

Dermatological and endocrine elements in Carney complex (Review)

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Abstract. Carney complex (CNC) is a very rare, autosomal dominant, hereditary syndrome. Seventy percent of individuals with CNC have germline inactivating or deleting mutations of the *CNC1* gene [currently known as protein kinase cAMP-dependent type I regulatory subunit α (*PRKARIA*), located at the 17q22-24 chromosome level], with 30% of cases presenting with phosphodiesterase gene mutations. A member of the lentiginosis family, dermatological features include: skin pigmentation, cutaneous/mucosal myxomas, usually diagnosed by the age of 20 years (neonatal presentation is exceptional, requiring a meticulous differential diagnosis). Melanocyte-derived tumors such as epithelioid blue nevi (with different levels of pigmentation) and pigmented epithelioid melanocytoma (previously 'animal-type melanoma') are often found. Myxomas, mesenchymal tumors with mostly a benign pattern, may be recurrent. Primary cutaneous melanotic schwannoma are atypical, while non-skin sites are frequent. Corticotropinomas or somatotropinomas are part of the

hereditary syndrome-related pituitary adenomas (representing 5% of all). Primary pigmented nodular adrenocortical disease involves bilateral cortical hyperplasia causing Cushing syndrome (CS) at an earlier age than non-CNC cases; osteoporotic fractures seem more prevalent compare to CS of other etiologies. Typically benign, a few cases of adrenocortical carcinoma have been identified. A total of 5% of familial non-medullary thyroid cancer is syndromic, also including CNC. CNC-related thyroid frame includes: hyperthyroidism, follicular hyperplasia/adenomas, follicular carcinoma (usually aggressive, bilateral or multifocal). Large cell calcifying Sertoli cell tumors of the testes have malignant behavior in adults; in children these may induce precocious puberty. Two particular mammary tumors are found: myxoid fibroadenomas and breast myxomatosis. Cutaneous/subcutaneous lesions, pigmented or not, or any focal swelling of non-identified cause needs careful examination, since dermatological elements are among the earliest and most discernable by which to detect lesions in CNC, a systemic condition with multi-level endocrine involvement.

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Abbreviations: CNC, Carney complex; ACTH, adrenocorticotrophic hormone; FNMTc, familial non-medullary thyroid cancer; GH, growth hormone

Key words: Carney complex, pigmented spot, lentiginosis, *PRKARIA* gene, acromegaly, Cushing syndrome, thyroid tumor, adrenal tumor, testicular tumor, primary pigmented nodular adrenocortical disease

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1. Introduction

Carney complex (CNC) is a very rare autosomal-dominant hereditary syndrome with high penetrance with underlying endocrine elements such as primary pigmented nodular adrenocortical disease at the level of the adrenal cortex [clinically associated with Cushing syndrome (CS)] pituitary adenomas secreting adrenocorticotrophic hormone (ACTH) and growth hormone (GH) thus causing Cushing disease, respective gigantism or acromegaly or giganto-acromegaly, and thyroid pathology of tumor type in addition to non-endocrine findings of various types (1). Among them, we mention myxomas located in the skin, mucosa, heart, and breast (2). In addition, at the skin level there are pigmented cutaneous lesions or lentiginosis (the core elements for diagnostic are pigmented maculas, myxoma, and primary pigmented nodular adrenocortical disease) (3,4). Moreover, schwannomas such as psammomatous melanotic type are related to the syndrome (5). Some tumors have a highly malignant potential such as osteochondromyxomas or adult types of testicular tumors (for instance, the malignant cases of large cell calcifying Sertoli cell tumors) (6,7).

CNC was identified in 1985 while two decades ago the associated mutations were beginning to be identified (8). A total 70% of individuals have a germline mutation of the *CNC1* gene [which today is called protein kinase cAMP-dependent type I regulatory subunit α (*PRKARIA*) gene, located at the 17q22-24 chromosome level]; the mutation includes an inactivating type or large deletions, while the gene encodes cyclic AMP-dependent protein kinase A (at the level of subunit 1 α or R1A) (9). Genotype-phenotype correlations have been described in *PRKARIA* gene mutations (10). Defects of catalytic subunits (*PRKACA*) are related to adrenal hyperplasia while other subunits such as *PRKACB* are connected to the presence of hypophyseal tumors, pigmented skin lesions and myxomas (11). A total of 30% of subjects have mutations of the phosphodiesterase genes, also of an inactivating type (12). These genetic aspects may be linked to particular adrenal tumors and testicular neoplasia in individuals with CNC (13).

No particular therapy has addressed the hereditary complex of diseases; once the mutation is identified starting from any type of lesion, then gene testing is indicated; a multidisciplinary team is required to adequately screen and approach further elements of CNC that are more likely to express later in life (14,15).

2. Aim of the review

We aimed to introduce a brief narrative presentation of skin lesions in CNC in addition to the overall picture, especially the endocrine panel.

