. Treatment modalities ($n = 37$)

Treatment	n (%)
Topical treatments	
Low- to medium-potency topical corticosteroids	16 (43.2)
High-potency topical corticosteroids	7 (18.9)
Capsaicin (0.075%) cream	1 (2.7)
Phototherapy	
UVBnb (311 nm)	1 (2.7)
UVA1	2 (5.4)
Bath PUVA	1 (2.7)
Combination treatments	
Low- to medium-potency topical corticosteroids and UVBnb	4 (10.8)
High-potency topical corticosteroids and UVA1	3 (7.3)
No treatment	2 (5.4)

Treatment modalities were divided into topical treatments, phototherapy, and combination treatments. The largest number of patients were treated with low- to medium-potency topical corticosteroids. UVBnb, UVB narrow band phototherapy, wavelength: 311 nm; UVA1, UVA1 phototherapy, wavelength: 380 nm; bath PUVA, whole body bath PUVA, wavelength: 320–400 nm.

tral Europe and Mediterranean countries were considered as Caucasian (23 patients, 61%).

The most common localization of PLCA was on the lower legs (15, 40.5%) and back (15, 40.5%). Several comorbidities were noted: 8 patients (21.6%) had a personal history of atopic eczema and 3 patients (8.1%) had thyroid disease (two cases with hypothyroidism and one with hyperthyroidism of probable autoimmune origin). None of the patients had a positive family history for PLCA. Patient characteristics are summarized in Table 1.

Table 3. Treatment efficacy (as measured by a treatment efficacy score – TES)

TES (0–6)	Patients, <i>n</i> (%)	Treatment modalities (number of patients)
0	2 (5.4)	No treatment (2)
1	2 (5.4)	TCS II–III (2)
2	11 (29.7)	TCS II–III (6), TCS IV (2), UVA1 (1), UVBnb (1), UVBnb/TCSII (1)
3	5 (12.7)	TCS II–III (2), TCS IV (2), UVBnb/TCSII (1)
4	8 (21.6)	TCS II–III (5), TCS IV (2), UVBnb/TCSII (1)
5	5 (12.7)	TCS IV (1), UVA1/TCSIV (1), PUVA (1), UVA1 (1), caps (1)
6	4 (10.8)	TCS IV (1), UVA1/TCSIV (3)

A score from 0 to 3 was applied to separately measure the reduction of skin changes including scaling, induration, hyperkeratosis, redness AND of itch with 0 = no effect, 1 = mild improvement, 2 = good improvement, 3 = very good improvement or complete resolution. The final score was calculated as the sum of both scores; a maximum score of 6 signifies very good improvement or complete resolution of itch and skin changes. A minimal score 0 stands for no treatment effect at all. TCS II–II, mild to moderate topical corticosteroids; TCS IV, high-potency topical corticosteroids; UVA1/TCS IV, UVA1 and high-potency topical corticosteroids; UVBnb/TCS II, UVBnb and low- to medium-potency topical corticosteroids; PUVA, full body bath PUVA (320–400 nm); UVA1, UVA1 phototherapy (380 nm); caps, capsaicin 0.075% cream; UVBnb, UVBnb phototherapy (311 nm).

Treatment, Treatment Regimens and Treatment Efficacy

Effect of treatment response was assessed in all patients after 3 months of treatment. Detailed information on treatment modalities and corresponding number of patients is given in Table 2. Most frequently, patients were treated with low- to medium-potency topical corticosteroids ($n = 16$, 43%), followed by high-potency topical corticosteroids alone ($n = 7$, 18.9%) and in combination with UVA1 phototherapy ($n = 4$, 10.8%) or with a combination with low- to medium-potency topical corticosteroids and UVBnb phototherapy ($n = 3$, 8.1%). Few patients were treated with phototherapy alone (UVA1: $n = 2$, 5.4%; UVBnb: $n = 1$, 2.7%), one patient received full body bath PUVA, and one patient was treated with topical capsaicin cream (0.075%).

