Characterization of the Clinical Features of Five Families with Hereditary Primary Cutaneous Lichen Amyloidosis and Multiple Endocrine Neoplasia Type 2

Marion F. Robinson
Eric J. Furst
Vincenzo Nunziata
Maria Luisa Brandi
Jorge P. Ferrer

See next page for additional authors

Follow this and additional works at: https://scholarlycommons.henryford.com/hfhmedjournal

Part of the Life Sciences Commons, Medical Specialties Commons, and the Public Health Commons

Recommended Citation
Robinson, Marion F.; Furst, Eric J.; Nunziata, Vincenzo; Brandi, Maria Luisa; Ferrer, Jorge P.; Martins Bugalho, Maria J. G.; di Giovanni, Guiseppe; Smith, Richard J. H.; Donovan, Donald T.; Alford, Bobby R.; Hejtmancik, James F.; Colantuoni, Vittorio; Quadro, Loredana; Limbert, Edward; Halperin, Irene; Vilardell, Enric; and Gagel, Robert F. (1992) "Characterization of the Clinical Features of Five Families with Hereditary Primary Cutaneous Lichen Amyloidosis and Multiple Endocrine Neoplasia Type 2," Henry Ford Hospital Medical Journal : Vol. 40 : No. 3 , 249-252. Available at: https://scholarlycommons.henryford.com/hfhmedjournal/vol40/iss3/23

This Article is brought to you for free and open access by Henry Ford Health System Scholarly Commons. It has been accepted for inclusion in Henry Ford Hospital Medical Journal by an authorized editor of Henry Ford Health System Scholarly Commons.
Characterization of the Clinical Features of Five Families with Hereditary Primary Cutaneous Lichen Amyloidosis and Multiple Endocrine Neoplasia Type 2

Authors
Characterization of the Clinical Features of Five Families with Hereditary Primary Cutaneous Lichen Amyloidosis and Multiple Endocrine Neoplasia Type 2

Marion F. Robinson,* Eric J. Furst,* Vincenzo Nunziata,† Maria Luisa Brandi,‡ Jorge P. Ferrer,§ Maria J. G. Martins Bugalho,‖ Guiseppe di Giovanni,‡ Richard J. H. Smith,* Donald T. Donovan,* Bobby R. Alford,* James F. Hejtmancik,* Vittorio Colantuoni,† Loredana Quadro,† Edward Limbert,‖ Irene Halperin,§ Enric Vilardell,§ and Robert F. Gagel*

The hereditary conditions of primary cutaneous lichen amyloidosis and multiple endocrine neoplasia type 2 (MEN 2) are rare clinical entities. The initial reports of two families in which the two conditions coincided have led to the identification of at least eight additional families with this clinical syndrome. In this report we describe the clinical features in five of these eight families. The salient feature in these five families is the presence of unilateral (46%) or bilateral (64%) pruritic and lichenoid skin lesions located over the upper portion of the back. Family members describe these skin lesions as intermittently intensely pruritic leading to scratching and excoriation of the upper back region. The presence of MEN 2 has been documented in 97% of family members with this skin lesion, the one exception being a child who is at risk for development of MEN 2A in whom the diagnosis has not yet been made. Of family members who have MEN 2A, 27% do not have an identifiable skin lesion, although the skin lesion developed in one patient two years after a curative thyroidectomy for medullary thyroid carcinoma (MTC). Four of the five families have members with pheochromocytoma; one with five affected members has only MTC. The finding of this clinical syndrome in geographically diverse portions of the world and the lack of overlap with MEN 2A without the skin lesion suggest it is a distinct clinical variant of MEN 2A. (Henry Ford Hosp Med J 1992;40:249-52)

The association of multiple endocrine neoplasia type 2A (MEN 2A) and hereditary localized pruritus was first observed in an Italian family (1). In a parallel series of observations, a Texas family was observed to have the same type of pruritus and histological examination demonstrated the presence of cutaneous lichen amyloid (CLA) characteristic of that found in classical cases of primary CLA (2). A more detailed evaluation in the Italian family subsequently confirmed the finding of amyloid (3), although the observation was made that family members may not have amyloid deposition early in the evolution of the skin lesion.

These initial reports were followed by reports of three additional families with this characteristic skin lesion in association with MEN 2A (4-6) from Spain, France, and the United States. In each of these families the skin lesion was found in the characteristic location on the upper back. In none of these family members was the skin lesion found in individuals who were not gene carriers or at risk for MEN 2A.

