



Thymic Carcinoid Tumor as Single Manifestation of Multiple Endocrine Neoplasia Type 1: A Clue to Suspect a Germline *MEN1* Mutation?

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Abstract

Multiple endocrine neoplasia type 1 (MEN1) is a familiar tumor syndrome of endocrine neoplasia involving parathyroid, anterior pituitary and enteropancreatic neuroendocrine tissues. Thymic carcinoid tumors are rare tumors that occur in 2-8.2% of patients with MEN1 and they exhibit a predilection for men over women. Published data of thymic carcinoid tumors in MEN1 are scarce and they seldom constitute the first manifestation in this syndrome. We present a case of a woman with a thymic carcinoid tumor diagnosed at a very young age with no other clinical features of MEN1, and apparently not significant family history (mother with breast cancer developed at the age of 35), which was genetically diagnosed of a splice site mutation in *MEN1* gene. Although no classical MEN1 clinical or familial criteria were met, the age of presentation of thymic carcinoid in our subject gave us the main clue of our clinical suspicion. Since MEN1 syndrome has a variable expression and it may not be exclusively correlated with endocrine tumors, we suggest that *MEN1* mutational analysis should also be considered in all patients with carcinoid thymic tumors, especially if it is presented at young age, independently of the absence of classical clinical or familial *MEN1* criteria.

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Introduction

MEN1 which is also referred as Wermer syndrome is characterized by the combined occurrence of tumors of the parathyroid glands, the pancreatic islet cells, and the anterior pituitary and it is inherited in an autosomal dominant manner with high penetrance [1]. In addition to these tumors, adrenal cortical tumors, carcinoid, facial angiofibromas, collagenomas and lipomatous tumors have been described [2]. Parathyroid tumors, resulting in primary hyperparathyroidism are the most common feature of MEN1 and occur in approximately 95% of patients [3]. Pancreatic neuroendocrine tumors (NETs) occur in 40% and anterior pituitary tumors occur in 30% [4]. The gene responsible for this syndrome is on chromosome 11q13 and encodes a 610 aminoacid protein, menin, which has functions in cell division, genome stability and transcription regulation [5].

Different molecular genetic studies have confirmed the occurrence of *de novo* mutations of the *MEN1* gene in approximately 10% of patients with this syndrome [6]. A study has suggested that near 70% of individuals with MEN1 currently die of causes directly related to MEN1 [7]; in particular, malignant pancreatic islet tumors and thymic carcinoid tumors are associated with a marked increase in risk of death.

A diagnosis of MEN1 may be established in an individual by one of the following three criteria: MEN1 may be clinically diagnosed in an individual on the basis of the occurrence of two or more MEN1 associated endocrine tumors; familial MEN1 is defined as an individual who has the occurrence of one of the MEN1 associated tumors and has a first degree relative with clinical diagnosis of MEN1; also a genetic diagnosis of MEN1 is made on identification of a germline *MEN1* mutation in an individual who may be asymptomatic [8].

Different germline *MEN1* mutations have been described: approximately 23% are nonsense mutations, 41% are frame shift deletions or insertions, 6% are in frame-deletions or insertions, 9%

