Familial Primary Localized Cutaneous Amyloidosis in Brazil

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Background: Macular and lichen amyloidosis are clinical variants of primary localized cutaneous amyloidosis (PLCA). Most cases are sporadic, but approximately 10% of cases may be familial. To our knowledge, the clinicopathologic abnormalities seen in cases of PLCA may be familial. We report findings from lesions in two Brazilian families with either lichen-type (family 1 had 14 affected subjects) or macular-type (family 2 had 7 affected subjects) PLCA. Typically, in both pedigrees, the onset of symptoms was around puberty, and pruritus usually began on the lower legs. Findings from lesions in biopsy samples from both families showed thioflavin T–positive material in the papillary dermis, which was more prominent in the lichen phenotype in family 1. Spontaneous improvement occurred in 3 subjects (from both families) after age 25 years. All affected individuals in family 1 had a heterozygous missense mutation in the OSMR gene (p.I691T), but no pathogenic mutation in OSMR was found in family 2.

Observations: We assessed 2 Brazilian families with either lichen-type (family 1 had 14 affected subjects) or macular-type (family 2 had 7 affected subjects) PLCA. Typically, in both pedigrees, the onset of symptoms was around puberty, and pruritus usually began on the lower legs. Findings from lesions in biopsy samples from both families showed thioflavin T–positive material in the papillary dermis, which was more prominent in the lichen phenotype in family 1. Spontaneous improvement occurred in 3 subjects (from both families) after age 25 years. All affected individuals in family 1 had a heterozygous missense mutation in the OSMR gene (p.I691T), but no pathogenic mutation in OSMR was found in family 2.

Conclusions: Familial PLCA shows autosomal dominant inheritance, but there is clinical and genetic heterogeneity and variable clinical penetrance. Demonstration of mutations in the OSMR gene provides new insight into mechanisms of itch and apoptosis in human skin.


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MACULAR-TYPE AND LICHEN-TYPE AMYLOIDOSIS

Macular and lichen amyloidosis are clinical variants of primary localized cutaneous amyloidosis (PLCA [OMIM 105250]). They are characterized histologically by focal deposition of immunoglobulins and serum amyloid P component on collections of basal keratinocytes in the superficial dermis that are undergoing filamentous degeneration or apoptosis.1,3 Macular and lichen amyloidosis are not associated with other systemic forms of amyloidosis.1,4 Primary localized cutaneous amyloidosis (PLCA) is rare among Europeans and North Americans but is much more common in South Americans, Middle Easterners, and Asians.3 Although most cases are sporadic, approximately 10% of cases of PLCA may be familial. We report the clinicopathologic abnormalities seen in 2 Brazilian families with either lichen-type (family 1) or macular-type (family 2) variants of PLCA (Table). Family 1 represents, to our knowledge, the largest Brazilian family with PLCA to be reported and the third largest in the world.1,14

RESULTS

The families’ pedigrees are illustrated in Figure 1A and Figure 2A. Family 1 presented with the lichen-type variant. The age at onset of the disease ranged from 5 to 18 years. Symptoms typically started on the lower legs with severe pruritus, followed by local lichenification and appearance of papules (Figure 1B). Later, in some family members the papules spread to other areas, involving the abdomen, chest, back, arms, forearms, thighs, dorsa of the feet, and buttocks. Patient 3 also presented with a brownish macular lesion on the scapular region, suggesting coexistence of both lichen and macular variants. The same patient also had small papules grouped on the auricular concha of both ears, an uncommon feature of familial PLCA13 (Figure 1C). Family 2 presented with the macular amyloid variant. The age at onset was older (15-39 years), but the symptoms also started mainly on the lower legs with pruritus, followed by lichenification and

METHODS

Following ethics approval and informed consent, clinical evaluation, photography of the patients, and skin biopsies were performed. Of the 14 affected individuals in family 1, PLCA has been confirmed clinically in 12 (with additional skin biopsy confirmation in 8) and the other 2 have been reported by relatives to have the disease. Of the 7 affected members in family 2, all have been examined clinically and 5 have histopathologically confirmed PLCA.
### Table. Clinical Data of Families 1 and 2