The instrumentation of research was PubMed starting from several key words in different combinations as mentioned in the specific 'Key words' section. A number of 82 papers are cited; they were published between 2021 and 2012. We included the papers with the most clinical relevance; the approach of the presentation was multidisciplinary. As expected, due to the rarity of the syndrome, the level of statistical evidence involving most of the cited papers was low.

3. Lentiginosis

CNC is a type of genodermatoses, hereditary syndromes with skin involvement and tumorigenic findings, some of them being highly malignant (16). Skin pigmentation and myxomas are usually diagnosed in CNC by the age of 20 years, although neonatal presentation has been rarely reported and a specific panel of differential diagnosis is required at early ages (17). Spotty skin pigmentation are described with a disposition all over the body (18).

Different melanocyte-derived tumors have been identified such as epithelioid blue nevi and pigmented epithelioid melanocytoma (19,20). Pigmented epithelioid melanocytoma was previously termed 'animal-type melanoma' (21). Despite being linked to this hereditary syndrome, blue nevus-derived tumors, underlying different grades of pigmentation, do not typically have a neonatal presentation (22). Congenital, epithelioid and spindle cell-derived neoplasia are described in sporadic cases even in multiple sites accounting for up to 1,000 lesions per individual in some cases (23). Acquired cases of epithelioid blue nevus are described in individuals with chronic sun exposure and associated skin damage (24).

Any cutaneous and subcutaneous lesion, pigmented or not or any focal swelling of non-identified cause needs careful dermatological evaluation since dermatological elements are among the earliest and most easy to detect lesions in an otherwise multi-organ disease (25).

4. Myxomas

Myxoma is a mesenchymal tumor which usually has a benign behavior; the most frequent sites being the skin, mucosa, and heart in relationship with CNC (26). Recurrence of skin myxomas is found in some cases (27). In 2018, the largest skin myxoma of 15 cm was reported in an 18-year-old patient (28).

Rarely do they embrace other scenarios such as intra-oral myxomas and facio-oral deformations that need to be differentiated from acromegaly-related changes if the co-presence of a somatotropinoma is also confirmed (29). Atypical presentations or the identification of a myxoma in patients who are not yet diagnosed with CNC requires differentiation upon clinical and mainly histological findings in addition to gene testing; for instance, an eyelid myxoma may be mistaken as a chalazion or a superficial angiomyxoma (a benign tumor with underlying multiple vessels and a large matrix) (30,31).

Cardiac myxoma may lead to atypical cardio-embolic stroke in individuals with CNC or it may be incidentally detected at autopsy (32). In other cases, a massive embolic event may cause sudden death (33). Recurrent atrial presentation has also been reported (34). In 2020, a series of 41 cases with pediatric presentation in addition to arterial ischemic stroke was reported (a median age of 11 years; 56% male predominance) in subjects with CNC (35).

5. Schwannomas

Subjects with CNC may develop a particular neoplasia, melanotic schwannoma, derived from the spinal nerves and ganglia, a very rare tumor (36). This is a tumor with two

subtypes: Psammomatous or non-psammomatous; overall, the neoplasia is malignant in one out of 10 patients and aggressive profile is less likely to be predicted from the initial diagnosis (37). The tumor may be developed in sporadic cases and in *PRKARIA* carriers (38). Cases with a primary cutaneous location have been reported in individuals confirmed with CNC (39).

6. Pituitary adenomas

CNC includes the presentation of pituitary adenomas, as seen in other hereditary syndromes such as multiple endocrine neoplasia type 1, Lynch syndrome, neurofibromatosis type 1, and rarely in von Hippel-Lindau disease (40,41). A total of 95% of pituitary adenomas are sporadic; the others involve the mentioned inherited syndromes as well as isolated pituitary conditions as seen in individuals with *AIP* mutations (42). CNC-related pituitary tumors are secretors: corticotropinoma or somatotropinoma (43).

7. Adrenal disease

In individuals with CNC, one in 10 adults has a tumor at the level of the adrenal cortex, mostly an age-dependent, so called 'adrenal incidentaloma' (44). Adrenal tumor-related genetic backup is identified with regard to channel anomalies as found in some cases of primary hyperaldosteronism; in *TP53* mutations (such as Li-Fraumeni syndrome) causing adrenocortical carcinoma, especially in pediatric individuals, or pigmented adrenal lesions induced by CNC (45,46). Other syndromic circumstances associated with an adrenal tumor involves multiple endocrine neoplasia type 2A, neurofibromatosis type 1, McCune-Albright syndrome, Beckwith-Wiedemann syndrome, and von Hippel-Lindau disease (47).

PRKARIA gene-associated tumors are typically benign; yet in 2012 the first case of adrenal cancer was reported in one family (48). Generally, adrenocortical carcinoma is regarded as a highly aggressive tumor and prompt intervention is required to achieve a better prognosis but the overall prognosis remains very poor (49).

