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Solid Tumors Associated with Multiple Endocrine Neoplasias

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Abstract

We present an update on molecular and clinical genetics of solid tumors associated with the various multiple endocrine neoplasias (MEN) syndromes. MEN type 1 (MEN 1) describes the association of pituitary, parathyroid, pancreatic islet cell tumors with a variety of many other lesions; MEN type 2 (MEN 2) conditions represent at least four different syndromes that associate pheochromocytoma with medullary thyroid carcinoma, hyperparathyroidism, and a number of other manifestations. Other pheochromocytoma-associated syndromes include von Hippel-Lindau disease, neurofibromatosis 1, and the recently defined paraganglioma syndromes type 1, 3 and 4, the Carney-Stratakis syndrome and the Carney triad. Carney-Stratakis syndrome is characterized by the association of paragangliomas and familial gastrointestinal stromal tumors (GIST). In the Carney triad, patients can manifest GIST, lung chondroma, paraganglioma, adrenal adenoma and pheochromocytoma, esophageal leiomyoma and other conditions. Carney complex is yet another form of MEN that is characterized by skin tumors and pigmented lesions, myxomas, schwannomas, and various endocrine neoplasias.

Keywords

MEN; medullary thyroid carcinoma; pheochromocytoma; paraganglioma; Carney complex

Introduction

The first case of Multiple Endocrine Neoplasia (MEN) was described in 1903 by Jacob Erdheim [1]. Erdheim reported a patient with acromegaly due to pituitary adenoma and tumors of the parathyroid glands [1]. In 1953, Underdahl *et al.* [2] reported eight patients with tumors of three endocrine glands, pituitary, parathyroid and pancreatic islets of Langerhans. In 1962, the first association between thyroid carcinoma and pheochromocytoma was reported [1]. After those initial reports, Steiner *et al.* [3] proposed the term “endocrine multiple neoplasia” to describe the associations of endocrine tumors and defined two types of MEN: Wermer syndrome or MEN1 (familial pituitary, parathyroid and pancreatic islet cell tumors), and Sipple syndrome or MEN 2 (familial pheochromocytoma, medullary thyroid carcinoma and

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hyperparathyroidism). In 1973, two distinct phenotypes for MEN2 were described: patients with hyperparathyroidism and a normal appearance (MEN2A); and patients without hyperparathyroidism but with mucosal neuromas and Marfanoid characteristics (MEN2B) [4].

In addition, two other syndromes (von Hippel-Lindau and neurofibromatosis type 1) were soon found to be associated with the development of pheochromocytoma [5,6]. Pheochromocytoma was first associated with von Hippel-Lindau (VHL) disease 50 years after the initial description of the condition [7]. Neurofibromatosis Type 1 (NF1) or von Recklinghausen disease [8,9] is also listed among the classic pheochromocytoma-associated syndromes [10], von Hippel-Lindau disease [11], and the recently defined paraganglioma syndromes type 1 [12], 3 [13] and 4 [14], Carney-Stratakis syndrome [15] and Carney triad [16].

Finally, the complex of “spotty skin pigmentation, myxomas, endocrine tumors, and schwannomas”, a disorder that is now known as Carney complex (CNC), was described in 1985 [17-19]. Isolated patients with some components of CNC had been previously diagnosed as NAME (nevi, atrial myxomas, and ephelides) and LAMB (lentigines, atrial myxoma and blue nevi) [20,21].

A. MEN 1

Patients with MEN1 may present with any combination of more than 20 endocrine and non-endocrine lesions (Table 1) [22]. MEN1 is diagnosed by the association of at least 2 of the 3 main MEN1-related endocrine tumors (parathyroid adenomas, entero-pancreatic endocrine tumors, and pituitary tumor). Familial MEN-1 is characterized by at least one MEN1 case associated with one or more first-degree relatives presenting at least one of those main endocrine tumors. The larger MEN1 families frequently show a more typical phenotype. Most of the cases (90%) are familial and present with an autosomal dominant inheritance [22].

