Cutaneous lesions associated to multiple endocrine neoplasia syndrome type 1

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Abstract
Background Multiple endocrine neoplasia type 1 (MEN1) is a genetic disease that predisposes to endocrine tumour development. Some cutaneous lesions (angiofibromas, collagenomas, melanosis guttata, lipomas, melanomas, ‘cafe au lait macules’) have been associated to this syndrome. We compare the prevalence of cutaneous lesion in affected patients with their non-carrier relatives.

Patients and method We studied 9 patients with MEN1 and 20 non-carrier, first-degree relatives. Genetic screening was realized in all of them. Patients were examined by dermatologist, and biopsy was performed when necessary.

Results Patients with MEN1 presented hyperparathyroidism (100%), neuroendocrine tumours of pancreas (66%) and pituitary adenomas (44%); their relatives were free of endocrine features of MEN1. The studied cutaneous lesions were more prevalent in affected patients than in non-carriers (55.5% vs. 25%; $P = 0.029$). Odds ratio of developing cutaneous lesions in MEN1 patients was 6.6 (95% confidence interval, 1.09–40.43). The frequency of angiofibromas was lower (22.2%) than the reported in other studies (43–88%), and we did not find any collagenoma.

Conclusions MEN1 is associated to some cutaneous lesions and could be useful for detecting MEN1 carriers in an affected family. Cutaneous lesions should be assessed in MEN1 patients.

Keywords Angiofibroma, collagenoma, lipoma, multiple endocrine neoplasia type 1
Introduction

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal-dominant disease that predisposes to early, synchronously or metachronously multicentric tumour development in many endocrine (mainly parathyroid, pituitary and pancreatic glands) and non-endocrine organs.1

The MEN1 gene (11q13) was identified and cloned in 1997,7-9 and germline10 and somatic mutations have been found in familial and sporadic MEN1 cases; somatic mutations are frequently found in sporadic endocrine tumours too.11 This gene encodes a 610-amino acid protein, called menin, that acts as a tumour suppressor protein that interacts with a transcription factor (JunD), thus decreasing its function.12 The inactivation of menin promotes cell replication, tissular hyperplasia and tumorigenesis. Diagnosis of MEN1 includes biochemical and radiological procedures (Table 1); genetic testing should be performed for carrier identification when two or more clinical features are present.2,13,14

Table 1. Clinical features and diagnosis of MEN1:2-6

<table>
<thead>
<tr>
<th>Mean clinical features</th>
<th>Biochemical assessment</th>
<th>Radiological assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperparathyroidism (90%).</td>
<td>Calcium, PTH</td>
<td>Te99m sestamibi scan</td>
</tr>
<tr>
<td>Entero-pancreatic tumours (70%):</td>
<td>Gastrin, Meal test</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>Gastrinoma (40%)</td>
<td>Chromogranin A</td>
<td></td>
</tr>
<tr>
<td>Non-functioning</td>
<td>Glucose, Insulin, Proinsulin</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>PP. Meal test</td>
<td>Octreoscan</td>
</tr>
<tr>
<td>PP-secretor tumour</td>
<td>Glucagon</td>
<td></td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>Somatostatinoma</td>
<td></td>
</tr>
<tr>
<td>Somatostatinoma</td>
<td>VIP</td>
<td></td>
</tr>
<tr>
<td>Pituitary tumours (40%):</td>
<td>Prolactin</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>Prolactinoma (20%)</td>
<td>GH</td>
<td></td>
</tr>
<tr>
<td>Non-functioning</td>
<td>GH, IGF-1</td>
<td></td>
</tr>
<tr>
<td>GH</td>
<td>Others: ACTH, TSH</td>
<td></td>
</tr>
<tr>
<td>Others:</td>
<td>Carcinoid tumours</td>
<td></td>
</tr>
<tr>
<td>Others:</td>
<td>Pheochromocitoma</td>
<td></td>
</tr>
</tbody>
</table>

PTH, parathyroid hormone; GH, growth hormone; IGF-1, insulin-like growth factor-1; ACTH, adrenocorticotropic hormone; TSH, thyroid-stimulating hormone.

