Clinical and Histopathological Characteristics of Primary Cutaneous Amyloidosis in 794 Chinese Patients

Wen-Jen Wang
Yun-Ting Chang
Chun-Yu Huang
Ding-Dar Lee

Department of Dermatology, Taipei Veterans General Hospital; and National Yang-Ming University School of Medicine, Taipei, Taiwan, R.O.C.

Key Words
amyloid; amyloidosis; pathology

Background. Primary cutaneous amyloidosis (PCA) is not uncommon in Chinese patients. The disease is usually persistent and quite pruritic. Patients who suffer from this disease usually respond poorly to conventional treatment. We thus reviewed our cases of PCA to discuss the clinical and pathological characteristics.

Methods. Seven hundred and ninety-four Chinese patients with PCA who visited the Department of Dermatology, Taipei Veterans General Hospital during the last 26-year period were examined and retrospectively studied. The diagnosis in these patients was confirmed by histopathological studies.

Results. Among the many types of PCA, lichen amyloidus was the most common clinical variant (67%). Pure cases of macular amyloidosis accounted only 8% and were often associated with lichenoid lesions to form biphasic amyloidosis, which was composed of 25% in our series. Other rare types of PCA, such as nodular, anosacral, and vitiliginous amyloidosis, always require a careful differential diagnosis clinically from other similar skin disorders. In addition, 56 familial cases were found. Histopathologically, the most common epidermal findings of PCA were hyperkeratosis, irregular acanthosis with thinning of rete ridges, and expansion of dermal papillae by amyloid deposition. Special histochemical stains were helpful for confirming the existence of amyloid.

Conclusions. Our study represents the largest number of cases of PCA collected to date. Based on the data, most cases are sporadic, except 56 familial cases which may suggest the possible genetic role. Rare types of PCA, such as anosacral and vitiliginous amyloidosis which need special attention, compose a diagnostic challenge to a dermatologist. Histochemically, H&E stain can give a primary clue for the diagnosis of amyloidosis and crystal violet stain is a very simple and sensitive method to detect the existence of amyloid.

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like cutaneous amyloidosis, bullous amyloidosis, vitiliginous amyloidosis and anosacral amyloidosis have been reported occasionally. Secondary localized cutaneous amyloid deposits can be detected pathologically and histochemically in various epithelial tumors, solar keratoses, and psoriatic lesions after PUVA therapy.\textsuperscript{1-4} There is a high incidence of PCA, such as lichenoid or macular amyloidosis, in South East Asia\textsuperscript{5} as well as in some South American countries.\textsuperscript{6}

It is well known that LA is a relatively common skin disorder in Taiwan,\textsuperscript{7,8} and in the immigrant Chinese residing in Singapore.\textsuperscript{5} In the Department of Dermatology, Taipei Veterans General Hospital, we have collected 794 cases of PCA during the period between 1973 and 1999 to analyze its male-female ratio, onset of the lesions, the duration of illness, the distribution of skin lesions, the clinical types, familial cases, and the histopathological features.

Methods

Seven hundred and ninety-four Chinese patients with PCA were examined and retrospectively studied at Taipei Veterans General Hospital, from Aug. 1973 through Sep. 1999. The diagnosis in these patients was confirmed by histopathological studies. During this period, the total number of new patients who visited our out-patient Department of Dermatology was approximately 41,600. Thus, an average of 30.5 new cases with PCA can be encountered every year, accounting for 1.9% of the total number of new out-patients seen in our clinic each year.

Clinical features

We analyzed the male-female ratio, on set of the lesions, the duration of illness, the distribution of skin lesions, the clinical types, and familial cases.

Histopathological studies

In addition to routine hematoxylin-eosin stain, special stains including Congo red, crystal violet, and Pa Goda red were also performed to confirm the existence of amyloid.

Results

Clinical features

Age and sex

From Aug. 1973 through Sep. 1999, to tally 794 patients with PCA were encountered (532 males and 262 females). The male-female ratio was 2.026. The age of the youngest and oldest patient was 11 and 92 years, respectively (median, 53 years). The peak incidence was between 51-60 years of age, followed by interval 61-70 (Fig. 1).

![Fig. 1. Age when seen of primary cutaneous amyloidosis (n = 794)](image-url)
The duration of PCA varied from 6 months to 40 years (median, 14 years). Most cases had the condition for 2 to 20 years.

Distribution of skin lesions

As shown in Table 1, the extensor aspects of the pretibial region and forearms were the most frequent sites to be affected, although other parts of the body, such as the face, neck, trunk, and anosacral area could also be occasionally involved.

Clinical types

In our study, “lichen amyloidosus” was the most common type of skin lesions (Fig. 2), followed by biphasic amyloidosis, and macular amyloidosis (Fig. 3).