Primary hyperparathyroidism (HPT) is the most precocious and frequent clinical presentation of MEN1 with a prevalence of 100% at 50 years of age [23]. HPT is usually diagnosed at around 20-25 years of age. However, the initial biochemical screening for HPT in carriers of *MEN1* germline mutations should begin at 8 years of age and consists on the annual measurement of calcium and parathormone (PTH) levels. Subtotal parathyroidectomy with near-total thymectomy is the procedure of choice in patients with MEN1 and HPT. Alternatively, total parathyroidectomy can be performed and a parathyroid autograft is implanted in the forearm to avoid hypoparathyroidism [22].

The prevalence of entero-pancreatic islet tumors in MEN1 varies from 30-75% and can affect approximately 80% of the patients in autopsy studies [22,24]. Gastrinomas are diagnosed in 40% of the patients with MEN1 and produce hypergastrinemia and Zollinger-Ellison syndrome, characterized by upper abdominal pain, diarrhea, esophageal reflux and acid-peptic ulcers. Gastrinomas in MEN1 patients are often multiple and small tumors (less than 0.5 cm) located mainly in the duodenal submucosa. Metastases at the diagnosis are found in around 50% of these patients [25]. MEN1 subjects may also present hypoglycemia caused by insulinomas. MEN1-insulinomas are diagnosed 10 years earlier than the sporadic cases. Rare functioning entero-pancreatic islet tumors include VIPomas, glucagonomas or somatostatinomas, usually presenting a higher size than gastrinomas and insulinomas [22]. The frequency of non-functioning pancreatic endocrine tumors in MEN1 is higher (54.9%) than previously thought. The size and number of these tumors can increase and pancreatic endoscopic US should be performed at the diagnosis and to monitor disease progression [26].

The frequency of pituitary tumors in MEN1 may range from 10% to 60%. The pituitary tumors are microadenomas in 60% of the cases. Prolactin-secreting adenoma is the most frequent

(20%) pituitary tumor in MEN1 [27]. Non-functioning bilateral adrenal tumors or hyperplasia may be found in 20-40% of individuals with MEN1 [22]. Most of the carcinoid tumors in MEN1 syndrome originate in the foregut and occur in 10% of the cases. These tumors rarely secrete ACTH, calcitonin and other substances. Thymic carcinoids are diagnosed mostly in males and can be asymptomatic until an advanced stage [28]. Non-endocrine tumors associated with MEN1 include facial angiofibromas, collagenomas, lipomas, meningiomas, ependymomas and leiomyomas [22]. *MEN1* gene mutations have been identified in 80-90% of the MEN-1 cases. *MEN1* gene is located at chromosome 11q13 and encodes the menin protein, which functions as a tumor suppressor gene [22].

Recently, Pellegata *et al.* [29] identified a homozygous germline mutation in *Cdkn1b*, the gene coding for the cyclin-dependent kinase inhibitor p27 in the rat MENX (or MEN4) syndrome. The p27Kip1 protein regulates the cell cycle progression by binding to and inhibiting cyclin/Cdk complexes. Germline *CDKN1B* nonsense mutations should therefore be sought in patients with MEN1-like conditions that are negative for *MEN1* mutation [29].

B. MEN 2 syndromes

MEN2 is characterized by medullary thyroid carcinoma (MTC), with or without pheochromocytoma and hyperparathyroidism [22]. MEN2A consists on the association of MTC (90%), pheochromocytoma (50%) and primary hyperparathyroidism (20-30%). Variants of MEN2 include familial MTC (FMTC), MEN2A or FMTC with Hirshsprung's disease and MEN2A with cutaneous lichen amyloidosis. MEN2B is characterized by clinically aggressive MTC, pheochromocytoma, a Marfanoid habitus, mucosal and intestinal ganglioneuromatosis. MEN2B is not typically associated with hyperparathyroidism [22,30].