Some endocrine tumour syndromes have characteristic cutaneous manifestations (neurofibromas in MEN 2B, ‘cafe au lait macules’ in McCune–Albright syndrome). Ten years ago, Darling et al. described the association of some cutaneous lesions as collagenomas, angiofibromas, lipomas and ‘cafe au lait macules’ with MEN1.15 The association with angiofibromas was confirmed by Sakurai et al.16 Recently, collagenomas and angiofibromas have been signaled as potential useful markers of MEN1.17

The aim of this study is to compare the cutaneous manifestations of patients affected by MEN1 with their relatives that do not carry the mutation.
Patients and methods

We studied 29 patients (9 with MEN1 and 20 non-carrier, first-degree relatives). All patients underwent a detailed evaluation to determine the possible presence and extent of MEN1 involvement. Briefly, this included a review of the personal and family history for MEN1-related symptoms, laboratory studies to assess the possible presence of hormonal overactivity (parathyroid, pituitary, pancreas) and imaging studies for possible tumours/adenomas (Table 1). Serum hormonal determinations were made by our clinical laboratories. Insulin, growth hormone, prolactin and insulin-like growth factor-I were measured by a chemiluminescent immunometric assay. Parathyroid hormone, gastrin, glucagon and cortisol were measured by radioimmunoassay.

For genetic analysis, DNA was extracted from peripheral blood leucocytes by standard procedures. All the coding exons as well as the intron-exon boundaries of the MEN1 gene were polymerase chain reaction (PCR) amplified with pairs of primers and conditions already described. The PCR products were purified and both strands were subjected to cycle sequencing using the BigDye terminator kit and run in the 3730 xl DNA Analyser (Applied Biosystems, Foster City, CA, USA).

All subjects were examined by a dermatologist to detect skin lesions associated with MEN1 (angiofibromas, collagenomas, melanosis guttata, lipomas, melanomas, ‘café au lait macules’); cutaneous biopsy was made when necessary to confirm the diagnosis.

Quantitative variables are expressed as mean and standard deviation and compared with Student’s t-test. Qualitative variables are expressed as percentages and compared with chi-squared test. Fisher correction was used when necessary. Odds Ratio (OR) was calculated with 95% confidence interval (95% CI). Statistical significance was accepted as $P < 0.05$.

Results

Patients with MEN1 were 43.4 (9.1) years old, and 55.5% were women. Their relatives were 37.8 (13.9) years old ($P = 0.22$), and 55% were men ($P = 0.59$). Affected patients carried the ins360TG (88.9%) or the P12L (11.1%) mutation; carriers of the former were from the same kindred. None of these mutations were found in their relatives. All the affected patients had been diagnosed of hyperparathyroidism; 66% of them presented neuroendocrine tumours of pancreas (40% gastrinomas, 40% insulinomas, 20% somatostatinoma), and 44% presented pituitary adenomas (50% microprolactinomas, 50% non-functioning adenomas). One patient was diagnosed of atypical thymic carcinoid. None of the non-carriers had any endocrine manifestation of MEN1.

Cutaneous lesions, including melanomas and ‘café au lait macules’, were found in 55.5% of MEN1 patients and 25% of non-carriers ($P = 0.029$). OR was 6.6 (95% CI, 1.09–40.43) for cutaneous manifestation in MEN1 patients. The frequency of each cutaneous lesion is summarized in Table 2. In MEN1, all lipomas were multiple, and we did not find multiple melanomas. One patient presented a melanoma in their right leg, which was surgically treated. The melanoma was diagnosed during her usual clinical following of the MEN1 syndrome. She did not present an increased number of nevi.
Table 2. Frequency of cutaneous lesions. Comparison with other studies