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**Table 1. Clinical features of primary cutaneous amyloidosis in different areas**

<table>
<thead>
<tr>
<th>Features</th>
<th>Tan⁵ (Singapore)</th>
<th>Ollague et al.⁶ (South America)</th>
<th>Present study (Taiwan, ROC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case number</td>
<td>265</td>
<td>604</td>
<td>794</td>
</tr>
<tr>
<td>Sex ratio (M:F)</td>
<td>1:3</td>
<td>1:3</td>
<td>2:1</td>
</tr>
<tr>
<td>Peak incidence (age interval, years)</td>
<td>30-50</td>
<td>35-44</td>
<td>51-60</td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>1-30</td>
<td>ND</td>
<td>1-40</td>
</tr>
<tr>
<td>Distribution (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower legs</td>
<td>53</td>
<td>ND</td>
<td>75.5</td>
</tr>
<tr>
<td>Thighs</td>
<td>15</td>
<td>ND</td>
<td>20.0</td>
</tr>
<tr>
<td>Forearms</td>
<td>32.8</td>
<td>ND</td>
<td>62.3</td>
</tr>
<tr>
<td>Back</td>
<td>14.2</td>
<td>ND</td>
<td>49.2</td>
</tr>
<tr>
<td>Frequency of Clinical type (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA</td>
<td>80</td>
<td>32.15</td>
<td>67</td>
</tr>
<tr>
<td>MA</td>
<td>6</td>
<td>35.71</td>
<td>8</td>
</tr>
<tr>
<td>BA</td>
<td>14</td>
<td>15.71</td>
<td>25</td>
</tr>
<tr>
<td>Family history (%)</td>
<td>ND</td>
<td>33.86</td>
<td>7.06</td>
</tr>
</tbody>
</table>

BA = biphasic amyloidosis; LA = lichen amyloidosus; MA = macular amyloidosis; ND = no available data.

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*Fig. 2. Clinical picture of lichen amyloidosus.*

*Fig. 3. Clinical picture of macular amyloidosis.*
Rare types e.g. nodular amyloidosis (2 cases), anoscral amyloidosis (10 cases), vitiliginous amyloidosis (9 cases), could also be seen.

Familial Cases

In our series, 56 patients had a positive family history. The familial members showed similar skin lesions.

Histopathological Features

In PCA (MA & LA), subepidermal deposition of amyloid was detected only in the dermal papillae and the subpapillary layers by crystal violet stain (Fig. 4). The most common dermal changes of PCA were hyperkeratosis, irregular acanthosis, thinning of rete ridges, and expansion of the dermal papillae by amyloid material. Other less common histopathological findings were pigment incontinence, and increase of epidermal melanin. The similarity of amyloid distribution made it difficult to differentiate LA from MA in pathology, since amyloid deposition was demonstrated only in the upper portion of dermis in both conditions.

Discussion

Many reviews of PCA, including the statistical analysis of sex ratio, the age in incidence, and the clinical types of PCA, have been published. The clinical features of PCA in different areas are summarized in Table 1. Although PCA was common in women with female to male ratio of 3:1 in Singapore and in South America, from our series, the female to male ratio was 1:2. Since our hospital served mainly male veterans patients, the sex difference in incidence was not meaningful.

PCA usually occurred during the fourth or fifth decade of age. In our series, the peak in incidence was between 51-60 years of age, older than the report from Singapore and South America series. No patient was younger than 11 years old. The duration of illness varied from 6 months to 40 years. This finding was consistent with previous studies and confirmed the chronicity of this disorder.

As shown in Table 1, the extensor aspects of pretibial region and forearms were the most frequent sites to be affected, which was also seen with other reports.5-6 The majority of our patients presented with lichenoid type of PCA (LA). Patients in this category usually showed persistent pruritic eruptions on both shins. As shown in Fig. 2, the lesions were discrete, firm, nonelastic, non-tender, scaly, closely set, matchhead to pea-sized, skin-colored or brownish, dome-shaped or hemispheric papules. Ulceration and purpura were not the usual features. Although the pretibial area was the most common in involved site, the thighs, calves, ankles, and dorsa of the feet were also occasionally severely affected. Small keratotic papules became larger and confluent to form verrucoid plaques with a rough crater-like surface. Large isolated nodules resembling prurigo nodularis were seen as the result of severe pruritus, after repeated excoriation. In the severe cases, extensive lesions could be found on the face, chest, abdominal wall and anoscral region. Lichen simplex chronicus, prurigo simplex, prurigo nodularis, keratosis pilaris, papular mucinosis, and colloid milium, etc. were the main skin disorders which required a careful consideration in differential diagnosis.

In macular type of PCA (MA), the up per back and extensor aspect of lower legs were the common involved sites, although lesions might also be seen on the arms and thighs. The lesions dem onstrated poorly-
de lin eated brown ish pig mented patches or lin ear ripp ling of the skin with closely aggregated grayish brown macules. A follicular configuration was fre quently found and the papular lesions of LA often co-existed with the macular lesion, thus the term “biphasic amyloidosis” (LA + MA) was coined. In our se ries, the biphasic amyloidosis con sisted of 25% of the to tal cases.