Of particular interest is the report of a French family (5,7) which noted the dermatome-specific localization of the skin lesion and postulated a neurologic condition affecting these dermatomes as the primary cause of the lesion. They cited the clinical syndrome "notalgia paresthetica," a localized pruritic lesion seen at the tip of the scapula and associated with characteristic EMG abnormalities in the affected dermatomes (8), as a model for how a neurologic abnormality might cause the formation of the skin lesion and amyloid. Unfortunately, they were unable to find any evidence of neurologic deficit in their family members.

This report describes the clinical features of five families with this clinical syndrome, two of whom are previously unreported.

Materials and Methods

Three of the five families have been the subjects of previous reports (2,4,9). There were a total of 44 affected patients of whom 31 exhibited both MEN 2A and either the cutaneous lesion or intermittent pruritus. One patient, a young child, mani-
Table 1
Incidence of MEN 2A in Five Families

<table>
<thead>
<tr>
<th>Family</th>
<th>Females</th>
<th>Males</th>
<th>F + M</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>17</td>
<td>44</td>
</tr>
</tbody>
</table>

No significant sex difference was observed for the occurrence of MEN 2A ($\chi^2 = 2.22$, $P > 0.15$).

Table 2
Incidence of CLA in Five Families

<table>
<thead>
<tr>
<th>Family</th>
<th>Females</th>
<th>Males</th>
<th>F + M</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>13</td>
<td>32</td>
</tr>
</tbody>
</table>

No significant difference was observed for the occurrence of CLA ($\chi^2 = 0.78$, $P > 0.30$).

No significant sex difference was observed for the occurrence of MEN 2A ($\chi^2 = 2.22$, $P > 0.15$).

Results

Tables 1 and 2 show the respective incidences of MEN 2A and CLA in the five families. In both cases, chi-square analysis did not show significant differences in disease occurrence between males and females. As demonstrated (Fig 1), most patients (31 of 44) manifested both MEN 2A and CLA; some had only MEN 2A (12 of 44); one, a child, had CLA alone. The location of the skin lesions (Fig 2) was either predominantly unilateral from the right side to the midline (10 of 26) or bilateral extending across the midline (14 of 26). Of note, in the one family documented to be affected with only MTC, the cutaneous lesions were multifocal.

The age of onset of CLA (Fig 3) occurred mainly before the age of 20 years with the median age of onset being 13 years (range 3 to 26 years; $n = 26$). The median age for diagnosis of MEN 2A in those patients with both diseases was 29 years (range 8 to 80 years; $n = 26$).

With the exception of one family member, 30 of 31 patients with both MEN 2A and CLA presented with symptoms of CLA prior to the diagnosis of MEN 2A. This one patient developed the skin lesion after curative treatment for MTC. She was found to have an abnormal pentagastrin test (basal CT 28 pg/mL; postpentagastrin 2,486 pg/mL) on her initial screening at age 26 but had no detectable skin lesion. The diagnosis of MEN 2A was confirmed by the finding of MTC in both lobes of her thyroid. Postoperative and two-year pentagastrin test results showed a basal CT value of 7 pg/mL with no increase after pentagastrin. On her two-year follow-up visit, a left-sided pruritic skin lesion, consistent with early CLA, was noted for the first time. Tests for pheochromocytoma, including magnetic resonance imaging of the adrenal glands, were negative.

As shown in the plot of age versus area of skin lesion (Fig 4), there was a weak coefficient of determination ($R^2 = 0.24$) indicating a tendency for larger lesions to be associated with increasing age. Of a total of 26 lesions analyzed (10 in males; 16 in females), the three largest lesions of 200, 180, and 130 cm² were on histologic findings of medullary thyroid carcinoma (MTC) or abnormal levels of calcitonin (CT) for either basal serum levels and/or upon stimulation of the patient with pentagastrin (0.5 µg/kg) as previously described (10). Nonparametric statistical analysis was performed using Statworks on an Apple Macintosh computer.
Fig 3—Histograms showing the relative ages at onset for either MEN 2A or CLA in 26 affected patients.

Fig 4—A plot of the age of the patients versus the size of their skin lesion (n = 26). Linear regression analysis yielded a coefficient of determination $R^2 = 0.24$. 