Treatment regimen of topical corticosteroids consisted in all cases of a once daily application for a maximum of 3 weeks and a subsequent tapering down of the application frequency over several weeks. Four patients received topical corticosteroids of moderate potency under occlusion using plastic film or occlusive dressings.

Medium-dose UVA1 (wavelength: 380 nm), whole body bath PUVA (wavelength: 320–400 nm), and UVB narrowband (UVBnb) (wavelength: 311 nm) were performed. UVA1 was initiated after phototesting on a small area and conducted at 50 J/cm². We performed 2–3 sessions per week for a maximum of 30 sessions, resulting in a maximal cumulative dose of 1,500 J/cm².

UVBnb phototherapy (311 nm) was started at 0.1 J/cm² per session and increased by 20% from session to session. The maximum dose for UVBnb was 2.0 J/cm² and 2 to 3 sessions were held per week for a maximum of 12 weeks.

Bath PUVA was performed three times weekly for a duration of 12 weeks. The patient treated with capsaicin cream used a final concentration of capsaicin 0.075% cream three times daily on affected areas for a period of 12 weeks. All patients underwent a clinical re-evaluation after 12 weeks.

The maximum TES of 6 was achieved in four cases receiving high-potency topical corticosteroids in combination with UVA1 phototherapy ($n = 3$) or high-potency topical corticosteroids alone ($n = 1$). A submaximal score of 5 was achieved in 5 patients receiving high-potency topical corticosteroids ($n = 1$), UVA1 phototherapy ($n = 1$), combination of high-potency topical corticosteroids and UVA1 phototherapy ($n = 1$), PUVA therapy ($n = 1$) and capsaicin (0.075%) cream ($n = 1$). TES of 2–4 representing intermediate treatment responses was achieved by low- to medium-potency topical corticosteroids ($n = 13$), by high-potency topical corticosteroids ($n = 3$), by a combination of topical corticosteroids and UVBnb phototherapy ($n = 2$) and by UVA1 phototherapy ($n = 1$) and UVBnb phototherapy ($n = 1$), respectively. No treatment response (score: 0) and very mild treatment response (score: 1) was seen in 4 patients either not receiving any treatment at all ($n = 2$) or low- to medium-potency topical corticosteroids ($n = 2$). Table 3 summarizes the effi-

Fig. 6. a, b Interscapular, biphasic amyloidosis in a female patient (54 years, phototype IV) undergoing treatment with bath PUVA. Panel **a** shows the skin changes before and panel **b** shows the reduction of hyperpigmentation and erythema after 3 months of treatment. Bath PUVA had only minimal anti-pruritic effect in this patient.

cacy of the different treatment modalities. Figure 6 shows a patient with BA before and after treatment with bath PUVA for 3 months.

Discussion

The aim of this retrospective study was to analyze demographic characteristics and treatment outcomes of patients with PLCA in a tertiary care center in Switzerland. This is of relevance, since it is the first study on PLCA in a predominantly Caucasian population and analyzes the treatment efficacy in a larger group of patients. Knowledge on treatment modalities and efficacy in PLCA is very limited as there are only small studies and case reports on therapeutic strategies available.

In the dermatological outpatient department of the University Hospital Zurich, Switzerland, more than 22,000 patients are treated every year. Over a period of 20 years (2000–2020), we identified a total of 79 patients with PLCA, but only 37 patients met the inclusion criteria for this study. The low number of PLCA cases confirms that PLCA is a rare skin disease.

PLCA most frequently occurs in patients from Southeast Asia, China, and South America [11–13].

Interestingly, almost 60% of all patients in our study had skin phototype II or III and were of central European and Mediterranean origin. Our results underline that Caucasians with fairer skin can develop PLCA even though, worldwide, the disease is more common in darker phototypes and probably more expectable in non-Caucasian patients.

Our study did not show any gender differences and confirmed that PLCA usually affects middle-aged patients [8]. As expected, LA was the most common subtype of PLCA found in our study group [14]. Almost 30% of our patients had either a history of atopic skin disease or of thyroid disease – a relationship of these pruritic diseases that has been well established [12, 15–20].