Germline activating mutations of *RET* (Rearranged during Transfection) proto-oncogene have been identified in 98% of the individuals with MEN2 [10,22]. In addition, there is an important genotype-phenotype correlation in MEN2 [22]. *RET* encodes a tyrosine kinase receptor expressed primarily in neuroendocrine cells (including thyroid C cells and adrenal medullary cells), neural cells (including parasympathetic and sympathetic ganglion cells), urogenital tract cells, and testis germ cells [31,32]. One of four glial-derived neurotrophic factor (GDNF) family ligands, GDNF, neurturin, artemin, or persephin, binds RET in conjunction with one of four glycosylphosphatidylinositol-anchored co-receptors, designated GDNF-family α receptors (GFR α): GFR α 1, GFR α 2, GFR α 3, and GFR α 4. GDNF primarily associates with GFR α 1, whereas neurturin, artemin, and persephin preferentially bind GFR α 2, GFR α 3, or GFR α 4, respectively [31]. RET activation can be caused by RET homodimerization in most MEN2A mutations or by RET kinase enzyme's catalytic site activation in MEN2B [22]. *RET* mutations lead to the activation of major intracellular oncogenic pathways, such as RAS/ERK, PI3K/AKT, nuclear factor κ B (NF κ B) and JUN kinase pathways [33-35].

C. Isolated medullary thyroid carcinoma (MTC)

MTC is a calcitonin (CT)-producing tumor originated from the parafollicular or C cells of the thyroid gland and represents 5-10% of all thyroid cancers. Most of the cases are sporadic (75%), but the prevalence of familial MTC is high (25%) (Table 2) [36]. The clinical behavior of MTC correlates with the type of MEN2 syndrome and with the mutated *RET* codon. CT levels constitute the most important tumor marker for the diagnosis and follow-up of MTC; high CT levels indicate persistent or recurrent disease. MTC can spread locally (central and lateral, cervical and mediastinal lymph nodes) or to lung, liver and bone [36].

Most of the cases of hereditary MTC represent MEN2A cases, about 80% of the total hereditary MTC cases. Few MEN2B subjects may present with MTC but in these patients there is almost

always a Marfanoid habitus; MEN2B patients develop multifocal MTC with almost 100% of penetrance and an early and more aggressive form of MTC [36].

Thus, every patient presenting with newly diagnosed MTC should be counseled about the possibility of familial disease and offered genetic testing. The probability of a *RET* germline mutation in an individual with apparent sporadic MTC is 1-7%, but this screening is justified by the critical clinical implications of a *RET* mutation [37].

The best chance of cure in familial MTC is provided by complete surgical resection before malignant transformation or spread beyond the thyroid gland. Patients with specific germ-line *RET* mutations are stratified into specific risk groups based on reported age of onset and aggressiveness of the disease. Children with MEN2B or *RET* codon 883, 918 or 922 mutations are classified as level III and present the most aggressive form of MTC and should undergo total thyroidectomy within the first 6 months of age [22,36]. Surgical approach for MEN2B should include a central nodal resection or even a more extensive resection if local lymph node dissemination is identified. Individuals with MEN 2A mutations (codons 611, 618, 620, and 634) are considered high risk (level II) and should have thyroidectomy performed before 5 years of age. Although *RET* codon 609, 768, 790, 791, 804 and 891 mutations are classified as level I or having the lowest risk among the three groups of *RET* mutations, the level I individuals should also undergo thyroidectomy by the age of 5 years [22,36].

Systemic chemotherapy in patients with locally advanced or metastatic MTC has so far produced modest clinical responses. Targeting angiogenesis (and specifically VEGF receptors) has produced the most impressive clinical responses to date in MTC [38]. However, eventual disease progression during VEGF receptor inhibitor treatment suggests that the up-regulation of other pathways promote tumor growth and metastasis [39].

D. Genetic syndromes associated with pheochromocytoma

Pheochromocytomas and paragangliomas are catecholamine-secreting tumors of neural crest origin arising from the adrenal medulla or extra-adrenal paraganglial sympathetic nervous system. Hereditary etiologies of pheochromocytoma include: MEN2A and MEN2B caused by *RET* mutations [10]; von Hippel-Lindau disease caused by *VHL* gene mutations [11]; mutations of the *NF1* gene, responsible for neurofibromatosis [40]; and familial paraganglioma syndromes caused by mutations in subunits *B*, *C* or *D* of the *succinate dehydrogenase* (SDH) complex (Table 3) [12-14].