<table>
<thead>
<tr>
<th>Patient No./Family No.</th>
<th>Sex/Age, y</th>
<th>AO, y</th>
<th>Site of Onset</th>
<th>Status</th>
<th>LS, Age, y</th>
<th>Localization</th>
<th>Type of Lesion</th>
<th>Ex or RR</th>
<th>BC</th>
<th>Associated Disease</th>
<th>Pruritus</th>
<th>EF</th>
<th>GM</th>
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<tbody>
<tr>
<td>1/1/F/59</td>
<td>12/13</td>
<td>Lower legs*</td>
<td>Stable 35</td>
<td>Limbs, chest, upper back, lower back</td>
<td>Mult SCPs, excoriation on upper back</td>
<td>Ex +</td>
<td>Hypertension, DM 2</td>
<td>Rarely</td>
<td>–</td>
<td>OSMR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/1/M/56</td>
<td>5</td>
<td>Lower legs</td>
<td>Stable 25</td>
<td>Abdomen, limbs, chest, back</td>
<td>Mult SCPs, excoriation on upper back</td>
<td>Ex +</td>
<td>Hypertension</td>
<td>Rarely</td>
<td>Dry skin, winter</td>
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<td>3/1/F/45</td>
<td>13</td>
<td>Lower legs*</td>
<td>CGNL –</td>
<td>Limbs, upper back, auricular concha, buttocks, dorsa of feet</td>
<td>Mult SCPs, brownish macule (upper back)</td>
<td>Ex +</td>
<td>Hysterectomy (fibroids) + depression</td>
<td>+</td>
<td>Scratching</td>
<td>OSMR</td>
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<td></td>
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<tr>
<td>4/1/F/43</td>
<td>11</td>
<td>Lower legs*</td>
<td>Stable –</td>
<td>Limbs, upper back, lower back</td>
<td>Mult SCPs, brownish papules</td>
<td>Ex –</td>
<td>Sinusitis, rhinitis</td>
<td>+</td>
<td>Scratching, sun exposure</td>
<td>OSMR</td>
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<td>5/1/F/38</td>
<td>18</td>
<td>Lower legs*</td>
<td>Stable –</td>
<td>Limbs, upper back</td>
<td>Mult SCPs, brownish papules</td>
<td>Ex –</td>
<td>AB (food allergies)</td>
<td>+</td>
<td>Scratching</td>
<td>OSMR</td>
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<td>6/1/M/32</td>
<td>13</td>
<td>Lower legs*</td>
<td>CGNL –</td>
<td>Arm, forearm, dorsa of feet</td>
<td>Mult SCPs, lichen on dorsa of feet</td>
<td>Ex –</td>
<td>Bronchitis (in childhood)</td>
<td>+</td>
<td>Scratching</td>
<td>OSMR</td>
<td></td>
<td></td>
<td></td>
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<td>7/1/F/39</td>
<td>12</td>
<td>Lower legs*</td>
<td>CGNL –</td>
<td>Limbs, lower abdomen, upper back, dorsa of hands</td>
<td>Mult SCPs, mult excoriations</td>
<td>Ex +</td>
<td>AB (insect bite reactions)</td>
<td>+</td>
<td>Scratching, dry skin</td>
<td>OSMR</td>
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<tr>
<td>8/1/F/20</td>
<td>8</td>
<td>Lower legs*</td>
<td>CGNL –</td>
<td>Dorsa of feet, knees, hands, heels</td>
<td>Sparse SCPs on heels, lichen on other parts</td>
<td>Ex –</td>
<td>–</td>
<td>Stress, scratching</td>
<td>OSMR</td>
<td></td>
<td></td>
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<td>9/1/M/36</td>
<td>9</td>
<td>Lower legs*</td>
<td>CGNL –</td>
<td>Limbs</td>
<td>Mult SCPs</td>
<td>Ex +</td>
<td>Depression, irritable bowel syndrome</td>
<td>+</td>
<td>Scratching</td>
<td>OSMR</td>
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<td></td>
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<td>11</td>
<td>Lower legs*</td>
<td>CGNL –</td>
<td>Shins, dorsa of feet, hands</td>