Most of the cases diagnosed with primary bilateral hyperplasia of micronodular adrenocortical type at imaging scan are associated with the hormonal picture of Cushing syndrome (50). The typical picture of tumor-related hypercortisolemia is expected such as cardiovascular risk, obesity, and osteoporosis (51,52). The age of diagnosis is decreased when compared with other types of adrenal Cushing syndromes (50,53). A paper published in 2020 found, based on two retrospective studies, a higher risk of osteoporotic fractures vs. Cushing syndrome of other causes (50,54). Since the gene-related adrenal masses are bilateral, unilateral adrenalectomy rarely cures the persistent hypercorticism (55).

8. Thyroid conditions

Familial non-medullary thyroid cancer (FNMTTC) involves one affected individual and at least two of his first-degree relatives (56). It represents 3-9% of all primary thyroid cancers (57). A total of 95% are non-syndromic (for instance,

mutations of *FOXE1* or *TTF1* genes) which, in the absence of gene testing, have a presentation very similar with sporadic cases (58). A total of 5% of individuals with FNMTTC are syndromic with underlying driven germline mutations similar to CNC, but also Gardner syndrome, Cowden syndrome or *DICER1* syndrome (59).

In CNC, thyroid gland involvement may be completely asymptomatic or associated with hyperthyroidism (60). Benign lesions are follicular hyperplasia and adenomas while follicular carcinoma is more aggressive than usual with bilateral and multifocal presentation and early lymph node metastases (60).

9. Testicular tumors

As seen in Peutz-Jaghers syndrome, large cell calcifying Sertoli cell tumors, even very rare, are associated with CNC (61). They are identified either in pediatric or in adult individuals (62). No particular endocrine constellation is expected, unless precocious puberty is developed in children; while local pain may be present, including a bilateral pattern (63). The echoic aspect of testicular calcifications is very suggestive (64). Testes-sparing surgery is indicated in cases that are not suggestive for a malignant behavior (which is mostly seen in adults, not in children) (65,66).

10. Mammary tumors

In females with CNC, mammary tumors with particular histological features have been reported, namely myxoid fibroadenomas that are distinctive from traditional fibroadenomas (67). Breast myxomatosis has also been reported (68).

11. Discussion

CNC needs to be differentiated from Carney triad which is a very rare combination of unknown cause, associated with three different types of tumors: pulmonary chondroma, gastric leiomyosarcoma [very similar to gastrointestinal stromal tumor (GIST) presentation] and paraganglioma (69,70).

Other tumorigenic risks have been reported in CNC including melanoma; yet currently it is considered incidental, but a clear histological and immunohistochemically differentiation from melanotic schwannoma is required (71,72). Uveal melanoma has also been reported in cases with CNC, but the association is not typical (73).

When it comes to skin changes in individuals with CNC, many of these are actually related to the hormone excess of endocrine tumors such as acromegaly, Cushing syndrome/disease, and thyrotoxicosis (74,75). Cortisol or GH excess may be complicated with secondary diabetes mellitus, and chronic hyperglycemia-related dermatological findings are precisely connected to the endocrine disease control (76,77). Endocrine tumors may be the first step that helps denote the findings of CNC or they may be revealed in subjects with skin lesions suggestive of a lentiginosis or in carriers of a *PRKARIA* mutation (78). One multicenter trial on 70 patients (with a median age of 35.4 years) that were either known with Carney complex or with primary pigmented bilateral hyperplasia or they were *PRKARIA* carriers identified acromegaly in 11.4% of all the cases. Also, in this cohort

there was one subject confirmed with testicular lesions and two individuals identified with heart myxomas. Overall, the interval of follow-up was 36 months (78).

Another distinctive aspect is the fact that acromegalic patients, especially with long-term undetected or uncontrolled disease, are traditionally described as having a higher risk than the general population for presenting with associated second non-pituitary tumor, either benign such as nodular goiter, colonic polyps, even testicular tumors and mammary fibro-adenomas in females, or malign such as thyroid cancer (79,80). In these cases, evaluation of dermatological elements is a valuable clue for implementing *PRKACA* gene testing in order to differentiate a cluster of tumors related to GH excess or related to CNC itself (81,82).

12. Conclusions

Cutaneous manifestations such as skin myxomas and pigmented lesions are essential clues for identifying individuals with Carney complex. The endocrine panel of manifestations varies from pituitary, adrenal, and thyroid glands to testicular tumors and breast anomalies in females. Despite being a rare entity, close multidisciplinary work is required on a lifelong basis, and early tumor identification improves the overall prognosis.

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Authors' contributions

FS drafted the manuscript and critically revised the final form in light of the literature data. MCD is the corresponding author and helped the revision of the literature data. AP researched the literature data, and MC drafted the manuscript in light of the literature findings. RCP drafted the manuscript in light of the literature findings and DLP approved the final form after reviewing all the literature data. All authors read and approved the final manuscript for publication.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare they have no competing interests.

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