Germline mutations in the susceptibility genes for pheochromocytoma can also be found in about 25% of the non-syndromic cases [41]. Therefore, genetic screening for mutations of *RET*, *VHL*, *SDHD* and *SDHB* is indicated to identify pheochromocytoma-related syndromes in non-familial cases. Recently, Erlic *et al.* [42] found 19% of germline mutations in 989 apparently nonsyndromic pheochromocytoma cases. Predictors for presence of mutation are age < 45 years, multiple pheochromocytoma, extra-adrenal location, and previous head and neck paraganglioma [42]. Individuals with multiple and adrenal tumors should be first screened for *VHL* and *RET*. The diagnosis of head and neck paragangliomas is highly suggestive of *SDHD* mutations [42].

MEN2

Unilateral or bilateral pheochromocytomas are diagnosed in 50% of MEN2 subjects. Laparoscopic adrenalectomy is the procedure of choice for pheochromocytoma treatment. Pheochromocytoma has been found in kindreds with all *RET* mutations except those in codons 609, 768, 804 and 891. In addition, pheochromocytomas have been identified with codon 634 mutations as early as 5 and 10 years of age [22].

VHL

VHL disease arises from *de novo* mutations without a family history in 20% of the cases. VHL disease most commonly presents with retinal or cerebellar hemangioblastomas. The third major feature is clear cell renal carcinoma, and cystic disease affecting the kidneys, pancreas and epididymis is also associated with VHL [5]. Pheochromocytoma has an overall frequency of 10–20%, but its prevalence is extremely variable between families [43]. The mean age at diagnosis of pheochromocytoma in VHL disease is 20 years compared with 43.9 years in sporadic cases, reflecting both an increased detection through surveillance and a predisposition to early onset tumors [41]. Pheochromocytoma in VHL disease is usually intra-adrenal but 10% of the cases may be extra-adrenal [44].

The VHL protein (pVHL) is part of an E3 ubiquitin ligase complex that targets proteins for proteasome degradation. Its main function is the degradation of members of the hypoxia-inducible factor protein family [45]. Hypoxia-inducible factor transcription factors are tightly controlled under normoxic conditions. Low oxygen tension prevents the post-translational modifications of hypoxia-inducible factors, necessary for their ubiquitylation by the pVHL containing E3 ubiquitin ligase complex. Hypoxia-inducible factors are up-regulated in renal cancers in VHL disease and in a large proportion of sporadic clear cell carcinomas [46].

NF1

NF1 is characterized by pigmentary abnormalities and the neoplastic growth of neural crest-derived cells. Cardinal clinical features are multiple dermal neurofibromas, café-au-lait spots, axillary or inguinal freckling, and hamartomas of the iris [47]. Pheochromocytoma occurs in approximately 1% of patients with NF1 [8]. Despite the low prevalence of pheochromocytoma in NF1, genetic evidence suggests that pheochromocytoma is a true component of NF1. Loss-of-heterozygosity of NF1 markers in NF1-related pheochromocytoma was significantly more frequent than in sporadic pheochromocytoma [6]. The age at diagnosis of pheochromocytoma in NF-1 patients is similar to sporadic pheochromocytoma and higher than in MEN2- and VHL-related pheochromocytomas. Most of the cases are intra-adrenal, but less frequently multifocal when compared to MEN2 and VHL [8].

Inherited Paraganglioma syndromes

Paraganglioma syndromes are caused by mutations in the *SDH* genes: paraganglioma syndrome type 1 (*SDHD*) [12], paraganglioma syndrome type 3 (*SDHC*) [13], paraganglioma syndrome type 4 (*SDHB*) [14]. Hereditary head and neck paragangliomas are most exclusively caused with germline *SDHB*, *SDHC* and *SDHD* mutations [48]. Pheochromocytomas can be associated with 5 (*RET*, *VHL*, *NF1*, *SDHB*, *SDHD*) out of the 6 susceptibility genes [49]. Germline *SDHC* mutations are a very rare cause of pheochromocytomas [50]. Mutations of the *SDHB* gene are more frequently associated with malignant disease [51].