<td>Mult SCPs on shins, lichen on other parts</td>
<td>Ex +</td>
<td>AB</td>
<td>+</td>
<td>–</td>
<td>OSMR</td>
<td></td>
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<td>11/1/M/9</td>
<td>8</td>
<td>Feet*</td>
<td>CGNL –</td>
<td>Dorsa of feet</td>
<td>Sparse SCPs</td>
<td>Ex +</td>
<td>AB</td>
<td>+</td>
<td>–</td>
<td>OSMR</td>
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<td>12/1/M/31*</td>
<td>RR</td>
<td>13</td>
<td>Lower legs*</td>
<td>Stable –</td>
<td>Dorsa of feet</td>
<td>Sparse SCPs</td>
<td>Ex –</td>
<td>–</td>
<td>Winter, scratching</td>
<td>OSMR</td>
<td></td>
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<tr>
<td>14/1/M/21</td>
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<td>Lower legs*</td>
<td>Stable –</td>
<td>Limbs, minimal signs of disease</td>
<td>Dry skin, lichen on dorsa of feet and knees</td>
<td>Ex –</td>
<td>Gastritis, osteoporosis</td>
<td>Rarely (just with sun exposure)</td>
<td>Sun exposure</td>
<td>ND</td>
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<tr>
<td>15/2/F/82</td>
<td>18</td>
<td>Limbs*</td>
<td>Stable 38</td>
<td>Limbs, minimal signs of disease</td>
<td>Dry skin, lichen on dorsa of feet and knees</td>
<td>Ex –</td>
<td>–</td>
<td>Gastritis, osteoporosis</td>
<td>Rarely (just with sun exposure)</td>
<td>Sun exposure</td>
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<tr>
<td>16/2/F/43</td>
<td>18</td>
<td>Lower legs*</td>
<td>CGNL –</td>
<td>Right arm, lower legs, upper back</td>
<td>PD brownish HP areas, brownish papules on upper back</td>
<td>Ex +</td>
<td>AB (irritant dermatitis)</td>
<td>+</td>
<td>Scratching, sun exposure</td>
<td>ND</td>
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<td></td>
<td></td>
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<tr>
<td>17/2/F/42</td>
<td>39</td>
<td>Lower legs*</td>
<td>CGNL –</td>
<td>Shins, knees</td>
<td>PD brownish HP areas, lichen on dorsa of feet</td>
<td>Ex +</td>
<td>AB (cleansing products), depression</td>
<td>+</td>
<td>Sun exposure, winter, stress</td>
<td>ND</td>
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<tr>
<td>18/2/M/39</td>
<td>16</td>
<td>Lower legs*</td>
<td>Stable –</td>
<td>Lower legs, upper back</td>
<td>PD brownish (upper back) and grayish (lower legs) HP areas</td>
<td>Ex +</td>
<td>–</td>
<td>Sun exposure</td>
<td>ND</td>
<td></td>
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<tr>
<td>19/2/F/31</td>
<td>15</td>
<td>Lower legs*</td>
<td>CGNL –</td>
<td>Limbs, upper back</td>
<td>Brownish macule (upper back), PD brownish HP areas (limbs)</td>
<td>Ex +</td>
<td>–</td>
<td>+</td>
<td>Scratching</td>
<td>ND</td>
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<tr>
<td>20/2/M/29</td>
<td>20</td>
<td>Lower legs*</td>
<td>Stable –</td>
<td>Chest, lower legs</td>
<td>PD grayish HP</td>
<td>Ex –</td>
<td>Right-sided deafness</td>
<td>–</td>
<td>–</td>
<td>ND</td>
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<td></td>
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<tr>
<td>21/2/M/27</td>
<td>22</td>
<td>Neck*</td>
<td>CGNL –</td>
<td>Limbs, chest, lower back, upper back, neck</td>
<td>Grayish macules with rippled appearance</td>
<td>+ +</td>
<td>–</td>
<td>Sun exposure, dust</td>
<td>ND</td>
<td></td>
<td></td>
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</table>