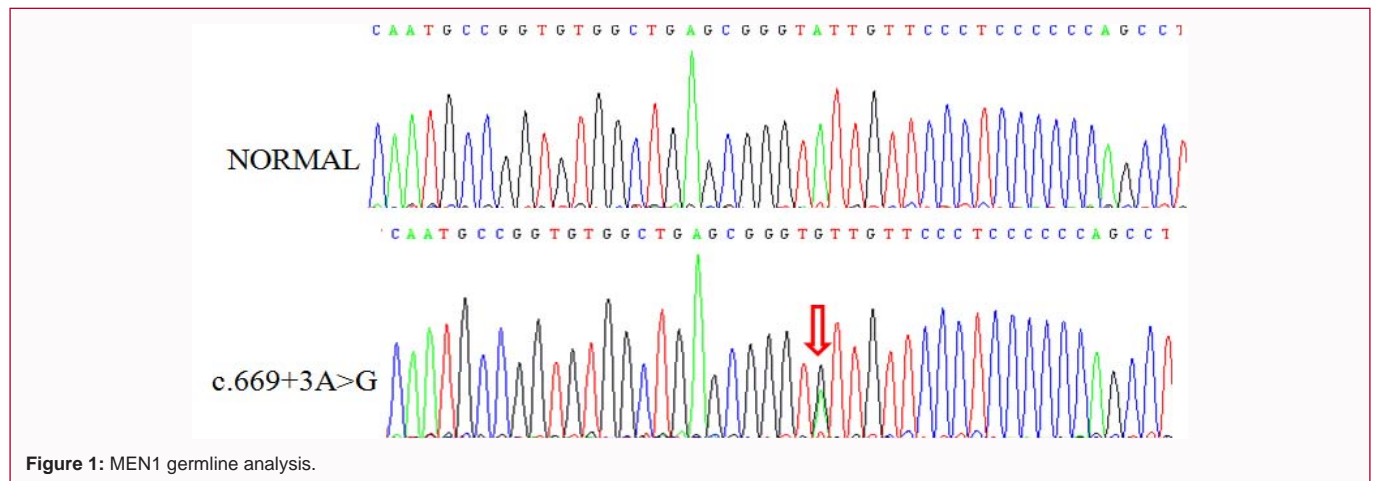


Figure 1: MEN1 germline analysis.

are splice-site mutations and 20% are missense mutations, and 1% are whole or partial gene deletions [9].

The current guidelines recommend that *MEN1* mutational analysis should be performed in: 1) an index case with two or more *MEN1* typical associated endocrine tumors (parathyroid, pancreatic or pituitary tumors), 2) asymptomatic first degree relative of a known *MEN1* mutation carrier, 3) a first degree relative of a *MEN1* mutation carrier expressing familial *MEN1* (having symptoms, signs, biochemical or radiological evidence for one or more *MEN1* associated tumors) [10]. In addition *MEN1* mutational analysis should be performed in patients with suspicious or atypical *MEN1*: parathyroid adenomas before the age of 30 years or multigland parathyroid disease, gastrinoma and multiple pancreatic islet cells tumors any age or individuals who have two or more *MEN1* associated tumors, which are not part of the classical triad of parathyroid, pancreatic islet cell and anterior pituitary tumors [10].

Thymic carcinoids are rare neuroendocrine tumors. The prevalence of thymic carcinoid tumors in patient with *MEN1* ranged from 2% to 8.2% in different series, and they exhibit a predilection for men over women, with a male/female ratio of 20:1 [11]. With scarce data reported in the literature of thymic carcinoids in patients with *MEN1*, all available information of these tumors is relevant. A retrospective study of MD Anderson Cancer Centre in 291 patients who fulfilled clinical, genetic and or familial criteria for diagnosis of *MEN1* showed 9 cases (3.1%) of thymic carcinoids. The male/female ratio was 2:1 and the mean age of diagnosis was 38.6 years. Almost half of the patients already had distant metastases at the time of their diagnosis [12].

Case Presentation

A 38 year old female was reported to our Medical Oncology Genetic Counseling Department with diagnosis of thymic carcinoid tumor. She was diagnosed at the age of 29. On December 2007 extended thymectomy was performed in spite of unresectable macroscopic residual disease and the pathologist reported a thymic classical carcinoid tumor. Chromogranin, synaptophysin and neuron specific enolase had strong positive staining and also weak Follicle - Stimulating Hormone (FSH) staining was detected. Brain magnetic resonance and body computed tomography scan did not detect distant lesions. Blood analysis showed FSH increased values in concordance with self-reported difficulty in conceiving. Octreoscan revealed anterior mediastinal disease and treatment with

somatostatin analogues was initiated. Partial response was observed until September 2013 when mediastinal mass increased in size and left supraclavicular adenopathy and bone metastases were detected. Everolimus treatment was added with good tolerability profile and disease stabilization.