Carney-Stratakis syndrome

Recently, germline *SDHB*, *SDHC* and *SDHD* mutations were identified in patients with both gastrointestinal stromal tumors and paragangliomas. This condition has been referred to as “the dyad of paraganglioma and gastrointestinal stromal tumors” or the “Carney–Stratakis syndrome” (or “Carney–Stratakis dyad”). Germline *SDHB*, *SDHC*, and *SDHD* mutations were associated with familial gastrointestinal stromal tumors, but abdominal paragangliomas associated with gastrointestinal tumors were exclusively caused by *SDHC* mutations [15].

Carney triad

Carney triad is a syndrome of tumors affecting at least five organs, the stomach, the lung, the paraganglionic system, the adrenal (cortex and medulla), and the esophagus. Individuals with

Carney triad can present with gastrointestinal stromal tumor (GIST) (Figure 1), lung chondroma, paraganglioma, adrenal adenoma and pheochromocytoma, esophageal leiomyoma and other hamartomatous lesions. These tumors frequently are multifocal. Carney triad mainly affects women, although male patients have also been reported rarely. It is a chronic, persistent, and frequently (but not always) indolent condition. The etiology of the syndrome is unknown and although it is certainly genetic there are very few cases, if any, that are inherited, possibly pointing to a disorder that is due to somatic mosaicism [16].

E. Carney complex

Spotty skin pigmentation is the most common clinical manifestation (above 80%) of CNC (Table 4). Cutaneous manifestations constitute three of the major disease criteria: lentigines, cutaneous or mucosal myxomas; and blue nevi (multiple) or epithelioid blue nevus [52,53]. Cardiac myxomas occurred in 32% of the patients [54]. Cardiac myxomas were frequently multicentric and often affected any or all cardiac chambers. Skin and breast myxomas occurred in 20% of the total, and in 20% of the female patients, respectively [54-56].

Primary pigmented nodular adrenocortical disease (PPNAD) is the most common endocrine tumor associated with CNC, occurring in 60% of the CNC patients [54]. Isolated PPNAD is the only manifestation in 12% of the CNC patients. GH-producing pituitary adenomas affect 12% of the CNC patients [57,58]. Thyroid tumors are diagnosed in 25% of the patients, with nine cases of thyroid cancer (papillary or follicular or both) previously described (2.5%) [54]. Multicentric and bilateral testicular tumors [large-cell calcifying Sertoli cell tumor (LCCSCT)] are diagnosed in around 40% of the male patients. Psammomatous melanotic schwannoma (PMS) is found in 8% of the patients and occurs mainly in the gastrointestinal tract and paraspinal sympathetic chain.

Inactivating mutations of the *PRKARIA* gene coding for the regulatory type I- α (RI α) subunit of protein kinase A (PKA) are responsible for the disease in most CNC patients [59]. The overall penetrance of CNC among *PRKARIA* mutation carriers is near 98%. Most *PRKARIA* mutations result in premature stop codon generation and lead to nonsense-mediated mRNA decay [60]. CNC is genetically and clinically heterogeneous, with specific mutations providing some genotype-phenotype correlation [54]. Phosphodiesterase-11A (the *PDE11A* gene) and -8B (the *PDE8B* gene) mutations were found in patients with isolated adrenal hyperplasia and Cushing syndrome, as well in patients with PPNAD [61,62].