Discussion

The results from this study demonstrate that in five families there is a variant of the classic MEN 2A syndrome in that 31 (71%) of 44 affected members presented with both MEN 2A and pruritic lichenoid skin lesion localized over the upper back from dermatomes C4 to T6. The cutaneous skin lesion, which shows autosomal dominant inheritance, appears to evolve over a period of years from an area of pruritis, usually first noticed in childhood, to form a dark protruding interscapular lesion in adulthood that endures throughout the patient’s lifetime. Biopsy specimens taken from more advanced stages of the skin lesions have been found to be positive for amyloid with Congo Red staining (2-4) leading to the classification of this syndrome as primary CLA (2). With the exception of the CLA-like skin lesions, these patients appear to follow a clinical course similar to classical MEN 2A patients, or, in the case of one of the pedigrees (4), to classical hereditary MTC. To our knowledge, there are no common ancestors between the five families.

Classical primary CLA, exhibiting autosomal dominant inheritance of variable penetrance for the rare familial form of the disorder, has been thoroughly reviewed in a recent symposium on the subject (11). The salient clinical, epidemiological, and biochemical features of this syndrome may be briefly summarized. Patients present with persistent pruritic lesions which are discrete, firm, hyperkeratotic papules which can be brown in color. These early macular lesions, which tend later to become lichenoid, are most often observed in the lower extremities and less frequently on the upper back (11). The CLA tends to occur in middle-age, with a peak incidence between 30 and 50 years, and usually follows a chronic course although it can be of short duration. Classical primary CLA is regarded as a rare clinical entity in Europe but is fairly common in Southeast Asia and some South American countries and is observed more often in females (12). It is not clear, however, whether this unequal gender distribution is also observed for the hereditary form of the syndrome. In the South American cases, about one-third have a family history of the disorder (13). The amyloid deposits occur in the dermal papillae, and biochemical analysis of the amyloid has shown that molecular species of keratin probably result from degenerated epidermal cells (14). The etiology of this syndrome remains unknown although chronic irritation has been suggested as a cause for CLA termed “friction amyloidosis” (15).

In contrast, the affected patients we observed in the five pedigrees had a much earlier onset of CLA, usually in childhood, and with an apparently equal gender distribution. Also, the lesions are confined to the interscapular region of the back. As in
classical primary CLA, however, for both nonfamilial and familial forms, the amyloid, when detected, is found in the papillary layer of the dermis and stains positive for keratin (2–4).

The form of CLA which we have described may be related to notalgia paresthetica (5,7) which is an inherited sensory neuropathy of the posterior rami of the dorsal nerves from T2 to T6 (8,16). However, further research is needed to better delineate and characterize the skin lesion and the possible relationship to either an underlying neurosensory or neuromuscular disorder. Nonetheless, it is reasonable to postulate that the cause of the familial CLA we have described probably arises from the intense localized intermittent pruritus leading to repeated scratching. The effect of such constant irritation, in turn, could thus be construed as “friction amyloidosis” manifesting at first as macular amyloidosis and progressing over time to the lichenoid form. Proof of this hypothesis awaits the demonstration of an inherited neurologic abnormality.

In most patients, with the exception of one, the diagnosis of CLA has preceded the diagnosis of MEN 2A. In one patient we observed the development of a skin lesion consistent with CLA after curative treatment for MTC and she has no evidence of pheochromocytoma. Therefore, it seems unlikely that a tumor product derived from MTC caused the development of the skin lesion in this patient. In several other patients there has been continued pruritus and no regression of the skin lesion despite curative thyroidectomy for MTC.

In conclusion, we have characterized a distinct variant of the MEN 2A syndrome and have summarized our findings in five of eight families who appear to manifest both MEN 2A and CLA. It appears that greater than 5% of reported family pedigrees affected with MEN 2A exhibit this variant form of the syndrome. Perhaps the most interesting feature of this syndrome is the possibility that isolation and cloning of the gene for MEN 2 on chromosome 10, likely to be a unique cancer gene, may lead to insight with regard to the causative mechanism for certain forms of cutaneous lichen amyloidosis, a much more common disorder.

Acknowledgments

This work was supported in part by Merit Review and Career Development awards from the Department of Veteran Affairs; grants M01-RR00350 and R01-DK38146 from the National Institutes of Health; and a grant from the Bin Mahfouz family. V. Nunziata and L. Quadro are the recipients of a grant from the Associazione Italiana Ricerca sul Cancro. Other support for hospital care was provided by the Baylor College of Medicine from the Department of Otolaryngology and the Methodist Hospital Clinic Fund.

We thank the Bin Mahfouz family and the staff of the General Clinical Research Center of the Methodist Hospital for their support.

References