Primary localized cutaneous amyloidosis: association with atopic dermatitis

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Abstract

Background
Primary localized cutaneous amyloidosis (PLCA) is a chronic pruritic dermatological disorder of unknown aetiology. Genetic mutations in cases of familial PLCA have been mapped to the oncostatin-M receptor (OSMR) β, a subunit of interleukin (IL)-31 receptor. IL-31 has been implicated in the pathogenesis of atopic dermatitis (AD).

Objectives
To assess if AD is more prevalent in patients with PLCA compared to patients with other conditions attending the same dermatology clinic. Secondarily, to investigate if the prevalence of AD, severity of itch, morphology and locations of PLCA differ between familial and sporadic forms.

Methods
Consecutive patients with the clinical diagnosis of PLCA visiting a dermatology clinic were evaluated by a single investigator. Data on demographics, family history, morphological types and locations of PLCA, and itch score were collected and they were screened for concomitant AD based on history and physical examination. The control population consisted of consecutive patients with diagnoses other than PLCA seen in the same clinic.

Results
A total of 44 patients with and 97 controls were evaluated. The prevalence of AD in patients with PLCA was significantly higher than in controls, at 75% and 39.2% respectively (OR = 4.66, 95% CI = 2.10 to 10.3, p < 0.0005). The prevalence of AD in sporadic cases was significantly higher than familial cases, at 84.4% and 50% respectively (OR = 5.4, 95% CI = 1.23 to 23.7). Mean itch levels, morphological types and locations of PLCA did not differ between familial and sporadic cases.

Conclusions
AD was associated with PLCA and the association was stronger with the sporadic compared to the familial cases.

Received: 12 December 2012; Accepted: 20 February 2013

Conflict of interest
None declared.

Funding sources
None declared.

Introduction

Primary localized cutaneous amyloidosis (PLCA) is a chronic pruritic dermatological disorder most prevalent in Southeast Asia and South America, of which lichen and macular amyloidosis are the most common variants. Lichen amyloidosis classically presents as multiple discrete hyperkeratotic papules, most frequently affecting the shins, and can be intensely pruritic. Lichen amyloidosis is more common in Chinese, whereas macular amyloidosis is more common among Central and South Americans, Middle Easterners and non-Chinese Asians. Most cases are sporadic, but an autosomal dominant condition may be present in up to 10% of cases. Pathogenic heterozygous missense mutations have been identified in the OSMR gene in pedigrees with familial PLCA. This gene encodes the oncostatin M receptor (OSMR), which is one of the interleukin (IL)-6 family cytokine receptors. PLCA results from the deposition of amyloid fibrils derived from galectin-7 and this can occur following epidermal damage and keratinocyte apoptosis. Histologically, cutaneous amyloidosis is characterized by eosinophilic amorphous collections in the papillary dermis, which comprise of amyloid protein, grouped colloid bodies, immunoglobulins, kappa and lambda light chains and complements.

The majority of cases of PLCA are idiopathic; however, there have been reported associations with connective tissue disorders,
such as systemic lupus erythematosus and Sjögren syndrome, as well as a few kindred with pachyonychia congenital and multiple endocrine neoplasia type 2a. Pruritus is a common finding in PLCA but may be absent in 10% to 40% of patients, indicating that it is not secondary to chronic scratching. PLCA is clinically distinct and biopsies are seldom performed by dermatologists in prevalent regions as histological confirmation is often unnecessary.

Lee et al. reported an association between PLCA and AD; however, the prevalence was derived based on coded diagnoses for insurance claims and thus may be an underestimate. In addition, the differences in the prevalence of AD between patients with sporadic and familial PLCA were not investigated. In this study, we aimed to assess if AD is more prevalent in patients with PLCA, using patients with other conditions attending the same general dermatology clinic as a comparison. Secondly, we aimed to investigate if the prevalence of AD, severity of itch, morphological types and locations of PLCA differ between familial and sporadic forms of PLCA.

Methods
Consecutive patients with the diagnosis of PLCA who visited a general dermatology clinic in the National Skin Centre, Singapore, over a 1-year period from 01 Jun 2011 were evaluated by a single investigator. The diagnosis of PLCA was made clinically based on typical morphology and distribution of the lesions (typically shins, outer arms and back). We also ensured that lesions occurred spontaneously and did not arise due to chronic scratching. Demographic data and data on a family history of PLCA, location and types of PLCA were collected and they were routinely screened (by history and examination) for concomitant AD by the same investigator.

The statistical analysis was performed using SPSS version 16 statistical package (SPSS, Inc., Chicago, IL, USA). Results are expressed as mean ± SD. Categorical variables were tested for using chi-squared or Fisher’s exact test, as appropriate. Itch scores were compared using the Mann–Whitney U-test. A P-value of <0.05 was taken to be statistically significant. The study was approved in the institution where it was conducted.

Results
Forty-four patients with PLCA and ninety-seven controls were evaluated. The mean age of the patients with PLCA was 54 years and the majority of them (82%) were Chinese (Table 1). The demographic characteristics of the controls were similar to the patients, except that they were younger. Most of the patients in the control group presented with atopic dermatitis (28.9%), followed by viral warts (8.5%) and acne (5.67%).