Abbreviations: AB, atopic background; AO, age at onset; BC, biopsy confirmed; CGNL, continuing to get new lesions; DM 2, type 2 diabetes mellitus; Ex, examined; EF, exacerbating factor; GM, genetic mutation; lichen, lichenification; HP, hyperpigmented; LS, lessening of symptoms; Mult, multiple; ND, not demonstrated in the OSMR gene; PD, poorly defined; RR, reliably reported; SCP, skin-colored papules; +, yes; −, no.

*Pruritus

*These patients lived in another state but had a clinical diagnosis of lichen amyloidosis made by a dermatologist. They sent us their blood samples via Federal Express.
darkening of local skin. The lesions were characterized by poorly delineated grayish or brownish pigmented macules, distributed mainly on the limbs and upper back. Patient 16 in family 2 also presented with brownish papules on the upper back, suggesting the coexistence of both macular and lichen variants. The symptoms and lesions in family 2 were less dramatic than in family 1, apart from patient 21, whose skin lesions also involved the arms, forearms, lower legs, neck, and upper and lower back (Figure 2B). For both families, the main symptom was pruritus, and there were concerns as well about the cosmetic appearances of the PLCA. Spontaneous improvement, however, especially in the severity of the pruritus, was observed in some subjects (patients 1, 2, and 15) and usually began after the age of 25 years.

To date, none of the family members has had symptoms, signs, or other evidence of systemic amyloidosis or of multiple endocrine neoplasia type 2A. Patients 4, 5, 6, 7, 10, 11, 16, and 17 all had an atopic background, which may have served as an exacerbating factor because scratching was reported as an important worsening factor in several individuals in both families. Most members of family 2 also described sun exposure as a further exacerbating factor. More clinical details are listed in the Table.

All affected individuals in family 1 had a heterozygous missense mutation in the OSMR gene (p.I691T), but no pathogenic mutation in OSMR was found in family 2. We then performed linkage analysis for the OSMR locus in family 2 using the microsatellite marker D5S418, as described previously. This analysis showed different alleles in the affected mother being transmitted to the affected offspring. Specifically, the marker sizes for D5S418 in the mother were 156/165. We found that 4 of 6 affected offspring had inherited the 165 allele, whereas the other 2 had inherited the 156 allele (the marker sizes in their father were 150/150). These data indicate that this locus on chromosome 5 does not harbor the mutant gene in this particular family.

Family 1 presented with the typical clinical features of lichen amyloidosis, characterized by multiple, discrete, closely set, hyperkeratotic, brownish or skin-colored papules, distributed principally on the shins, although the heels, dorsa of the feet, thighs, extensor area of the arms,
forearms, abdomen, chest, back, auricular concha, and buttocks were also affected in some members. Family 2 presented with very discrete, poorly delineated, brownish or grayish pigmented patches; only patient 21 had the characteristic linear rippled appearance of macular-type amyloidosis.

Patients 3 and 16 showed that both papules and macules can coexist in the same individual and that the histopathologic findings of macular and lichen forms of PLCA also overlap. Indeed, it has been shown previously that there are no important differences between lichen- and macular-type amyloidosis regarding the ultrastructure of the amyloid deposits.2 The precise clinical presentation of PLCA, therefore, seems to depend on the quantity of amyloid deposition and/or by secondary epidermal changes. Lichen amyloidosis corresponds to larger amyloid deposits and more pronounced epidermal changes compared with the macular variety.1,4 Various stains are useful for demonstrating amyloid deposits in tissue sections. Amyloid demonstrates periodic acid–Schiff positivity, crystal violet metachromasia, and thioflavin T fluorescence (Figure 1D and Figure 1E). Congo red stains amyloid red and produces an apple-green birefringence under polarized light, directly related to its B-pleated configuration.7,18