Chronic scratching is believed to lead to apoptosis of keratinocytes and consecutive amyloid deposition in the dermis [18–20]. Therefore, treatment should aim to reduce pruritus as much as possible, as amyloid formation is potentially the end-stage rather than the cause of the skin disease. We found that the best treatment responses were achieved with a combination of UVA1 phototherapy and a once daily application of high-potency topical corticosteroids.

The use of low- to medium-potency topical corticosteroids and/or UVBnb phototherapy and a series of other treatments seemed to show lower efficacy.

Topical corticosteroids reduce itch by inhibiting the release of pruritogenic pro-inflammatory cytokines [21]. Phototherapy is thought to modulate cutaneous sensory nerve fibers directly or by inducing mediator release from skin cells, reducing pruritus [22]. We suppose that UVA1 phototherapy led to better treatment outcomes in our patients than UVBnb phototherapy as longer wavelength light (UVA1) can penetrate deeper into the skin, which is frequently thickened and shows significant acanthosis and hyperkeratosis, especially in LA [23].

An explanation for the favorable treatment response on skin changes to the combination of topical corticosteroids and phototherapy might be the reduction in keratinocyte hyperproliferation, as has been shown in psoriasis [24–26]. As a consequence, combining the two treatment modalities can result in less thickening and hyperkeratosis of the epidermis, two of the typical clinical features of PLCA.

Our study has several limitations. An important limitation of our study is the retrospective, monocentric design, and the lack of a control cohort. Furthermore, the total number of patients is low and the number of patients with different treatments and treatment outcomes is high, which does not allow for robust statistics to be made. Forty out of 79 patients with suspected PLCA could not be included in this study due to the unavailability of follow-up information or a lack of histological confirmation of the diagnosis. One might suspect that patients with complete remission of symptoms or well-controlled disease were lost to follow-up, and therefore are not represented in this study.

However, our data contribute to the increasing effort in defining appropriate treatment strategies in this group of rarer, benign, and noninfectious skin diseases. High-potency topical corticosteroids in combination with UVA1 phototherapy seem to have a superior efficacy compared to mild- to medium-potency topical corticosteroids and UVBn phototherapy. Further studies on larger patient cohorts and with prospective, randomized study designs will be needed to identify the best treatment options.

Key Message

Primary localized cutaneous amyloidosis is most effectively treated with high-potency topical corticosteroids and UVA1 phototherapy.

Statement of Ethics

This study was conducted ethically in accordance with the guidelines for human studies and in accordance with the World Medical Association Declaration of Helsinki.

The study protocol was approved by the Institute's committee on human research (Kantonale Ethik-Kommission Zürich, BASEC Nr.: 2019-02410).

Written informed consent was obtained from all participants if diagnosed after 2016. An exemption to retrospectively collect anonymized clinical data was made by abovementioned ethics committee if they diagnosis was made before 2016 and patients could not be contacted (BASEC Nr.: 2019-02410).

Conflict of Interest Statement

C.G. has served as advisor and/or received speaking fees and/or participated in clinical trials sponsored by AbbVie, Almirall, Amgen, Celgene, Eli Lilly, Novartis. T.M. has served as advisor

and/or received speaking fees and/or participated in clinical trials sponsored by AbbVie, Almirall, Amgen, BMS, Celgene, Eli Lilly, LEO Pharma, Janssen-Cilag, MSD, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi, UCB. S.S., I.K.: no conflicts of interest to declare.

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Author Contributions

C.G.: Conception and design, acquisition/analysis and interpretation, drafting of the manuscript, final approval, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. I.K.: Conception and design, data interpretation, drafting of the manuscript, final approval, Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. J.T.M.: Conception and design, data interpretation, critical revision for important intellectual content, final approval, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. S.S.: Conception and design, data interpretation, critical revision for important intellectual content, final approval, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

The raw data that support the findings of this study are available on request from the corresponding authors (C.G. or I.K.).

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