The prevalence of AD in patients with PLCA was significantly higher than in controls, at 75% and 39.2% respectively (OR = 4.66, 95% CI = 2.10 to 10.3, P < 0.0005). This higher prevalence of AD was found in both the sporadic and familial cases of PLCA, but it is significantly higher in the former

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Comparison of characteristics between patients with PLCA and controls</th>
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<tr>
<td>Patients (n = 44)</td>
<td>Controls (n = 97)</td>
</tr>
<tr>
<td>Mean age (years) ± Standard deviation (range)</td>
<td>54.1 ± 14.9 (23–89)</td>
</tr>
<tr>
<td>Female</td>
<td>26 (59.1%)</td>
</tr>
<tr>
<td>Race</td>
<td>Chinese</td>
</tr>
<tr>
<td>Malay</td>
<td>1 (2.3%)</td>
</tr>
<tr>
<td>Indian</td>
<td>6 (13.6%)</td>
</tr>
<tr>
<td>Eurasian</td>
<td>1 (2.3%)</td>
</tr>
<tr>
<td>Prevalence of atopic dermatitis</td>
<td>33 (75.0%)</td>
</tr>
</tbody>
</table>

PLCA, Primary localized cutaneous amyloidosis.
(84.4% vs. 50%, OR = 5.4, 95% CI = 1.23 to 23.7, P < 0.045). With regards to the secondary endpoints, the mean itch scores were not significantly different between the familial and sporadic cases (2.9 and 4.4, respectively, P = 0.198). The morphological types and locations of PLCA lesions between the familial and sporadic cases were similar (Table 2).

Among all the patients with PLCA, the most common type of lesion observed was lichen amyloidosis (59.1%) and most of them (68.6%) had PLCA involving more than one location of the body. Amongst patients with PLCA involving one location of the body, the most common location was the shin (11.4%), followed by the back (8.6%) and the arm (5.7%). Majority of the patients (68.2%) experienced itch in their PLCA lesions and the mean itch score was 3.97. The prevalence of AD in patients with itchy PLCA lesions was similar to those without itchy lesions (73.3% vs. 78.6%, P = 0.709). Patients with PLCA involving more than one location also had a greater mean itch score (4.19) compared to patients with PLCA of one location (2.18). Patients with both lichen and macular amyloidosis had the highest mean itch score (4.39) followed by lichen amyloidosis (4.04) and macular amyloidosis (3.00). The above differences in itch scores, however, were not statistically different.

Discussion
The characteristics of our study population were consistent with the known epidemiology of PLCA – occurring most commonly in the fifth decade, being more prevalent in the Chinese and consisting of the lichenoid morphology predominantly. The prevalence of itch in our population is comparable to a previous study from Singapore (62%) published in 1970,7 and it is much lower than studies conducted in Saudi Arabia (82%)8 and India (90%).9 The population with PLCA was comparable to the control group except for their older age, reflecting the older age of onset of the disease. We found that PLCA was strongly associated with AD in our study population and this association was true for both familial and sporadic forms of PLCA. The prevalence of AD in the patients with PLCA (75.0%) was much higher than that in the controls (39.2%), even though the latter consisted of a younger population (in which AD is known to be more common). In addition, the prevalence of AD in all the patients who presented to the National Skin Centre over the same 1-year period (n = 76736) was 16.8%, which is also much lower than that found in the patients with PLCA.

Familial PLCA is an autosomal dominant condition and recently, genetic mutations have been mapped to a locus spanning the centromere of chromosome 5 in Taiwanese,6 Brazilian7 and Caucasian pedigrees. The mutations involve heterozygous amino acid substitutions in the fibronectin III repeat domains in specific extracellular regions of OSMRβ. OSMRβ is a subunit of both the OSMR and interleukin (IL)-31 receptor. The fibronectin III component plays a key role in receptor dimerization15 and missense mutations in this region result in reduced levels of phosphorylated STATs, ERK1/2 and Akt. These lead to increased keratinocyte apoptosis and probably the deposition of amyloid proteins in the dermoepidermal junction and the clinical lesions of PLCA.

The IL-31 receptor comprises the heterodimerization of OSMRβ with IL-31RA. The IL-31 receptor, rather than OSMR, has been suggested to be responsible for PLCA16 as a point mutation in the IL-31 receptor A gene that was linked to familial PLCA in a pedigree.10 On the other hand, IL-31, the ligand for the IL-31 receptor, has been found to be overexpressed in AD and other pruritic skin lesions17 and has been implicated in the pathogenesis of these conditions. We postulate that in PLCA, reduced function of the IL-31 receptor, which predominantly affects the keratinocytes, leads to keratinocyte apoptosis and corresponding increased levels of IL-31 in the skin. The latter can result in increased inflammation and itch by acting on immune and nerve cells, respectively, contributing to the development of AD in predisposed individuals. Another possible mechanism is that the missense mutations result in gain-of-function of the IL-31 receptor. Increased downstream signaling in keratinocytes and immune and nerve cells subsequently leads to keratinocyte apoptosis, increased inflammation and itch respectively. Further studies will be required to elucidate these possible mechanisms.

In the literature, there was deficient data comparing the differences between familial and sporadic forms of PLCA. In our study, we did not find any significant difference in the clinical characteristics between the two types with regards to itch score, morphology of the lesions and the locations of the body affected. The prevalence of AD, however, was found to be significantly higher in the sporadic compared with the familial cases. One postulate to explain this observation is that in congenital defects (such as that of the IL-31 receptor), compensatory mechanisms established are better able to mitigate the resultant effects (such as increased levels of IL-31) compared with sporadic cases in which the onset of disease is more acute.

In conclusion, AD is strongly associated with PLCA and the strength of this association is greater in sporadic compared with familial PLCA.

References