Recent genome-wide scans for familial PLCA in Taiwan suggested genetic linkage to 5p13.1-q11.2.19 With respect to the families in our study, Arita et al26 mapped family 1 to the same locus and went on to identify missense mutations in the OSMR gene, which encodes the oncostatin M receptor B (OSMRB) in all affected individuals of family 1. Mutations in this gene were also identified in other pedigrees outside Brazil. To our knowledge, these data represent the first human germline mutations in this cytokine receptor complex and provide new insight into mechanisms of itching and apoptosis. Nevertheless, no pathogenic mutations were identified in family 2, and our additional linkage findings indicate that the chromosome 5 locus is not the correct one for this family. Not all families with PLCA therefore seem to have mutations in the OSMR gene, and genetic heterogeneity is present. Our linkage findings in family 2 also exclude the other interleukin 6 (IL-6) family gene receptors close to OSMR (IL6ST, LIFR, and IL31RA) as alternative candidate genes for PLCA in family 2.

OSMRB is a component of the oncostatin M (OSM) type II receptor and the IL-31 receptor, and cultured familial primary localized cutaneous amyloidosis keratinocytes showed reduced activation of Jak/STAT, MAPK, and PI3K/Akt pathways after OSM or IL-31 cytokine stimulation.16 These pathways have been reported to have antiapoptotic effects in several tumor cell lines.20-23 Also, Ibuki and Goto24 suggested that the PI3-kinase/Akt pathway might be implicated, at least partially, in anti-apoptotic signaling after UV-B irradiation in cells detached from the extracellular matrix.

An interesting clinical observation was that most individuals experienced pruritus—the main symptom—before the skin lesions appeared, and many individuals of both families reported the habit of scratching as a worsening factor.

Weyers et al25 identified scratching as the most important trigger in the development of lichen amyloidosis, considering it a variant of lichen simplex chronicus. However, they could not explain the accumulation of amyloid in lichen amyloidosis, absent in most cases of LSC, and attributed it to an additional unknown factor.25

With regard to family 1, however, the new molecular data start to provide some new insight to account for the clinicopathologic abnormalities found in PLCA. It is plausible that chronic frictional epidermal damage in an individual whose genetic basis underpins a greater susceptibility to keratinocyte apoptosis determines greater cell death and leads to accumulation of degenerate keratinous material in the superficial dermis.

It is also possible that the triggering stimulus originates outside the skin, perhaps in the dorsal root ganglion, where OSMR is expressed.26 Therefore, PLCA may indeed be a “neurodermatitis,” although the mechanism of how OSMR gene mutations might affect the function of nociceptive neurons has not yet been fully elucidated.16,26

In summary, we have described 2 Brazilian families with either lichen-type or macular-type amyloidosis. Both pedigrees show similar histologic abnormalities and share pruritus as the main symptom. Family 1 (patient 3) had features of both lichen and macular PLCA, but all affected individuals had the same pathogenic mutation in OSMR. However, no pathogenic mutation in OSMR was found in family 2, and linkage excluded OSMR as the candidate gene, data that establish PLCA as a genetically heterogeneous disorder.

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Author Contributions: Drs Sakuma, Hans-Filho, and McGrath had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Sakuma, Hans-Filho, and McGrath. Acquisition of data: Sakuma, Hans-Filho, Arita, M. Odashiro, D. N. Odashiro, Hans, Hans-Neto, and McGrath. Analysis and interpretation of data: Sakuma, Hans-Filho, and McGrath. Drafting of the manuscript: Sakuma, Hans-Filho, Arita, M. Odashiro, D. N. Odashiro, Hans, Hans-Neto, and McGrath. Critical revision of the manuscript for important intellectual content: McGrath. Obtained funding: McGrath. Administrative, technical, and material support: Sakuma, Hans-Filho, Arita, M. Odashiro, D. N. Odashiro, Hans, and Hans-Neto. Study supervision: Hans-Filho and McGrath.

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Additional Contributions: Patients of both families volunteered their time to participate in the research that led to this case report.
REFERENCES