<table>
<thead>
<tr>
<th>Cutaneous lesion</th>
<th>Vidal et al.</th>
<th>Asgharian et al.</th>
<th>Darling et al.</th>
<th>Sakurai et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MEN1</td>
<td>No-MEN</td>
<td>MEN1</td>
<td>No-MEN</td>
</tr>
<tr>
<td>Angiofibroma</td>
<td>22.2%</td>
<td>5%</td>
<td>64%</td>
<td>8%†</td>
</tr>
<tr>
<td>Collagenoma</td>
<td>0%</td>
<td>0%*</td>
<td>62%</td>
<td>5%†</td>
</tr>
<tr>
<td>Lipomas</td>
<td>33.3%</td>
<td>10%*</td>
<td>17%</td>
<td>16%*</td>
</tr>
<tr>
<td>Melanomas</td>
<td>11.1%</td>
<td>0%*</td>
<td>4%</td>
<td>0%*</td>
</tr>
<tr>
<td>Hypomelanosis</td>
<td>11.1%</td>
<td>5%*</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Macules</td>
<td>0%</td>
<td>10%*</td>
<td>4%</td>
<td>0%*</td>
</tr>
<tr>
<td>Any cutaneous lesion</td>
<td>55.5%</td>
<td>25%†</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

* Not significant.
† P < 0.05.

Discussion

Classically, MEN1 has been focused in endocrine features, but recent reports have raised the interest about other pathologies related to this syndrome. In 1997 was published the first report that associated some cutaneous lesions to MEN1, mainly facial angiofibromas and collagenomas. These findings were of great interest because multiple facial angiofibromas were previously considered pathognomonic of tuberous sclerosis. In MEN1 syndrome, these cutaneous lesions develop when a somatic mutation of the MEN1 gene adds to the germline mutation, which leads to cellular replication; a similar mechanism has been described in endocrine tumours. Mutations of this gene have been described in sporadic melanomas, sporadic brown fat tumours and angiofibromas as well as in sporadic endocrine tumours.

In the present study, we compare patients with MEN1 and their non-carrier relatives. Patients with MEN1 presented the classical endocrine manifestations, but not their relatives. The frequency of the endocrine characteristics was similar to the expected. We found that the studied cutaneous lesions were more frequent in patients with MEN1, although we did not find significant differences in each kind of lesion probably due to the small size of the sample. This result is consistent with previous studies. Surprisingly, the prevalence of angiofibromas was lower in our patients (22.2%) than the one reported in literature (43–88%), and we did not find collagenomas or ‘café au lait macules’. The small number of studied patients may explain this difference. Nevertheless, MEN1 syndrome is characterized by heterogeneity of the clinical manifestations, and any relationship between genotype and phenotype has not been established. Burgess et al. suggested that a second genetic defect could be involved in phenotype heterogeneity, but this second mutation has not been found. The lower prevalence of angiofibromas may be related to this heterogeneity or could be explained by the shared mutation of our patients (ins360TG).

Sakurai et al. explained the lower frequency of angiofibromas that they found by ethnic differences, related to lower frequency of somatic mutations in Japanese people and higher incidence of non-melanoma skin cancer in white population, but this explanation is not applicable to our Caucasian patients. Finally, environmental factors (e.g. ultraviolet radiation exposure) should be considered.
The combination of multiple angiofibromas and any collagenoma has a high sensitivity (75%) and specificity (95%), similar to hyperparathyroidism and gastrinomas, and may be useful for the diagnosis of this syndrome.\textsuperscript{17} The findings of our study confirm the elevated risk of some cutaneous lesions in MEN1 patients. Although we cannot confirm the conclusions reported by Asgharian \textit{et al.}\textsuperscript{17} due to the small size of the sample, probably the cutaneous lesions may be useful for detecting MEN1 carriers in an affected family and should be systematically assessed.

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\textbf{References}