Concluding remarks: new genes to be identified

The so far recognized MEN syndromes are familial disorders with autosomal dominant inheritance. Genetic screening for the known germline mutations associated with MENs has important implications for genetic counseling, treatment and follow-up. *RET* mutations should be investigated in all apparent sporadic MTC. *VHL*, *RET*, *SDHD* and *SDHB* mutations should also be screened in non-familial cases of pheochromocytomas and paragangliomas. However, new genetic defects are to be identified in the future: for example, although most of CNC cases are caused by *PRKARIA*-inactivating mutations, a genetic etiology has not been identified in one third of the patients. Also, to date, no coding sequence mutations of the *KIT* and *PDGFRA* genes (frequent in GISTs), or the *SDHB*, *SDHC*, and *SDHD* genes that are responsible for sporadic GIST and familial paraganglioma, respectively, have been found in patients with Carney triad [63].

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Figure 1.

GIST in a patient with Carney Triad: multiple lesions, as often is the case, are seen covering the mucosa of the duodenum. These GISTs are negative for *KIT* and *PDGFA* mutations and the responsible genetic defect remains unidentified.

Table 1

Prevalence of endocrine and non-endocrine tumors associated with MEN 1

Endocrine tumors	Prevalence at 40 years
Parathyroid adenomas	90%
Entero-pancreatic tumors	Gastrinoma 40%, Insulinoma 10% Others (VIPoma, glucagonoma) 2% Non-functioning 20%
Pituitary adenomas	Prolactinoma 20%, GH 5% GH/PRL 5%, TSH < 1%, ACTH-secreting 2% Non-functioning 17%
Foregut carcinoids	Thymic 2%, Bronchial 2%, Gastric 10%
Adrenal gland	Non-functioning 20-40% (most of them bilateral hyperplasia)
Non-endocrine tumors	
Cutaneous tumors	Facial angiofibroma 85% Collagenoma 70% Lipoma 30%
Central nervous system lesions	Meningioma 5-8% Ependymoma 1%

Table 2

Clinical syndromes associated with hereditary medullary thyroid carcinoma (MTC)

Syndrome	Frequency (%)	<i>RET</i> mutations (most frequent affected codons)
MEN2A	70-80%	609, 611, 618, 620 or 634; mutations in codon 634 account for 87% of the cases
MEN2A variants:		
Familial MTC	10-20%	609, 611, 618, 620 or 634
Association with Hirshsprung's disease or cutaneous lichen amyloidosis	Rare variants	
MEN2B	5%	918, 883

Table 3

Hereditary syndromes associated with pheochromocytomas or paragangliomas and their genetic defects

Syndrome	Gene	Tumors
MEN2	<i>RET</i>	Medullary thyroid carcinoma Pheochromocytomas Parathyroid adenomas
VHL	<i>VHL</i>	Retinal or cerebellar hemangioblastomas Clear cell renal carcinoma Cystic disease (kidneys, pancreas and epididymis) Pheochromocytomas
NF1	<i>NF1</i>	Multiple dermal neurofibromas Café-au-lait spots axillary or inguinal freckling Hamartomas of the iris Pheochromocytomas
Paraganglioma syndrome type 1	<i>SDHD</i>	Paragangliomas (more often head and neck) Pheochromocytomas
Paraganglioma syndrome type 3	<i>SDHC</i>	Paragangliomas
Paraganglioma syndrome type 4	<i>SDHB</i>	Paragangliomas and Pheochromocytomas (high prevalence of malignant disease)
Carney-Stratakis syndrome	<i>SDHB</i> <i>SDHC</i> <i>SDHD</i>	Familial gastrointestinal tumors Paragangliomas
Carney triad	unknown	Gastrointestinal stromal tumor Lung chondroma Paraganglioma and/or pheochromocytoma Adrenal adenoma Esophageal leiomyoma, other

Table 4

Clinical manifestations of patients with Carney complex

Manifestation	%
Spotty skin pigmentation	70
Cardiac myxoma	32
Skin myxoma	20
PPNAD	60
LCCSCT	41% of the males
Ovarian lesion	14% of the females
Acromegaly	12
Thyroid tumor	25
PMS	8

CNC, Carney complex; PPNAD, primary pigmented nodular adrenocortical disease; LCCSCT, large-cell calcifying Sertoli cell tumor; PMS, psammomatous melanotic schwannoma.