Our patient was the middle sister of three women. No relevant clinical history was reported in her sisters. Her mother, 67 years old, was diagnosed of breast cancer when she was 35 and she was under clinical research of hypercalcemia when the patient was referred to our Genetic Counseling Unit. The mother had only one sister, who died at the age of 54 as a consequence of a brain hemorrhage. Maternal grandmother died at advanced age (unspecified cause) and maternal grandfather died in an accident when he was 40. No other familial information was available.

Although no classical *MEN1* clinical criteria were met, the age of presentation of thymic carcinoid tumor in our subject with the recently hypercalcemia detected in her mother gave us the main clue of our clinical suspicion.

Methodology and Genetic Studies Results

Methodology

After written informed consent peripheral blood analysis were collected from the patient. Mutation screening was performed on genomic DNA, extracted by peripheral blood in EDTA, analyzing the coding region (exon 2–10) and the exon-intron junctions (splicing sites) of the *MEN1* gene by PCR and Sanger sequencing (primers and conditions available upon request). Obtained sequences were compared to wild type reference sequence of the *MEN1* gene, and mutations were classified using the standard nomenclature for the description of human DNA sequence variants. When a *MEN1* mutation was detected, the mutation screening was extended to first degree relatives of the proband, independently of the presence of specific *MEN1*-related signs and symptoms.

Results

MEN1 germline analysis showed a substitution of an adenine for guanine, in splicing donor site of intron 3, c.669+3A>G (Figure 1). This change was previously reported by Hai et al [13] suggesting that this variation affects splicing between exon 3 and 4. RT-PCR with primers derived from exons 2 and 6 showed an aberrant 631 base pair (bp) band in addition to the 736 bp wild-type band. Direct sequencing of the aberrant band revealed that a cryptic splice site in

the middle of exon 3 was used and 105 bp 3' half of exon 3 was spliced out. Once the *MEN1* mutation was identified, study was offered to her first degree relatives, confirming that her 67 years old mother, under clinical study of hypercalcemia at the moment that germline mutation was detected, was also carrier of c.669+3A->G *MEN1* mutation. The patient's oldest sister was also asymptomatic carrier of the germline *MEN1* mutation.

Discussion

The present study reports the case of a patient with thymic carcinoid tumor at the age of 29, with no other features of classical *MEN1* and no previous familial criteria of suspicion, in which we identified a germline mutation in *MEN1* of maternal inheritance. Thymic carcinoid tumors are generally a late manifestation of *MEN1* syndrome and few are the cases reported of very young patients and only thymic carcinoids, without any other *MEN1* related diseases [14]. Approximately 90% of individuals diagnosed with *MEN1* syndrome have an affected parent. However, the family history may appear to be insignificant because of difficulty recognizing the disease in family members, early death before the onset of symptoms or late onset of the disorder in affected parent. Also the penetrance of this syndrome approaches 100% with increasing age and with a variable expression [15].

The mother was diagnosed of breast cancer when she was 35 years old and germline *MEN1* analysis confirmed she was also carrier of the described pathologic mutation. To the best of our knowledge there have been few studies regarding the association between breast cancer and *MEN1* [16] and further studies are needed, but we cannot exclude that the breast cancer described in the mother of our patient could be related to this syndrome.

Germline analysis of *MEN1* gene revealed a mutation in splicing donor site of intron 3, c.669+3A>G, which is a known mutation of the *MEN1* gene associated with the syndrome. Clinical manifestations of the patient and affected family members in our report are different from those of other studies with the same germline mutation [17], which is in concordance with the absence of a *MEN1* genotype-phenotype correlation [18].

The incidence of thymic carcinoids in patients with *MEN1* has been reported to be 3.6-8.4% and 25% of all thymic carcinoids occur in patients with *MEN1* [19]. The age of presentation of a thymic carcinoid in different series is between 30 and 50 years [11]. Different guidelines describe that *MEN1* germline mutational analysis should be considered in those presenting at an early age with a single, apparently sporadic *MEN1* associated tumor [20]. We suggest that *MEN1* mutational analysis should also be considered in all patients with carcinoid thymic tumors, especially if early onset presentation, regardless of the presence or absence of other clinical or familial *MEN1* features.

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