In our series, only two cases of nodular amyloidosis were found, the rare type of PCA. Although nod u lar amyloidosis might oc cu r ei ther as a pri mary con di tion lo cal ized in the skin or as a man i festa tion of sys temic amyloidosis, our cases only dem on strated a pri mary lo cal ized con di tion af ter ex ten sive in vesti gations.

Ten cases of anosacral amyloidosis, an other rare type of PCA, were seen in our se ries. The skin le sion radi ated from the anus as scaly, dark-brown linear macules or lichenoid papules in which a thin layer of am y loid de posit was eas ily proved in skin bi opsy spec i men by crys tal vi o let and other spe cial am y loid stains. The dif fer ential diag no sis should in clude li chen sim plex chronicus, postinflam matory hy perpig me nta tion, tinea cruris, and pru ri tus ani.

Nine cases of vitiliginous amyloidosis were found in our se ries. It ac counted for about 10% of the cases in a study from Ec ua dor. Al though it pre sented as typ i cal vitiligo le sions, in histopathology, ac cu mu la tion of am y loid sub stance in the pap il lary dermis was quite frequent find ing. Melanocytes were dam aged and de gen er ated, lead ing to a loss of pig ment in the lesion and clin ical a vitiligo-like ap pear ance.

In our se ries, most cases were spo radic but 56 pa tients had a fam ily his tory, sug gest ing that ge netic fac tors might play an im por tant role in its pathogen es. On the other hand, about one-third of the South Amer i can cases had a fam ily his tory of this dis or der. In the re ported cases of fa mil i al PCA, the dis ease was in her ited as a Mendelian auto somal dom inant trait with vari able pen etrance. Some pa tients with mul ti ple en do crine neo plas ia type 2A also had a clin ical pic ture of PCA. It was thus sug gested that the gene of fa mil i al PCA was linked to the pericen tromeric re gion of chro mosome 10, the lo ca tion of the RET proto-oncogene. We have car ried out link age anal y sis in seven fam i lies us ing four dinucleo tide re peat mark ers from the RET region and found no evi dence for linkage between Chi nese fam i lies with PCA and the pericen tromeric re gion of chro mosome 10. The dis tinct ge netic ba sis, plus their ap par ent phenotypic dif fer ence in sex ra tio, age, of on set and sites of cu ta ne ous le sions, sug gested that fam ial PCA was attri but able to ge netic het ero ge neity.

From histopathological and histochemical points of view, it is well known that cu ta ne ous amyloidosis did not re veal much dif fer ences from other types of amyloidosis. In ha ematoxylin-eosin stain showed amor phous eosinophilic masses. If there was only a small amount of am yloid, such as in MA, histochemical stains might make it eas ier to be iden ti fied. Three classes of histochemical stains were em ployed for the dem on stra tion of am yloid in its sue sec tions: (1) metachromatic stains, such as methyl vi o let and crys tal vi o let; (2) fluore nce with thioflavin T; and (3) stains with cot ton dyes, such as Congo red and Pa goda red. Among these stains, Crys tal vi o let was rou tinely used in the de tec tion of am yloid de p os its and was a rel a tively sim ple and sen si tive method. Congo red had been widely ap plied for stain ing, which stained am yloid red and pro duced a green ref renge under a polarizing micro scope. How ever, it stained col lagen, and elas tic tis sue as well as am yloid, with or with out polarization microcopy. Be sides, in some derma toses such as colloid milium and lipoid proteinosis, amor phous mate ri als sim i lar to amyloid can be seen in the up per per der mis histopathologically. Both crys tal vi o let and Congo red may stain colloid milium and lipoid proteinosis pos i tively. An other cot ton dye, Pa goda red, had been re ported to stain am y loid brighter and was long last ing and quite spe cific. Un like crys tal vi o let and Congo red, it did not re act with colloid of colloid milium and hy aline of lipoid proteinosis.

West ermark had pre vi ously re ported that lique factive de gen eration and pig ment in con tinence were spe cific find ings in PCA. In our se ries, how ever, we sel dom found lique factive de gen er a tion of the basal cell layer in PCA, but pig ment in con tinence was a quite fre quent find ing.
Although the true pathogenesis of PCA is yet to be determined, some progress has been made recently. In one study, Epstein-Barr virus (EBV) genome was found in 40.7% cases of PCA. It is suggested that EBV may be associated with some cases of PCA. Another study tried to elucidate the role of apoptosis in PCA. Their results proposed that the keratinocyte destruction in PCA may occur as an initial result of apoptosis, which in turn leads to amyloid formation. However, more in vivo studies are required to further clarify the mechanism of cutaneous amyloid deposits.

References